ADMINISTRATIVE

MANUAL OF PROCEDURES

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Sponsored by the National Institutes of Health
National Heart, Lung, and Blood Institute
National Cancer Institute

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CHAPTER 1

NETWORK ORGANIZATION

1. NETWORK ORGANIZATION

1.1. Mission Statement and Organizational Overview

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was established in 2001 to conduct large multi-institutional clinical trials addressing important issues in hematopoietic cell transplantation (HCT) thereby furthering understanding of the best possible treatment approaches.

Participating investigators in the BMT CTN collaborate through an organization designed to maintain continuity of operations and to facilitate effective communication and cooperation among the units.

The Statistical Center of the Center for International Blood and Marrow Transplant Research (CIBMTR®) at the Medical College of Wisconsin, the Coordinating Center of the National Marrow Donor Program® (NMDP)/Be The Match, and The Emmes Company, LLC (Emmes) comprise the Data and Coordinating Center (DCC).

The National Heart, Lung, and Blood Institute (NHLBI) Project Officer, the National Cancer Institute (NCI) Project Officer, and Principal Investigators from the participating Core Clinical Centers and the DCC comprise the Steering Committee, which is responsible for the prioritization, design, execution, and analysis of Network studies.

BMT CTN trials are conducted in both Core and Affiliate Centers. The latter access trials through the DCC. Selected Affiliate Centers are also represented on the Steering Committee.

The Administrative Manual of Procedures (MOP) describes the Network organization, study policies, and participating center procedures, and is ratified by the Steering Committee. This chapter provides detailed description of the BMT CTN's organizational structure and defines the roles and purposes of the collaborating units.

The success of a multi-center endeavor depends on the cooperation of the staff in all participating units to perform their tasks and responsibilities in an efficient, effective, and timely manner. The participating units in the BMT CTN (i.e., participating clinical centers, DCC, and Project Officers) are posted on the BMT CTN private website.

1.2. Steering Committee

The BMT CTN Steering Committee is responsible for the operation of the Network. The Steering Committee formulates and implements all policy decisions related to the work of the BMT CTN and establishes its scientific agenda.

The Steering Committee consists of the following voting members:

- Core Clinical Center Principal Investigators (20) including (one vote each)
    - Chairperson
    - Chair-Elect
    - Vice-Chair
    - Immediate Past-Chair

- Representatives of Affiliate Centers selected by the Steering Committee for exemplary performance (see Section 1.3.2.3)
- NHLBI Project Officer
- NCI Project Officer
- DCC Principal Investigators (3) (The Principal Investigator from the CIBMTR is the only voting member)
- NCI's National Clinical Trials Network (NCTN) BMT Committee Representatives from ECOG-ACRIN, SWOG, Alliance for Clinical Trials in Oncology (Alliance) and Children's Oncology Group (COG)

The following observers may attend and participate in Steering Committee meetings but do not have voting privileges:

- Other NHLBI and NCI staff members
- Co-Investigators from participating Core and Affiliate Centers
- Clinical Research Associates/Coordinators from participating Core and Affiliate Centers
- Other DCC staff
- Other relevant consultants and contributors by invitation for specific agenda items
- Executive sessions of the Steering Committee are limited to voting members and others specifically invited by the Chair

The terms of the Steering Committee members and Chairperson are as follows:

- Steering Committee Membership is indefinite dependent upon continuing participation of the member's institution in the Network
- Chairperson is presented by the Nominating Committee for Steering Committee approval and is constrained by the following conventions:

    1. Six-year total term, served in the subsequent order:

        - Two years as Vice-Chair
        - One year as Chair-Elect
        - Two years as Chairperson
        - One year as Immediate Past-Chair

    2. Can serve more than one term but not consecutive terms

The functions of the Steering Committee include:

- Develop Manuals of Procedures (Administrative and Technical) and Technical Documents
- Ratify major changes in the Manuals of Procedures and Technical Documents
- Review Concept Proposals and appoint Protocol Teams
- Prioritize protocols and set timelines for implementation
- Recommend to the NHLBI and NCI Project Officers changes or modifications in BMT CTN protocols that may be necessary or desirable (but not based on Data and Safety Monitoring Board (DSMB) reports)
- Advise and assist the DCC and the Technical Committees on operational matters
- Resolve operational problems brought to the Executive Committee by Investigators, Clinical Research Associates/Coordinators, laboratories/repositories, or the DCC

- Monitor the performance of all participating centers based on information provided by the DCC. This evaluation includes assessment of accrual, the quality of data reported by center staff, laboratory sample compliance and adherence to all protocols. The Steering Committee advises the NHLBI and NCI Project Officers on the performance of participating centers and may recommend that NHLBI and/or NCI invite new participants or terminate centers showing unsatisfactory performance (see Chapter 5 for additional details).
- Assure study results are reported in the scientific literature in a timely manner
- Review decisions and recommendations of the Publications Committee, as needed
- Assume other responsibilities at the request of the BMT CTN Chairperson or the NHLBI or NCI Project Officers

The Steering Committee meets in person three times a year to monitor the progress of BMT CTN studies and consider special issues that may arise. Additional meetings and conference calls are held as necessary. The Steering Committee does not have access to blinded data from BMT CTN studies.

1.2.1. Steering Committee Chairperson

The Steering Committee elects a Chairperson who is primarily responsible for the scientific direction and administration of the BMT CTN. The Chairperson:

- Develops and maintains, with advice from Steering Committee members, an organizational structure that meets the needs of the Network studies, NHLBI and NCI
- Remains informed of all operational aspects of the studies and, working within the developed organization, formulates policy and takes necessary actions to ensure the smooth operation of all studies
- Collaborates on data monitoring and other issues of importance to the overall conduct of the studies
- Appoints individuals from BMT CTN Core and Affiliate centers to appropriate positions and committees
- Chairs the Steering Committee meetings
- Reviews potentially competing studies at participating centers

Elections are held one year prior to the end of the previous Chairperson's term so that the elected individual may serve two years as Vice-Chair. If the BMT CTN Chairperson is unable to serve because of resignation, serious illness or death the Chair-Elect or immediate Past-Chair will assume Acting Chairperson responsibilities. If the BMT CTN Chairperson is unable to fulfill this obligation for a limited period (up to six months), the Chair-Elect or immediate Past-Chair will serve as Acting Chairperson, and a new election for Chair-Elect will not be held; if the period of time exceeds six months, an election for a new Chair-Elect will be held. Similarly, if the Chair-Elect, Vice-Chair or Immediate Past-Chair are unable to fulfill the remainder of their term for more than six months, an election will be held to fill an appropriate leadership position to ensure there are three Steering Committee leaders in place.

1.3. Clinical Centers

1.3.1. Core Clinical Centers

There are 20 Core Clinical Centers (some of which are consortia of two or more centers) with cooperative agreements from the NHLBI and NCI to participate in the BMT CTN. Core Center Principal Investigators have voting representation on the Steering Committee (see Section 1.2) and have responsibility for chairing Protocol Teams, Administrative Committees, and Technical Committees. If a Core Center's Principal Investigator is unable to serve because of resignation, serious illness or death, the Center will nominate a new Principal Investigator (PI) with approval by the NHLBI.

Participating Core Clinical Centers are responsible for recruiting, examining, and treating study participants and for collecting all clinical, laboratory, demographic, and other data required by each BMT CTN study. The Principal Investigator for each Core Clinical Center is directly responsible for ensuring that all aspects of BMT CTN protocols are followed. Other key center staff includes other physicians, Co-Investigators, Clinical Research Associates/Coordinators (CRAs/CRCs) and related staff. The Principal Investigator of the Core Clinical Center may designate another individual at his or her center to serve as Lead Investigator for specific BMT CTN studies. This individual then assumes responsibility for ensuring that all aspects of the relevant protocol(s) are followed.

Core Clinical Center staff carry out the provisions of the Manuals of Procedures, Technical Documents, and BMT CTN protocol(s). They are responsible for registering and maintaining follow-up of all enrolled study participants. The responsibilities of the Principal Investigator and Clinical Research Coordinator are further defined in Chapter 9.

1.3.2. Affiliate Clinical Centers

The BMT CTN is a national resource for the advancement of knowledge and understanding in the field of HCT. Participation in Network trials may be open to qualified centers other than Core Clinical Centers through subcontracts with the DCC.

1.3.2.1. Participation in Protocols

BMT CTN protocols will be open to Affiliate Centers who:

- Meet the center qualifications required for the protocol and are approved by the Protocol Team
- Are either FACT-accredited (or pending), or an NMDP/Be The Match participant, or an approved transplant center in an NCI-funded National Clinical Trials Network (NCTN) Group
- Agree to register all transplant recipients (both on and off protocol) through the CIBMTR Statistical Center for the duration of the protocol
- Meet quality assurance standards of the Network

The DCC will actively recruit appropriate Affiliate Centers for Network protocols within the limits of financial resources and in accordance with accrual needs of each protocol. Affiliate Centers will

be subject to the same quality assurance procedures as Core Centers. Per patient fees for Core and Affiliate Centers will be decided on a per protocol basis.

Each Protocol Team is encouraged to have one representative from an Affiliate Center that is committed to enrolling significant numbers of study participants on the relevant trial. Selection of an appropriate Affiliate Center representative is at the discretion of the Protocol Chair in consultation with NHLBI/NCI representatives. The Protocol Team is formed after the study concept is approved by the Steering Committee. Affiliate Center investigators are also eligible to serve as Protocol Team Co-Chair, if they propose or contribute significantly to the Study Concept.

1.3.2.2. Participation in Committees

Individuals with relevant expertise from Affiliate Centers may be nominated to participate in Technical Committees. Terms are the same as for individuals from Core Centers. Technical Committees are encouraged to have at least one Affiliate Center representative.

1.3.2.3. Representation on Steering Committee

Affiliate Centers are typically not represented on the Steering Committee unless selected for this privilege to formally recognize exemplary performance in advancing the mission of the BMT CTN.

- An Investigator/PI from any Affiliate Center which enrolls patients on two or more BMT CTN trials with total accrual of at least 12 patients during the previous year is eligible to be named to the Steering Committee. At least 50% of the patients must be enrolled on BMT CTN-led studies. These criteria may be superseded by center performance metrics for the current year.
- The term of membership for Affiliate Center representatives is two years, with the possibility of annual renewal if
    - Enrollment continues to be at least 12 patients per year meeting above criteria;
    - Audited data meet Network requirements; and
    - The center's annual center performance report score is Outstanding or Acceptable.
- These positions hold full voting and participation privileges
- These members, or designee from their centers, are eligible to chair both Technical and Protocol Committees
- The BMT CTN will reimburse travel expenses for one investigator for each eligible Affiliate Center to attend Steering Committee meetings (other than those held in conjunction with national meetings)

1.4. Data and Coordinating Center (DCC)

The DCC plays a key role in developing and facilitating study protocols and is responsible for statistical planning and the collection of quality data from participating clinical centers. DCC functions are performed by a consortium that includes:

- The Statistical Center of the CIBMTR
- The Coordinating Center of the NMDP/Be The Match

- The Emmes Company

These three organizations have both separate and overlapping responsibilities for BMT CTN operations as shown by Exhibit 1-4.

DCC responsibilities include the following:

- Maintaining a computerized roster of participants with relevant contact information, BMT CTN roles and organizational affiliations
- Collaborating with the Steering Committee in developing study protocols, procedures, reports, manuscripts, Technical Documents and Manuals of Procedures
- Scheduling meetings and conference calls, determining site locations for meetings and providing travel arrangements for meetings
- Coordinating communications among participating centers
- Coordinating and supporting the work of Protocol Teams, including:
    - Designating a Protocol Statistician for each BMT CTN study who has primary responsibility for statistical design and analysis
    - Designating a Protocol Officer for each BMT CTN study who has primary responsibility for keeping the Protocol Team informed about the progress of the trial and providing scientific oversight to the protocol development process
    - Designating a Medical Monitor for each BMT CTN study who reviews safety issues, including protocol-specified safety provisions (e.g., assessment of stopping rules) and unexpected serious adverse events (SAEs)
    - Designating a Protocol Coordinator for each BMT CTN study who has responsibility for overseeing all aspects of developing the protocol document and serves as primary site liaison
    - Designating a Patient Services representative to coordinate development of patient education materials and developing resource materials to handle questions regarding BMT CTN studies
- Coordinating the implementation of BMT CTN studies including:
    - Developing master agreements and protocol riders with Core and Affiliate Centers
    - Identifying, developing contracts and coordinating communications with industry contributors for BMT CTN-led studies
    - Identifying, developing contracts and coordinating communications with suitable pharmacies, laboratories and repositories for support of BMT CTN studies
    - Coordinating the training and certification of clinical center staff in standardized data collection and BMT CTN quality control procedures
    - Reviewing all data submitted on standardized BMT CTN case report forms for completeness and accuracy
    - Communicating with participating centers regarding missing, delayed, incomplete, or erroneous data
    - Monitoring adverse events and participating center reporting
    - Preparing periodic reports on the performance of participating centers
    - Creating computerized data files for BMT CTN data
    - Analyzing study data

- Providing support to the Protocol Review Committee (PRC) and DSMB
- Assisting in preparing scientific reports for publication

Exhibit 1-4

DCC Member Responsibilities	CIBMTR/ MCW	CIBMTR/ NMDP	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 / Technical Documents / Standard Operating Procedures (SOPs)		Shared	Shared
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		Shared	Shared
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)		Shared	Shared
Contract with centers		Lead	
Identify and contract laboratories / repositories		Lead	
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)		Shared	Shared
Develop Case Report Forms		Shared	Shared
Coordinate laboratory and repository functions		Lead	
Centrally collect patient-reported outcomes data		Lead	

DCC Member Responsibilities	CIBMTR/ MCW	CIBMTR/ NMDP	Emmes
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		Shared	Shared
Monitor data accuracy and conduct data review sessions[9]	Shared		Shared
Prepare reports / manuscripts / coordinate dissemination of results[10]	Shared	Shared	Shared

1. Approximately 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 Protocol Coordinator and NMDP/Be The Match Program Manager 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, CIBMTR FormsNet, and Medidata Rave; 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 FormsNet3 and Medidata Rave, which are 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 Program Manager 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.

DCC Leadership Team

The DCC leadership team, consisting of the three DCC PIs and key DCC staff including Protocol Officers, Statisticians, program management staff members, and finance and contracting personnel, is responsible for continuous evaluation of Network performance. The team meets via teleconference weekly and reviews Network activities such as current protocol development, activation and accrual status; data compliance and adjudication; site monitoring results and site performance; and data analysis and publication status. DCC staff members escalate identified issues to the DCC leadership team as specified in the DCC Communication Plan. The DCC leadership team determines if and when issues are brought forth to the BMT CTN Executive and/or Steering Committees. The DCC leadership team also proposes revisions to BMT CTN policies and procedures to the Executive and Steering Committees as needed.

1.4.1. The Statistical Center of the CIBMTR

The CIBMTR, located at the Medical College of Wisconsin in Milwaukee and at the NMDP/Be The Match in Minneapolis, Minnesota, is responsible for overall scientific administrative leadership; concept development and review; development of BMT CTN protocols; and, development of reports and manuscripts. CIBMTR staff includes active HCT physicians and professionals with biostatistics, epidemiology, hematology, oncology, statistics, clinical trials and data analysis experience.

CIBMTR staff has responsibility for developing statistical designs and establishing operational and analytical methodology and analyzing data. CIBMTR staff is also responsible for monitoring accrual and identifying potential Affiliate Centers for participation in specific studies. Some specific functions of the CIBMTR staff are:

- Collaborating with the other members of the DCC in developing study procedures, forms, reports (including the BMT CTN Annual Progress Report), manuscripts, MOPs, and BMT CTN protocols
- Assisting in preparation of scientific reports for publication
- Designating a Protocol Statistician who has primary responsibility for design and analysis of studies
- Designating a Protocol Officer and/or Medical Monitor for specific BMT CTN studies as required

Additional details of CIBMTR activities are included in the Standard Operating Procedures (SOPs) maintained at the CIBMTR.

1.4.2. The Coordinating Center of the National Marrow Donor Program (NMDP)/Be The Match

The NMDP/Be The Match, located in Minneapolis, Minnesota, is responsible for development of protocols, medical monitoring duties, development of trial participant advocacy plans, contracting centers, laboratories, repositories, other suppliers, and participation in contract development for Affiliate Centers. NMDP/Be The Match staff includes HCT physicians, professionals in contracts, finance, data management, donor and recipient advocacy and transplant medicine. Some specific functions of the NMDP/Be The Match staff are:

- Collaborating with the other members of the DCC in development of study procedures, reports, manuscripts, MOPs, and study protocols
- Identifying site locations, schedules and providing travel arrangements for meetings
- Scheduling conference calls
- Developing contracts with Affiliate Centers
- Identifying suitable laboratories and repositories for other suppliers for support of BMT CTN studies
- Developing contracts with identified laboratories, pharmacies, repositories and other suppliers
- Developing contracts with third party contributors
- Providing a Laboratory/Repository Manager and a Program Manager
- Providing a Protocol Officer and/or Medical Monitor for specific BMT CTN studies as required
- Developing patient and physician educational materials

Additional details of NMDP/Be The Match activities are included in the SOPs maintained at the NMDP/Be The Match.

1.4.3. The Emmes Company

The Emmes Company, based in Rockville, Maryland, is responsible for developing BMT CTN MOPs, study protocols, and statistical designs, establishing operational and analytical methodology, coordinating study activities, and analyzing data. Emmes is also responsible for developing case report forms, collecting, editing, and storing all data received from participating centers. Emmes staff includes professionals in biostatistics, epidemiology, clinical trials, data processing, administration, and communication coordination.

Some of the specific functions of the Emmes staff are:

- Collaborating with the other members of the DCC in developing study procedures, forms, reports, manuscripts, MOPs, and BMT CTN protocols
- Coordinating communications among participating centers
- Coordinating communications among laboratories, pharmacies, repositories, contributors, and vendors
- Preparing administrative, recruitment, technical, and statistical reports for meetings
- Coordinating the training and certification of clinical center staff in standardized data collection and BMT CTN quality control procedures
- Reviewing all data submitted on standardized BMT CTN case report forms for completeness and accuracy

- Creating computerized data files for BMT CTN data
- Communicating with participating centers regarding missing, delayed, incomplete, or erroneous data and generating related queries
- Monitoring adverse events and verifying that they have been reported appropriately
- Preparing periodic reports on the performance of participating centers
- Preparing meeting materials and providing on-site meeting support for BMT CTN Steering Committee meetings
- Preparing materials for the PRC
- Planning and coordinating DSMB meetings and providing a DSMB Project Manager
- Analyzing study data and preparing reports for the DSMB
- Providing an Operational Statistician with responsibility for design and analysis, statistical monitoring programs, and participation in Endpoint Review Committee of specific protocols
- Providing a Protocol Coordinator, Data Manager and Safety Monitor to coordinate all aspects of a protocol
- Providing a Project Director/Leader
- Assisting in preparing scientific reports for publication

Additional details of Emmes' activities are included in the SOPs maintained at Emmes.

1.5. National Institutes of Health (NIH) Program Offices

The BMT CTN Program Offices are located in the Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI) and in the Division of Cancer Treatment and Diagnosis, National Cancer Institute (NCI).

1.5.1. National Heart, Lung, and Blood Institute

The NHLBI is responsible for organizing and providing support for the BMT CTN in accordance with the allocation of resources provided for this program. The NHLBI Project Team consists of NHLBI staff from the Division of Blood Diseases and Resources. The Office of Biostatistics Research, Division of Cardiovascular Sciences, provides statistical expertise and performs diverse functions in planning, designing, implementing and analyzing NHLBI-sponsored studies to the Principal Investigators and DCC.

The NHLBI Project Officer has substantial responsibilities in protocol development, quality control, interim data and safety monitoring, final data analysis and interpretation, preparation of publications, collaboration with awardees, and coordination and performance monitoring. The NHLBI Project Officer may have lead responsibilities in the preparation of some publications and assists in calculation of capitation budget rates. The Project Officer is an active and fully participating member of the Steering Committee.

1.5.2. National Cancer Institute

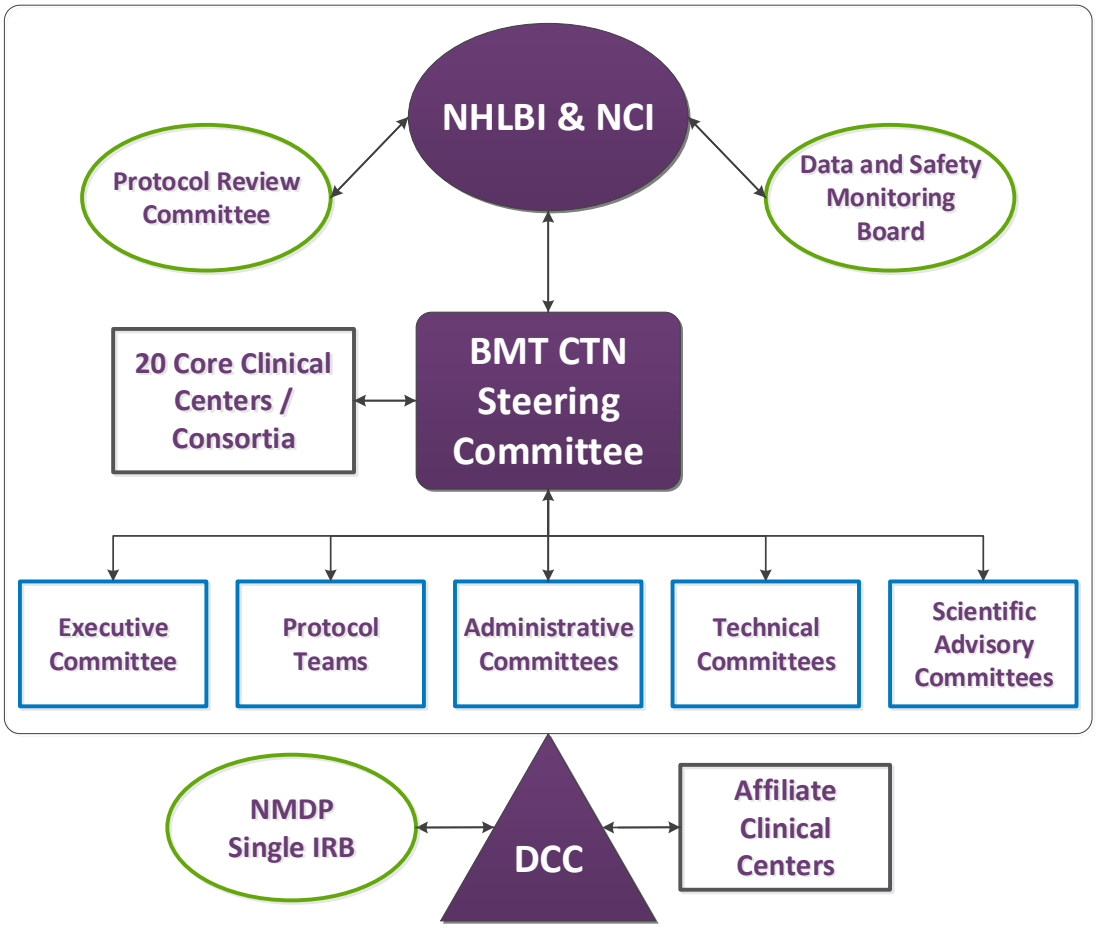
The NCI is responsible for organizing and providing support for the BMT CTN in accordance with the allocation of resources provided for this program. The NCI Project Team consists of NCI staff from the Division of Cancer Treatment and Diagnosis

The NCI Project Officer has substantial responsibilities in protocol development, quality control, interim data and safety monitoring, final data analysis and interpretation, preparation of publications, collaboration with awardees, and coordination and performance monitoring. The NCI Project Officer may have lead responsibilities in the preparation of some publications and assists in calculation of capitation budget rates. The Project Officer is an active and fully participating member of the Steering Committee.

1.6. Study Administration

The organizational structure for developing, implementing and completing a BMT CTN study is characterized in Exhibit 1-6.

Exhibit 1-6



1.6.1. Protocol Team

A Protocol Team is appointed for each approved Study Concept. The Protocol Team has primary responsibility for the development of protocol documents. The Team consists of:

- Protocol Chair(s)
- Core and Affiliate Clinical Center Investigators (3 or more)
- Protocol Officer (DCC physician)
- Primary Protocol Statistician (DCC statistician)
- Protocol Coordinator (DCC Coordinator)
- NHLBI and/or NCI representatives (1 each)
- NHLBI Statistician (1)
- DCC Business Representative
- Ad hoc members as deemed necessary by the Protocol Chair

Selection and terms of service are:

- Non-DCC and non-NIH members are appointed by the Executive Committee
- DCC members are appointed by DCC Principal Investigator
- NIH members are appointed by NHLBI and NCI Project Officers
- Protocol team members serve until the study is completed, analyzed and presented or decision is made to discontinue development

1.6.2. Protocol Review Committee

The PRC is appointed by the NHLBI. The PRC is responsible for providing peer review for final draft protocols including Informed Consent(s) and either approving a protocol and consent form(s) or requesting that changes and/or clarifications are made. If the PRC approves the protocol and informed consent form(s), an independent DSMB will review the study protocol, consent form(s), and monitoring plans, focusing on data quality and safety assurance. The DSMB, and applicable Institutional Review Boards (IRBs) of record must also approve the protocol and consent forms. FDA approval may also be required, if appropriate.

The PRC assesses the scientific merit of each protocol and consent form (s) as follows:

- Importance of the question to be addressed
- Need for a multi-center network to meet objectives
- Merit of experimental design, including appropriate controls
- Availability of adequate resources, including medications
- Adequacy and safety of study participant population and number of study participants, including appropriate representation of minorities, women, and children (if applicable)
- Appropriate recruitment strategies
- Adequacy of proposed plans for data acquisition, transfer, management and analysis
- Adequacy of quality control of data collection and monitoring and overall coordination of protocol management
- Description of appropriate plans to train center personnel to accomplish proposed research goals

The PRC includes a Chairperson and members whose experience reflects areas of expertise necessary to evaluate the scientific merit and design of BMT CTN protocols. Consultants may be added on an *ad hoc* basis to the Committee if greater representation of expertise in a specific scientific area is needed.

The PRC Executive Secretary coordinates the review of each study protocol. The Executive Secretary is an NHLBI staff member, other than the Project Officer, and is responsible for working with the PRC Chairperson to ensure the effective and efficient review of research design, specific aims, and outcomes; appropriateness of methods of intervention, measurement, and analysis; and recommendations for monitoring of safety and data quality.

Individuals are invited to serve on the PRC by the NHLBI Director. Members are required to complete a Conflict of Interest Certification for review and acceptance by the NHLBI prior to serving on the Committee. At the beginning of all meetings the PRC Chairperson or the Executive Secretary will verbally remind the members of the importance of avoiding conflicts of interest and that members must notify the Executive Secretary promptly if any changes occur which may pose a potential conflict of interest.

1.6.3. Data and Safety Monitoring Board

Due to the quantity of BMT CTN trials, the BMT CTN has two appointed DSMBs. Each DSMB is an independent board appointed by the NHLBI and/or NCI. Each DSMB is composed of a Chairperson and members with expertise in biostatistics, clinical trials, bioethics, and the specific research area(s) of the Network studies. Consultants may be added to the DSMB to have greater representation of expertise in the relevant scientific fields. All standing members of a DSMB may vote. Consultants have the same voting rights as an official DSMB member when reviewing the protocol. Additional information regarding the DSMBs can be found in the respective DSMB Charter, both of which are maintained by the NHLBI.

Each board has one full-day remote meeting each year in addition to monthly 2-hour remote meetings. Members are required to complete a Conflict-of-Interest Certification for review and acceptance by the NHLBI prior to serving on the Committee. At the beginning of all meetings the DSMB Chairperson or the Executive Secretary will verbally remind the members of the importance of avoiding conflicts of interest and that members must notify the Executive Secretary promptly if any changes occur which may pose a potential conflict of interest.

A general timeline of the tasks to be completed relative to the DSMB meeting date is provided in Exhibit 1-6-3 with more detailed information provided in Sections 3.4.6 and 4.3.1. The DSMB Meeting Tracker, template documents, and other DSMB resources are available on the DSMB Resources page of the BMT CTN website.

Exhibit 1-6-3

Timeline	Activity
ASAP	Notify DSMB PM of the protocol for upcoming DSMB review
3 weeks prior	Submit materials by 11am ET
1 week prior	DSMB reviewer comments are provided to the protocol team (if applicable)
1 day prior	Submit responses to DSMB reviewer comments by 11am ET

Timeline	Activity
DSMB Meeting	Submit PowerPoint presentation prior to meeting start
Within ~1 day after	NHLBI will provide confirmation of any DSMB issues/safety concerns
3 weeks after	Program notes and DSMB Recommendations IRB Memo provided

After PRC approval, the DSMB must approve the protocol and consent form(s). Thereafter, the principal role of the DSMB is to regularly monitor the data from the clinical trial, review and assess the performance of its operations, and make recommendations, as appropriate, to the NIH with respect to:

- Benefits/risks ratio of procedures and the burden under which the study participants are placed
- Completeness, quality, and analysis of measurements that are made
- Performance of individual centers (including possible recommendations on actions to be taken regarding any center that performs unsatisfactorily)
- Interim results of the study for evidence of efficacy or adverse effects
- Possible early termination of the study because of early attainment of study objectives, efficacy and/or safety concerns – if applicable, inadequate performance or accrual
- Desirability of proceeding to the full-scale trial at the completion of the feasibility phase, when applicable
- Possible modifications/amendments to the study protocol and/or consent form(s)

NHLBI appoints an Executive Secretary for the two DSMBs. The Executive Secretary is an NHLBI staff member, other than the Project Officer and PRC Executive Secretary, and is responsible for working with the DSMB Chairpersons to ensure the effective and efficient review of research design, specific aims, and outcomes; appropriateness of methods of intervention, measurement, and analysis; and recommendations for monitoring of safety and data quality. In addition, the DSMB Executive Secretary is responsible for maintaining meeting minutes.

1.6.4. NMDP IRB

Predicated on the single IRB mandate from NIH (*Policy on the Use of a Single Institutional Review Board for Multi-site Research;* June 21, 2016) and the anticipated revised U.S. Common Rule (*Federal Policy for the Protection of Human Subjects*; January 19, 2017), the BMT CTN DCC and Core Clinical Centers grant renewal included the provision that the BMT CTN will utilize a single IRB of record with the start of the new grant period on July 1, 2017. The NMDP IRB was selected to serve as the Network's single IRB and will be used for all BMT CTN protocols released after July 1, 2017, and is also used by some of the centers participating in the BMT CTN 1501 and 1503 NMDP IRB Pilot Project. The only exception is for centers outside the U.S. who will still follow their country's regulatory requirements for ethical board review.

The NMDP is fully accredited by the Association for the Accreditation of Human Research Protection Programs. The NMDP IRB maintains membership that satisfies the requirements of 45 CFR 46 and 21 CFR 56. The members of the NMDP IRB are a diverse group of distinguished healthcare professionals, donor advocates, and patient advocates with expertise in bone marrow transplantation and hematology/oncology. The majority of members are not affiliated with NMDP.

The NMDP IRB conducts the study-specific reviews as required by the regulations. This includes initial review, continuing review, and review of amendments/modifications to previously approved research. In addition, any other study-specific documents submitted to the NMDP IRB are reviewed per the NMDP IRB Standard Operating Procedures (SOPs) and federal regulations. Administrative functions of the NMDP IRB are managed by NMDP Human Research Protection Program staff members.

The NMDP IRB meets monthly. Board members are required to disclose conflicts of interest per the NMDP IRB SOPs. At the beginning of each study review members are also asked if they have a conflict of interest and, if they do, are recused from the review.

1.7. Administrative Committees

1.7.1. Executive Committee

Membership is by virtue of the following roles in the Network:

- Steering Committee Chairperson (1)
- Steering Committee Vice-Chair, Chair-Elect and/or Immediate Past-Chair (2)
- NHLBI and NCI Project Officers (2)
- DCC Principal Investigators (3)

The Executive Committee is responsible for developing Steering Committee agendas and promulgating recommendations for consideration by the Steering Committee. The Executive Committee will also provide direction between meetings of the Steering Committee, and review/approve all ancillary studies. The Executive Committee will provide initial review of proposals submitted for consideration by the BMT CTN and will approve development of a proposed Study Concept. The Executive Committee participates meets monthly via conference calls.

1.7.2. Publication/Presentation Committee

The Publication/Presentation Committee will consist of up to 10 members (excluding ex-officio):

- DCC Principal Investigators (ex officio)
- Core Clinical Center Principal Investigators (appointed)
- Affiliate Clinical Center representative (appointed)
- NHLBI and/or NCI Project Officers (ex officio)

The terms of membership and selection are as follows:

- Core and Affiliate Center members are identified from a slate of candidates put forth by the Nominating Committee and are approved by the Steering Committee
- Core Center representatives are elected for a three-year term and may serve a second three-year term
- Affiliate Center representative are elected for a three-year term
- Two Co-Chairs are elected by the Executive or Nominating Committee from the Core Clinical Center members for a two-year term**;** may serve more than one term but not two consecutive terms

The Publication/Presentation Committee is responsible for developing publication and presentation policies. All policies must be approved by the Steering Committee before implementation. The Committee reviews 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 may present or publish individual findings from work performed on study protocols without approval of the Publication/Presentation Committee, NHLBI and NCI.

1.8. Technical Committees

Technical committees are formed to address specific areas of Network activity. A Chairperson is elected by the Executive or Nominating Committee. Additional members are approved by the Steering Committee (see below). NHLBI and NCI Project Team staff, Steering Committee Chairperson, and DCC staff will be additional members on these committees. Each committee is limited to a maximum of ten non-DCC, non-NIH members.

The membership of each committee will be comprised of members as follows:

- DCC Representative (ex officio)
- Core Clinical Center members (appointed)
- Affiliate Center members (appointed)
- NHLBI and NCI Project Officers (ex officio) or their representatives
- BMT CTN 1202 Biomarkers Protocol Chairs (ex-officio: Biomarkers Committee)

The terms and selection of members is as follows:

- Core and Affiliate Center members are identified from a slate of candidates put forth by the Nominating Committee and approved by the Steering Committee
- Representatives are appointed for a three-year term

1.8.1. Technical Committees Descriptions

1.8.1.1. Biomarkers Committee

Introduction

BMT CTN protocols require the collection and utilization of high-quality biological specimens to facilitate study analysis. The Biomarkers Committee is a standing Network committee that establishes principles for specimen collection and usage, reviews new and current studies for opportunities to collect biological specimens for analysis of potential prognostic markers, and to makes protocol recommendations regarding immune reconstitution and laboratory procedures.

Purpose

The purpose of the Biomarkers Committee is to:

- Inform the Network's scientific agenda focusing on questions involving analysis of biologic specimens for genomic and proteomic markers
- Establish principles for specimen collection, including their use in ancillary studies

- Review new and existing studies for opportunities to collect blood and tissue samples for analysis of potential prognostic markers
- Advise the Network protocol teams in their review of ancillary study proposals that request the use of BMT CTN-related research samples

Membership

The Biomarkers Committee is primarily composed of Core and Affiliate Center transplant physicians. Like other Technical Committees, its membership includes ex-officio DCC, NHLBI and NCI members, as well as the BMT CTN 1202 Biomarkers Protocol Chair.

Policy

The Biomarkers Committee convenes for assessment and review of BMT CTN protocols and ancillary studies involving the collection and/or analysis of biospecimens.

Procedure: *Protocol development*

The Biomarkers Committee supports the development of new BMT CTN protocols, working with the Protocol Team to identify biological samples that will be required to address the proposed study's hypothesis and making recommendations regarding their optimal usage.

Procedure: *Evaluation of ancillary study proposals*

An **ancillary study** involves the collection from study participants of data and/or specimens or the conduct of additional analyses of existing materials or samples outside the specific objectives of the primary study. If an ancillary study proposal involves collection and/or analysis of biologic specimens, the Biomarkers Committee provides a secondary review of the study proposal following its initial assessment by the primary trial's Protocol Team. Focusing on laboratory aspects of a proposal's feasibility and scientific merit, the Biomarkers Committee considers the following:

- Significance and appropriateness of the proposed research question
- Design of the proposed research
- Qualifications of the investigator(s) to conduct the research
- Availability and source of funding
- Availability of biospecimens and requested clinical data required for the study

Proposals endorsed by the Biomarkers Committee are then submitted to the BMT CTN Executive committee for approval. The process for evaluation ancillary study proposals involving BMT CTN samples is described in **Chapter 11.**

In the case of the BMT CTN 1202 Protocol, the Biomarkers Committee provides guidance, support, and evaluation of proposals seeking to leverage the wealth of biospecimens and data comprising the BMT CTN Resource. Once the Biomarkers Committee has reviewed the proposal, providing feedback towards its optimization where needed, the proposal is submitted to the Executive Committee for their consideration for approval.

1.8.1.2. Clinical Research Associates (CRA) Committee

Introduction

Accurate and complete submission of data and related biologic samples are critical to the mission of the BMT CTN. Every attempt is made to maintain good channels of communication with center data managers/coordinators who are responsible for these activities. Clinical Research Associates (CRAs) from across the Network are selected to provide input and put forth recommendations to the BMT CTN in the design of forms, protocols and policies related to data collection.

Purpose

The purpose of the CRA Committee is to assure that data collection and logistical issues, from the viewpoint of a CRA or Data Manager, are considered in protocol development, data and sample collection, educational materials and protocol implementation.

Membership

This committee consists of CRAs and Data Managers from Core and Affiliate Centers. A DCC representative who serves as Chair coordinates monthly conference calls/meetings. Members of the CRA Committee may serve on the BMT CTN Coordinators' Meeting Planning Committee to guarantee relevant topics are being addressed such as AE reporting, data collection forms and accrual initiatives.

Policy

The committee will assist in the development of Case Report Forms (CRFs) and data collection systems for specific protocols; review and help resolve logistical issues in protocol implementation (e.g., issues related to shipping and receipt of specimens or drugs); and review educational materials for use at participating clinical centers.

Procedure: *Reviews new protocols prior to finalization*

This committee reviews all protocols from a CRA perspective. Members review the entire protocol focusing on treatment plans, required observations and the informed consent. This ensures that the protocol is accurate, reasonable and feasible. The relevant Protocol Coordinator functions as liaison between this committee and the Protocol Team. Every effort is made to reconcile differences to the satisfaction of the Protocol Team and CRA Committee.

Procedure: *Assists in development of CRFs*

This committee reviews the final draft protocol to assess whether existing data collection tools adequately capture data required to answer the primary question of the protocol or if a new, protocol-specific form is required. In the latter case, this committee helps develop the new form and assures that it is designed to meet data collection requirements of the protocol.

Procedure: *Helps resolve logistical issues in protocol implementation*

This committee addresses the logistics of issues such as shipping details, receipt of drugs, handling of biologic sampling, etc. It ensures that practices are standardized and that instructions are clearly stated and are practical enough to avoid problems at the transplant centers.

Procedure: *Ensures that educational materials for use at clinical centers are appropriate and are readily available*

Certain protocols require that the DCC prepare educational materials for use at the clinical site. This committee assures that these materials are practical and understandable for patient and/or staff use.

1.8.1.3. Pharmacy Committee

Introduction

It is anticipated that almost every BMT CTN protocol will employ pharmaceutical agents. In some protocols, these agents and their use in combination with other agents are established in the HCT setting and, therefore, will not require significant input from the Pharmacy Committee. In other protocols, the agents will be investigational or approved for indications other than HCT.

Purpose

The purpose of the Pharmacy Committee is to assure that proper precautions and considerations are employed to decrease the likelihood of adverse events or other unintended consequences from use of both approved and investigational agents in BMT CTN studies.

Membership

This committee consists of transplant pharmacists, one of whom serves as Chair, from Core and Affiliate Centers.

Policy

The Pharmacy Committee will: 1) review all BMT CTN protocols for proper description, use, administration, and risks of pharmaceuticals; 2) review and edit medication risk templates that will be included in future protocols; and, 3) convene to contribute knowledge, as applicable, when a concern or question presents.

Procedure: *Review Protocols for Proper Description, Use and Administration of Pharmaceuticals*

The primary purpose of the Committee is to critically review BMT CTN protocols for the use of all pharmaceutical agents including biologicals such as monoclonal antibodies and hematopoietic growth factors. This review will include details of formulation, administration, dose, and schedule. It will also include review for possible drug interactions. Descriptions of potential toxicities and adverse reactions of each pharmaceutical listed in the protocols will be reviewed for completeness and accuracy. In the case of investigational agents, the Committee will provide advice for monitoring usage, adverse events and data collection.

Procedure: *Review and Edit Medication Risks Templates*

The Committee will review templated risk language on an as needed basis that is developed by the Emmes Safety Monitor. After committee review, the compiled risk language will then be approved by a physician within the network leadership. At that point, the templates can be included in future protocols, for ease of outlining the risks of medication used per protocol, including conditioning regimen chemotherapies.

Procedure: *Convene to Contribute Knowledge When a Concern or Question Presents*

The Committee will be available for ad hoc meetings based on a concern or question that arises within the network. Some examples are medication shortages, pharmacokinetics questions, etc.

1.8.1.4. Special Populations (Pediatric/Human Subjects)

Introduction

NIH sponsored clinical trials and the Code of Federal Regulations state that study participants enrolled in clinical trials must include women, ethnic minorities and children (individuals under the age of18) to facilitate potential benefit to all persons at risk for a particular disease, disorder or condition under investigation unless there are scientific and/or ethical reasons for exclusion *(for more information, see Chapter 7).*

Protocol Teams for studies having a large pediatric component and/or address important pediatric issues include members with appropriate pediatric expertise. When differences from adult care are important, appropriate care for a pediatric patient is clearly outlined within the protocol.

Purpose

The purpose of the Special Populations Committee is to ensure that women, children, and racial and ethnic minority study participants are considered for inclusion in all BMT CTN investigational protocols, including those involving non-malignant marrow disorders. Other special patient populations should also be considered if they are underserved, e.g., HIV+, LGBTQI+, and/or older patients.

Membership

This committee consists primarily of transplant physicians, the majority of whom have expertise in the transplantation of a pediatric population. There are several adult transplant physicians who serve as well. An NHLBI and a DCC statistician serve along with the DCC PI and a DCC co-PI in ex-officio capacity.

Policy

The Committee ensures that, for studies involving pediatric participants, appropriate modifications are addressed in the informed consent, patient care and monitoring documents. These differences must be appropriately addressed within the protocol, including off-label use of drugs for children.

Accrual of women, children and racial and ethnic minority patients is monitored by the DCC to determine whether their rates of enrollment are reflective of the distribution of potentially eligible patients expected from data reported to the CIBMTR and from published data related to the topic at hand. The DCC conducts this review periodically and reports results to the DSMB.

Procedure: *Ensures that women, children and ethnic minority study participants are considered for inclusion in protocols*

In general, all proposals and protocols shall include women, children and racial and ethnic minority study participants. Should the exclusion of any of these patients be considered necessary, this must be clearly stated within the protocol and supported by appropriate evidence. Special attention is given by this committee to studies in which women, children or racial and ethnic minority participants are excluded. Every effort is made by Protocol Teams to find solutions to possible exclusions so as to allow women, children and racial and ethnic minorities onto BMT CTN trials. This may include the addition of a pediatric specialist on to the Protocol Team, or an alternative study design.

Examples of reasons to exclude these patients might include:

- Pediatric patients fall significantly outside the normal age range of a disease entity to suggest that inclusion of pediatric patients could introduce a significantly different biology of the disease/complication.
- No phase I testing of an experimental drug has previously been performed in children.
- The low incidence of a complication or rarity of a disease entity in the pediatric population could significantly underpower a study should a disproportionate or unexpectedly large number of children be enrolled.
- The protocol involves interviews of patients (and parents or guardians cannot serve as surrogates) and patient cooperation must be ensured.
- The disease or condition under study is unique to or is relatively rare in women or one or more racial and/or ethnic minority population.
- The information on the difference in adverse outcomes or risk profiles for pregnant women is unknown.

Every effort is made to reconcile differences to the satisfaction of the Protocol Team and Special Populations Committee. If differences cannot be resolved, the issue(s) is/are sent to the BMT CTN Executive Committee for adjudication.

1.8.1.5. Toxicity and Supportive Care Committee

Introduction

Organ toxicities can be, and often are, major complications following HCT. Because all or most study participants in BMT CTN trials will be receiving potentially toxic preparative therapy, significant regimen-related toxicity is anticipated (e.g., expected adverse events).

Purpose

The primary purpose of this Committee is to:

- Review the evaluation and toxicity monitoring requirements and the supportive care guidelines for BMT CTN protocols
- Provide advice to Protocol Teams regarding the frequency and detail of toxicity reporting that would be appropriate for each specific protocol

The Committee may also:

- Define methods for evaluation of AEs and toxicities after HCT;
- Review forms and procedures for collecting toxicity data, including standards for expedited reporting of certain AEs;
- Provide consensus guidelines for reporting toxicities; and,
- Describe appropriate procedures of supportive care.

Membership

This committee primarily consists of transplant physicians.

Policy

The amount of information regarding toxicities to be monitored and collected varies by protocol. A protocol specific BMT CTN *toxicity data collection form* is designed for each protocol though

these follow a Network standardized format. Individual protocol teams review the protocol specific toxicity data collection form and procedures. If there are questions on the toxicities to collect, the Toxicity and Supportive Care Committee may assist the protocol team by providing recommendations.

Supportive care guidelines are protocol specific and included in each study protocol. Individual Protocol Teams determine the extent to which variations in clinical standards of care are permitted for treatment and prevention of specific toxicities. If there are concerns regarding the effect of standard of care variations on primary or secondary protocol endpoints, the Toxicity and Supportive Care Committee assists the Protocol Team by providing recommendations for the standardization of such practices.

Procedure: *Define methods for evaluation of AEs and toxicities after HCT*

Expected toxicities and AEs are assessed at predetermined calendar endpoints (e.g., day 30, day 100 post HCT, etc.) and are defined by the Protocol Team in each protocol. Wherever possible, investigators are encouraged to report AEs as syndromes or diseases rather than the individual symptoms and/or laboratory data. For example, pneumonitis should be reported as a single entity rather than as separate toxicities of tachypnea, rales, cough, hypoxia and pulmonary infiltrates.

Procedure: *Review the evaluation and toxicity monitoring requirements for BMT CTN protocols*

Definitions of toxicity generally follow *Common Terminology Criteria for Adverse Events* (CTCAE) criteria. Prior to BMT CTN 0901, CTCAE version 3.0 was used. Version 4.03 was incorporated into data collection tools (BMT CTN *Core Toxicity Forms*) for protocols numbered between BMT CTN 0901 and BMT CTN 1507. CTCAE version 5.0 was utilized in protocols beginning with BMT CTN 1703. All BMT CTN protocols include a protocol-specific list of toxicities that are routinely monitored and reviewed by the DSMB. The level of detail and period of follow-up in reporting AE data is calibrated to the severity of the AE.

1.8.2. Protocol Review Responsibility

The following technical committees must review all BMT CTN protocols at some point in their development but no later than time of submission to the PRC:

- Biomarkers
- CRA
- Pharmacy, if applicable
- Special Populations (Pediatrics/Human Subjects)
- Toxicity and Supportive Care

Each technical committee has a primary DCC representative appointed by the DCC PI who has responsibility for coordinating committee conference calls and meetings. The DCC representative works with the Committee Chair to prepare and distribute an agenda and minutes for each meeting and ensure that the committee's findings are communicated to the protocol team.

1.9. Other Standing Committees

1.9.1. BMT CTN Patient and Caregiver Advocacy Committee

Introduction

This committee was formed and operates under these tenets:

- Patient and caregiver advocacy and engagement is important for successful clinical research that addresses issues that are important to the patients being served
- Patients and patient advocates provide important insights into barriers to transplant and trial access
- A patient-centric approach minimizes trial-imposed burdens to patients and increases participation of patients from all ages, genders, and racial, ethnic and socioeconomic groups
- Increased engagement by patients and care givers through diverse avenues, including social media, can lead to increased awareness of and participation in trials

Purpose

The purpose of the Patient and Caregiver Advocacy Committee is to ensure that patient and caregiver perspectives are included in the BMT CTN research portfolio and trial conduct.

Scope

The Committee's scope includes providing input on:

- Evaluation and prioritization of study concepts
- Interface with patient advocacy and/or community organizations
- Protocol team patient and caregiver engagement plans
- Patient, caregiver and family-facing materials, including protocols, consent forms and study and results summaries
- Website and social media content and communication plans

Responsibilities

The Committee will meet routinely by teleconference at least quarterly. There may also be work on projects outside of teleconferences, as needed. Responsibilities include:

- Identify areas of research most important to patients and caregivers
- Advise the BMT CTN on ways to increase patient participation in research with a focus on increasing access to a diverse group of patients
- Provide feedback on patient and caregiver-facing materials, including:
    - Final draft protocol and informed consent documents before or at the time of submission to the Protocol Review Committee (PRC), including study-related procedures and visit schedule
    - Protocol team patient engagement plan prior to study activation
    - Website and social media content
    - Study updates and results summaries
- Promote awareness among patients regarding research opportunities

- Address misconceptions about clinical trial participation

Membership

Members are identified from a slate of candidates put forth by the Nominating Committee and approved by the Steering Committee. They include:

- Up to 12 voting members involved with HCT either as a patient, caregiver, family member, donor, healthcare provider or staff person/volunteer with an agency that interacts with HCT patients or donors
- Committee Chair to serve 2-year term
- BMT CTN ex-officio members from the DCC and NIH

In addition, committee membership strives to represent a diversity of backgrounds, including persons who:

- Understand adult, adolescent and young adult, and/or pediatric HCT issues
- Understand issues that affect access to or outcomes of HCT secondary to demographics and diversity
- Have been or understand the needs of a related and/or unrelated donors
- Are actively involved in HCT-related research
- Have marketing, communications, social media and/or professional writing experience

Non-ex-officio members serve for three-year terms that are staggered to permit annual rotations.

1.9.2. BMT CTN Multiple Myeloma Intergroup

Mission

To develop studies that address clinically and biologically relevant questions and optimize the use of Blood and Marrow Transplant Clinical Trials Network (BMT CTN) and other National Clinical Trials Network (NCTN) Groups resources to collaborate and not compete on concurrent efforts advancing the field of transplantation for multiple myeloma.

Scope

- Develop, review or endorse current and future prospective or retrospective clinical and laboratory protocols on transplantation for multiple myeloma.
- Develop collaborations between the BMT CTN, NCTN Groups and other multiple myeloma stakeholders.
- Develop the BMT CTN scientific agenda for multiple myeloma transplant studies.

Composition

Committee members include:

- Representatives from NCTN groups and organizations involved in development of multiple myeloma studies:
    - BMT CTN Principal Investigators on multiple myeloma studies
    - BMT CTN Data Coordinator Center (DCC) staff members involved in multiple myeloma studies
    - The Alliance for Clinical Trials in Oncology

  - Eastern Cooperative Oncology Group and American College of Radiology Imaging Network (ECOG-ACRIN)
  - SWOG

- Protocol team members for current multiple myeloma clinical trials from BMT CTN and CIBMTR Resource for Clinical Investigation in Blood and Marrow Transplant (RCI BMT)
- Project Officers from the National Heart, Lung, and Blood Institute (NHLBI), and the National Cancer Institute (NCI) of the National Institute of Health (NIH).

Meetings

The Committee will meet via regularly scheduled conference calls during the year and one in-person meeting, generally during the annual BMT Tandem Meetings. The leadership team also meets monthly via conference call.

Leadership

Leadership positions include one Chairperson, one Chair-Elect, one Past Chair and representatives from each NCTN group: BMT CTN, Alliance, ECOG-ACRIN and SWOG.

Leadership Selection Process

The Chairperson should be from a Core or Affiliate BMT CTN institution. The Chair-Elect will be selected by vote during the face-to-face meeting the year the active Chairperson's term will finish.

The term for the Chairperson is 6 years served in subsequent order:

- One year as Chair-Elect
- Three years as Chairperson
- Two years as Past Chair

Membership terms are per calendar year. The Chairperson may serve up to one consecutive term.

Leadership Responsibilities

Chairperson

- Organize conference calls
- Organize yearly in-person meeting
- Lead conference calls and in-person meetings
- Develop action items and delegate responsibilities
- Report to the BMT CTN Steering Committee the activities of the Committee
- Other attributes as decided by the Committee

Chair-Elect

Responsible for all the Chair's responsibilities in their absence as well as other attributes as decided by the Committee.

Past Chair

The Past Chair will serve as a resource and will provide continuity to the activities of the Committee.

1.9.3. Patient-Reported Outcomes Working Group

Introduction

Many BMT CTN trials include patient-reported outcomes (PROs) as endpoints to capture the patient's health status and experience with transplantation and the intervention under study. PROs are defined as "information collected directly from the patient without an intermediary" and includes quality of life, symptoms, functioning, disability, and health status. PROs may be collected via surveys, interviews, diaries, or narratives. Selection of PRO instruments, guidance in clinical trial documents, systems for monitoring PRO data collection and interpretation of results require specific expertise that may not be represented on protocol teams.

Purpose

The purpose of the Patient-Reported Outcomes Working Group is to ensure that PROs are appropriately selected, collected, and analyzed, not only for the particular study in which they are collected, but in consideration of the PRO effort across the BMT CTN suite of studies.

Responsibilities related to BMT CTN protocols:

This Working Group will help write, review, and approve sections relevant to PROs in all draft protocols, lending expertise in PRO instrument selection, assessment, monitoring and analysis. If an existing protocol team member already fulfills that role (ideally, having joint clinical and PRO expertise) they will be invited to be part of the PRO Working Group and access knowledge and expertise for those areas in which they are not expert. If a protocol team member cannot fulfill this role, a member of the Working Group will be assigned to the protocol and participate on team calls as needed. Either the protocol team member or the ad hoc PRO working group member ensures that, for studies involving PROs, appropriate considerations are addressed in the protocol, informed consent form, analysis plan, and monitoring documents. In addition, they are responsible for tracking the PRO specific accrual and completeness throughout the duration of the study. If issues are identified, they will raise concerns and lead corrective efforts.

Responsibilities related to the PRO Working Group:

The PRO Working Group is comprised of both primary members of the working group assigned by BMT CTN based on their expertise in PRO research and protocol team members who fulfill the PRO role on specific protocols. The Working Group meets approximately every other month to address PRO issues that cross protocols, including methods, standardization, secondary analysis, policies and other relevant topics. Importantly they will also give input on corrective actions needed to address issues related to PRO accrual or completeness in individual studies.

1.9.4. Nominating Committee

The Nominating Committee is convened to review nominations and select members for Technical Committees, protocol teams, and ad hoc Task Forces and committees, as warranted. To finalize the Technical Committee member selection, the Nominating Committee puts forth a slate of candidates for Steering Committee approval.

Members of the Nominating Committee include current Steering Committee leaders (Chair, Chair-Elect, and Vice-Chair/Past-Chair); the previous two Steering Committee Past Chairs; NHLBI and NCI Project Officers; and DCC Principal Investigators.

1.10. Ad Hoc Committees

Additional administrative and technical committees are convened as needed, e.g., to discuss new study concepts, provide an update to the Steering Committee on recent advances in the field, or provide input into the Network's Technical Documents. These ad hoc committees include GVHD, Cellular Therapy, and Infectious Disease.

1.11. Collaboration with NCTN and Other Groups

1.11.1. Cross-Networks Collaboration

To enhance communication and partnership with the NCI-funded NCTN Groups, the BMT CTN has included NCTN Group representatives on the BMT CTN Steering Committee (see section 1.2.). In addition, there are appointed BMT CTN representatives that serve on the NCTN Disease-Specific Steering Committees. These investigators are responsible for representing the interests of the BMT CTN and the role it plays within the U.S. BMT community. They represent the Network's scientific agenda and keep the NCTN apprised of current and planned BMT CTN studies and initiatives relevant to the particular committee.

1.11.2. Standard Collaboration Practices with NCTN Groups

To assure fairness and standardization of practices to be followed when collaborating with the NCTN Groups, the NHLBI and NCI have established a set of guidelines to follow in the case of BMT CTN-led trials or NCTN Group-led trials.

Major areas defined in these documents include:

- Preserving the enrollment credit system of the NCI
- Establishing a collaborative per-patient payment system
- Opening trials through the NCI Clinical Trial Support Unit (CTSU)
- Expediting review by a single scientific review committee, either the NHLBI-appointed PRC or the NCI Cancer Therapy Evaluation Program PRC, and the leading group's DSMB

1.11.3. BMT CTN Endorsement of Studies Led by NCTN or Other Groups

The BMT CTN may endorse studies led by an NCTN Group or another group (e.g., another NIH Institute, PTCTC). In addition to the standard collaboration practices with NCTN Groups in the previous section, these practices apply to BMT CTN endorsement:

- The BMT CTN Steering Committee must vote to endorse a study led by another group. The study concept should be presented early so the BMT CTN can provide input on the study design.
- The key components of endorsement are to collaborate by providing scientific input, promoting the study, and assisting in troubleshooting any activation and accrual issues. The endorsement gives the lead group routine access to the BMT CTN Steering Committee to help ensure the study design is scientifically robust, innovative, feasible, and appealing to sites. By endorsing the study, the BMT CTN also agrees not to open a competing study.
- Once approved by the Steering Committee, the BMT CTN will:

  - Assign a BMT CTN PI to represent the BMT CTN while working with the protocol team/lead group; and to convey feedback on behalf of the BMT CTN Steering Committee.
  - Assign a BMT CTN protocol number. The study will be referred by its primary group number / BMT CTN number (e.g., SWOG S1803/BMT CTN 1706)
  - Add the study to the BMT CTN public and private website protocol lists with study title, Chairs BMT CTN PI contact information, and link to lead group protocol page

- Sites must activate the study via the lead group. BMT CTN is not involved in study activation or management.
- BMT CTN provides BMT CTN accrual credit for Core, Consortium and Affiliate sites for each enrolled patient. This is in addition to any NCTN Group or other group accrual credit sites receive from the lead group.
- BMT CTN must be acknowledged in the primary results manuscript and authorship must be awarded to the BMT CTN PI. Other BMT CTN investigators may be included as authors, as warranted by the lead group's authorship guidelines.

1.12. Conflict of Interest Policy

The intent of the BMT CTN Conflict of Interest (COI) policy is to manage financial or academic COI to minimize chance that conflicts could undermine the scientific integrity of BMT CTN projects. Conflict of Interest disclosures are obtained on the *BMT CTN Form for Disclosure of Potential Conflicts of Interest* from:

- Medical Monitors, with application, when assigned to a new study and annually
- Endpoint Review Committee members at time of selection
- Protocol team nominees
- Committee/Task Force nominees, if deemed necessary

Investigators presenting study concepts / results will include disclosures in slide presentations and verbally acknowledge any disclosures. Both financial and academic conflict of interest must be reported. Disclosure includes information within one year prior to submission of the disclosure form; and may be required to be updated. BMT CTN DCC leadership will review disclosures, with adjudication by Executive Committee as needed.

Conflict of Interest details will be requested from anyone reporting a relevant conflict, even if outside the identified BMT CTN work, including: the nature of the outside activity; the sponsor and whether the outside work addresses similar topics or endpoints as the BMT CTN protocol in question. The BMT CTN's goal is to obtain disclosure which does not necessarily preclude participation.

Possible outcomes for those with identified conflicts of interest of concern include exclusion from medical monitoring, protocol team/committee participation; Steering Committee discussion and/or Steering Committee vote. It is anticipated that in most situations, however, disclosure of such academic COI and honest efforts to exercise fair judgment will be sufficient.

If disclosure is omitted, the Executive Committee will adjudicate as needed.

CHAPTER 2

STUDY CONCEPT DEVELOPMENT AND APPROVAL

2. STUDY CONCEPT DEVELOPMENT AND APPROVAL

2.1 Developing a Proposed Study Concept

Proposals for clinical trials may be submitted from members of Core or Affiliate Clinical Centers or others outside the Network. The efficient development of a proposed study idea into a document is facilitated by the DCC, primarily the CIBMTR, in advance of the BMT CTN Steering Committee review. This chapter provides detailed descriptions of the process, timeline and documentation required to develop protocol ideas received by the BMT CTN.

2.2 Contents of the BMT CTN Proposed New Study Concept Form

All ideas for studies must be submitted to the DCC on the *BMT CTN Proposed New Study Concept Form*. The Form is posted on the BMT CTN public website and includes the following information:

- Submitting individual's name and affiliation
- Submitting individual's contact information
- Proposed study title
- Preliminary data and background
- Hypotheses to be tested
- Primary outcome
- Secondary outcomes
- Potential for laboratory, Quality of Life (QOL), and/or ancillary studies
- Study design, accrual and follow-up periods
- Patient population, including diagnosis and disease state, type of transplant, other inclusion and exclusion criteria
- Proposed intervention
- Proposed control therapy (if applicable)
- Statistical section including sample size calculations, and important variables for consideration in stratification (if applicable)
- Necessity for a FDA Investigational New Drug (IND) or Investigational Device Exemption (IDE)
- Central Pharmacy requirements
- Central Lab requirements
- Special specimen collection consideration
- Possible supplemental funding sources
- Potential Networks/NCTN Group involvement

2.3 Other Considerations of a Study Concept

2.3.1 Feasibility

A CIBMTR statistician and DCC physician will apply the primary inclusion and exclusion criteria of the study proposal to the CIBMTR and/or NMDP/Be The Match database(s) to determine the number of participants recorded in the database that would meet the primary eligibility criteria of the trial. Modifications to the inclusion and/or exclusion criteria may be proposed to increase the number of potentially available study participants.

2.3.2 IND or IDE Requirements

As part of the preparation of the study concept submission, the DCC identifies any aspect of the protocol that may require an IND or IDE from the FDA. The Report will also specify whether an IND or IDE is currently held by another party.

2.3.3 Competing Protocols

The DCC will review active and proposed clinical trials that may compete for the proposed study participant population. The DCC will describe the impact of the competing study on accrual to the proposed study based on accrual targets for the competing study.

The NCI NCTN Group BMT Committee Chairs (see Section 1.2) will advise the DCC of any NCI NCTN Group planned or active trials that may compete with the proposed study.

2.3.4 Central Pharmacy/BMT CTN Specimen Repository/Specialized or Centralized Laboratory Testing

The investigator proposing the study, in consultation with the DCC, will:

- Address the need for a central pharmacy
- Identify any samples that need to be collected for central review or for storage in the BMT CTN repository
- Determine whether centralized or specialized laboratory services are required to conduct the trial

Upon receipt of the *BMT CTN Proposed New Study Concept Form*, DCC staff is responsible for:

- Contacting the submitting individual(s) for missing information or for clarifications
- Preparing and forwarding the completed form to the BMT CTN Executive Committee for review on the monthly Executive Committee conference call.

The Executive Committee reviews the form to determine whether the proposed study is consistent with the overall mission of the BMT CTN, has no major conflicts with active BMT CTN protocols or BMT CTN protocols in development, and poses no major conflicts of interest. It is expected that most proposals will be approved by the Executive Committee and forwarded to the Steering Committee for determination of scientific merit, feasibility, and willingness to participate (see section 2.4).

2.4 Study Concept Review and Prioritization

Once approved by the Executive Committee, the proposed study will be discussed at the next Steering Committee meeting.

The investigator (or his/her designee) submitting the proposal presents the proposal to the Steering Committee; multiple presentations may be required. The Steering Committee reviews the proposal for scientific merit and alignment with scientific direction of the BMT CTN, feasibility and willingness to participate.

The relative importance of the following three measures is evaluated by the Steering Committee. It is expected that scientific merit will be the primary consideration after which the remaining two areas will be considered equally.

- Scientific Merit: The scientific merit of the proposed study will be rated using the NIH scale for grant/contract applications. Assessment of scientific merit will include consideration of the BMT CTN scientific direction.
- Feasibility: The feasibility of the proposed study will be based on the potential for accrual and ability of centers to conduct the proposed treatment interventions (e.g., studies requiring specialized graft manipulations available at only one center may be viewed as less feasible than a trial utilizing only standard graft manipulations). Budget considerations are also important in assessing feasibility.
- Willingness to Participate: It is anticipated that Core Centers will enroll the majority of study participants on BMT CTN trials. The willingness of Core Center participation is a key factor in assessing any proposal.

2.5 Review Cycle

Proposals for BMT CTN clinical trials may be submitted at any time. The review will be conducted in a timely fashion after receipt of the *BMT CTN Proposed New Study Concept Form*.

The Steering Committee reviews study concepts during regularly scheduled Steering Committee in-person meetings or teleconferences. This does not guarantee a study will be conducted. A study proposal must be approved by a two-thirds vote majority of Steering Committee members and achieve a sufficiently high priority score to be scheduled for development. Additionally, the investigator submitting the proposal needs to consider comments from Steering Committee. If comments are concerning enough, the Executive Committee may recommend re-review by Executive Committee.

CHAPTER 3

PROCEDURES FOR IMPLEMENTING APPROVED STUDY CONCEPTS

3. PROCEDURES FOR IMPLEMENTING APPROVED STUDY CONCEPTS

3.1. Tasks Following Approval of a Study Concept

Approval of a Study Concept by the Steering Committee requires that a number of activities be initiated. While outlined below as separate activities, in practice, they are carried out concurrently to the extent possible. Tasks include:

- Assignment of a study number
- Establishment of a Protocol Team
- Development of the protocol document and draft informed consent form(s)
- Consideration of regulatory requirements
- Consideration of contributor and/or collaborator requirements
- Identification of sites
- Identification and procurement of services that will be required from outside (non-Network) providers
- Preparation of a study budget
- Development of an accrual plan
- Preparation of study-related educational materials, if applicable
- Development of Case Report Forms and implementation of data system
- Development of protocol-specific site training
- Development of patient-specific materials
- Development of a Research Sample Information Guide
- Development of a Pharmacy Guide, if appropriate

3.2. Establishment of a Protocol Team

Each approved Study Concept has a Protocol Team responsible for protocol development, oversight of the trial, and analysis and publication of the study results. The Protocol Team includes the following members:

- Protocol Chair(s)
- Core and Affiliate Center Representatives
- Protocol Officer
- Protocol Statistician
- Protocol Coordinator
- NHLBI and/or NCI Representative
- NHLBI Statistician
- Other members (e.g., DCC Business Representative; NCI funded NCTN Group representatives; and ad hoc members as deemed necessary by the Protocol Chair)
- For studies involving Patient Reported Outcomes, a Quality of Life expert should be included on the protocol team whenever possible, or a QOL subcommittee should review the protocol prior to DSMB submission

Protocol Team Member Application Process for Core and Affiliate Center Representatives:

- Investigators must be nominated or endorsed by a Core center PI, DCC leadership, or by BMT CTN disease/discipline committee leadership
- Potential study members must formally apply to participate by submitting an NIH biosketch with a statement indicating pertinent expertise and commitment to study team; for Early-Stage investigators, identification of a senior mentor is encouraged. If applicable, an industry sponsor's process may also be incorporated for member selection.

Protocol Team Member Selection Process:

- Study team member applications will be reviewed by the Executive Committee, and, if applicable, Chair of the relevant disease/discipline-specific committee.
- Final team members will be selected based on the following criteria:
    - Prior involvement in developing the study concept
    - Relevant expertise
    - Early-Stage investigator with well-established senior mentor
    - Diversity:
        - Centers previously under-represented
        - Likelihood to make time commitment
        - Academic rank (mix of Early-Stage and senior members)
        - Unique skill sets
        - Affiliate Center representation

Protocol Chair(s): The Steering Committee Chairperson appoints one to four Protocol Chairs, in collaboration with the Past-Chair, Chair-Elect, Vice Chair and the DCC Principal Investigators. One of the Protocol Chairs is typically the person who submitted the Study Concept. Protocol Chairs must have experience with the patient population and therapy being studied and commit their center to enrolling a significant percentage of their eligible patients on the study. The Protocol Chair(s) has (have) primary responsibility for:

- The study throughout its course, including but not limited to, chairing Protocol Team meetings, reviewing protocol drafts and amendments prepared after discussions of the Protocol Team
- Presenting progress reports on protocol development, implementation, and progress to the Steering Committee
- Leading Investigators Meetings for the protocol
- Leading the scientific portion of Site Initiation webcasts for the protocol
- Addressing issues raised by the Protocol Officer and Protocol Coordinator; investigators at participating centers; and the PRC, DSMB and NMDP IRB in consultation with Steering Committee leadership
- Reviewing and approving all versions of the protocol, informed consent(s), and summary of changes documents before and after submission to the PRC, DSMB, and NMDP IRB (and FDA, if appropriate), and prior to release of the official version to sites
- Presenting protocol to the PRC and DSMB
- Preparing Frequently Asked Questions Document for the PRC
- Responding to queries from the Protocol Coordinator on behalf of site personnel in a timely manner

  - Responsible for making a determination in cases where it is unclear whether a patient meets the protocol inclusion/exclusion criteria. Majority ruling will determine the decision, unless there is strong disagreement, in which case the chair(s) will need to join a call for resolution
  - Responsible for making treatment decisions regarding study drug dosing, next line therapy, supportive care, and general questions not clearly described in the protocol or other study materials

- Attending a minimum of 70% of the Protocol Team calls throughout the development, implementation, maintenance, and endpoint review stages. A Protocol Chair cannot appoint another person as a substitute for Protocol Team calls. The Chair is responsible for reviewing the team minutes for a missed call upon receipt and providing feedback via email.
- Ensuring their center is among the top 4 ranked accruing centers or has accrual ≥ 80% of their DCC-approved accrual projection. Since accrual is integral to successful and timely completion of BMT CTN studies, accrual performance may impact Protocol Chair status, primary manuscript authorship order and/or center performance score.

Core and Affiliate Center Representatives: Approximately 6-10 Core and Affiliate Clinical Center representatives will serve as co-investigators on the Protocol Team to help develop the protocol document, supervise the study throughout its course and interpret and present study results. Specific responsibilities include:

- Addressing issues raised by the Protocol Officer, Protocol Chairs, fellow Protocol Team members and Protocol Coordinator, investigators at participating centers, the PRC, DSMB and NMDP IRB (and FDA, if appropriate) in consultation with Steering Committee leadership
- Participating in the review of all changes to the protocol before and after submission to the PRC, DSMB and NMDP IRB (and FDA, if appropriate) and prior to release of the official version to sites
- Attending a minimum of 70% of the Protocol Team calls throughout the development, implementation, and maintenance stages of the protocol. The time set for Protocol Team calls is based on the availability of the majority of team members. If a team member is generally unable to attend calls during the scheduled time, the team member should recuse themselves from the team. In the event of extenuating circumstances where a person has expertise deemed critical to the protocol, special arrangements for the member to consistently provide substantial input outside of the scheduled calls may be considered by the Protocol Officer. Any special arrangements must be approved by Steering Committee Leadership.
- A Protocol Team member cannot appoint another person as a substitute for Protocol Team calls. The member is responsible for reviewing the team minutes for a missed call upon receipt and providing feedback via email.
- Ensuring their center accrues ≥ 80% of their DCC-approved accrual projection. Since accrual is integral to successful and timely completion of BMT CTN studies, accrual performance may impact protocol team member status and/or center performance score.

Protocol Officer: Responsibilities of the Protocol Officer include:

- Working closely with the Protocol Coordinator and Protocol Chair(s) in developing the protocol and consent documents, responding to center queries, preparing materials/agenda for meetings and teleconferences, reviewing CRFs, etc.
- Providing an additional level of scrutiny of the proposed protocol specifications, specifically addressing whether they are sufficient to accomplish the scientific objectives of the study
- Monitoring delays in protocol development/review/accrual and addressing obstacles to progress promptly in consultation with the Protocol Chair(s)
- Communicating with the Protocol Chair(s) and Protocol Coordinator regarding the status and progress of the trial
- Presenting protocol progress to the Executive Committee
- Assisting in preparation of materials for the PRC, DSMB and NMDP IRB (and FDA, if appropriate)
- Review safety sections of protocols and help develop appropriate safety stopping rules as needed
- Assists with protocol amendments
- Responds to queries from the Protocol Coordinator on behalf of site personnel in a timely manner
    - Responsible for making a determination in cases where it is unclear whether a patient meets the protocol inclusion/exclusion criteria. Majority ruling will determine the decision, unless there is strong disagreement, in which case the chair(s) will need to join a call for resolution.
    - Responsible for making treatment decisions regarding study drug dosing, next line therapy, supportive care and general questions not clearly described in the protocol or other study materials.

Protocol Statistician: The Protocol Statistician has primary responsibility for the study's statistical design and analysis. For some protocols, a secondary Protocol Statistician may also be designated. Protocol statisticians are from the DCC and have PhDs. The Protocol Statistician:

- Interacts and communicates with the Secondary Protocol Statistician, if applicable, on a regular basis regarding issues of statistical design and for secondary review of the final study analysis plan and analysis
- Assists in preparing materials for the PRC, DSMB, NMDP IRB and FDA (if appropriate)
- Writes the Statistical Considerations protocol chapter and any supporting appendices if applicable
- Assists with development and review of case report forms to ensure appropriate data are collected in an analyzable matter
- Assists with protocol amendments if related to statistical considerations or endpoints/endpoint definitions
- Interacts and coordinates with the Operational Statistician for the preparation of the Endpoint Review Charter (see section 3.5)

Protocol Coordinator: The Protocol Coordinator is generally a member of the Emmes Data Management/Clinical Study Management staff or the NMDP. The Protocol Coordinator has responsibility for:

- Overseeing all aspects of development of the Protocol Document from initial concept though final draft including internal and external reviews, revisions, approvals, and final dissemination of initial protocol and subsequent amendments
- Preparing revised drafts of the protocol pursuant to discussions of the Protocol Team and ensuring completeness and internal consistency of the protocol and conformity with standards of protocol production and BMT CTN DCC policies and procedures
- Preparing agendas, minutes, regulatory documents, as needed, and protocol documents for meetings of the Protocol Team, Steering Committee, PRC, DSMB, NMDP IRB (and FDA, if applicable)
- Communicating with the Protocol Chair(s) and Protocol Officer to resolve site questions around eligibility, treatment decisions about study drug, next line therapy, supportive care and other general questions not clearly described in the protocol or other study materials

NHLBI and/or NCI Representative(s): Each Protocol Team will include two NIH representatives, one from NHLBI and one from NCI. In addition, an NHLBI statistician may participate.

Other members (e.g., DCC Business Representative, NCI funded NCTN Group representative if the study is being done in collaboration) are appointed to the Protocol Team, as necessary, for specific expertise related to the study.

3.3. Development of a Protocol

The Protocol Team will meet by teleconference as soon as possible after formation of the team and at frequent intervals thereafter. It is recommended that Protocol Team meet in person for a one-day meeting to expedite the protocol development process. The day/time of the teleconferences and recommended in person meeting are scheduled by the NMDP Project Coordinator. Each Protocol Team member is assigned access to the BMT CTN private website for electronic communications regarding the protocol.

3.3.1. First Protocol Draft/Outline

- The Protocol Team is responsible for generating the first draft of the protocol based on the BMT CTN Proposed New Study Concept Form and comments from the Steering Committee. Many of the critical elements of the protocol will be contained in the BMT CTN Proposed New Study Concept Form. The Protocol Document will follow the BMT CTN protocol template: protocol synopsis, background and rationale, eligibility criteria, study design, study treatment, study endpoints, patient enrollment and evaluations, and statistical considerations; and Appendices including human subject, laboratory procedures and references. The informed consent form and assent form(s) if necessary are drafted by a member of the NMDP Patient Services team after discussion with the protocol team and/or Protocol Coordinator. The Protocol Document is the primary study document used to guide conduct of the trial.

In advance of the first Protocol Team teleconference, the Protocol Chair(s), if needed, with the assistance of the Protocol Officer and Coordinator, prepares a first protocol draft/outline for distribution to the members of the Protocol Team. Prior to distribution, the following occur:

- The Protocol Officer reviews the draft/outline for medical/safety issues, agreement with the BMT CTN Proposed New Study Concept Form, and potential protocol design and feasibility issues.
- The Protocol Statistician identifies statistical issues that require Protocol Team input

3.3.2. Working Draft Protocol

After the first Protocol Team conference call, the Protocol Coordinator with assistance from the Protocol Chair(s) and/or Protocol Officer incorporates suggested revisions. This Working Draft Protocol is then circulated to the Protocol Team for further discussion and comment. Multiple iterations of this process are generally necessary to develop a Protocol Document that is ready for presentation to the Steering Committee.

The Protocol Document includes:

- Synopsis (including protocol schema) that concisely outlines the study design and objectives
- Background, scientific rationale, and objectives for the study
- Detailed eligibility (inclusion/exclusion) requirements for participation. BMT CTN protocols must include standardized inclusion and exclusion criteria as specified in Exhibit 3-3-2. To deviate from the criteria, protocol teams must provide a written request to the DCC with rationale based on individual study.
- Detailed description of the treatment plans and supportive care measures
- Detailed description of expected risks associated with the treatment plan
- Accurate clinical definition of all primary and secondary endpoints
- Details of registration and randomization procedures, if applicable
- Required clinical exams and specimen submission schedules
- Follow-up schedules and requirements for patient monitoring
- Unexpected Grades 3-5 adverse events reporting procedures
- Additional adverse event reporting requirements for study drug or device, if provided by industry partner
- Detailed statistical considerations section including a description of the experimental design and analysis plan, sample size estimates, randomization, analysis plan of primary and secondary outcome measures, plans for interim analyses (if required) and stopping guidelines. Sample size considerations will include power, baseline rate and precision.
- Description of the risk-based endpoint review process
- References laboratory procedures and human subjects considerations
- Other appendices and miscellaneous procedures (e.g., those for blinding study treatments)

Exhibit 3-3-2

BMT CTN Standardized Inclusion and Exclusion Criteria	
Age	• Myeloablative transplantation: Age must be < 66 years • Reduced intensity: no upper age limit • Autologous transplantation: no upper age limit
Cardiac Function	• Reduced intensity conditioning: LVEF >30% with no clinical signs of cardiac failure • Myeloablative conditioning: LVEF >45%
Hepatic, Pulmonary, and Renal Function	• More careful consideration of organ function criteria using institutional normal ranges rather than universal cutoff points after taking into account regimens and drugs used in protocol. • Hepatic: Bilirubin <2.0mg/dl unless Gilbert's present • Pulmonary: DLCO or FEV1 >50% • Renal: Glomerular filtration rate > 60 mL/min calculated by equation
HIV status	• HIV that is well-controlled on combination antiretroviral therapy and no AIDS-related complications other than cancer within the past 12 months are eligible
Infections other than HIV	• Prior infections must be controlled • Hepatitis B patients are eligible if on effective suppressive therapy and otherwise meet inclusion/exclusion criteria • Hepatitis C patients are eligible if otherwise meet inclusion/exclusion criteria
Prior Malignancies	• Patients with a prior/concurrent malignancy whose natural history or ongoing treatment is not expected to interfere with the safety or efficacy assessment of the intervention should be allowed in absence of good rationale for safety concerns • Concurrent Malignancy: Patients eligible if clinically stable and not requiring tumor-directed therapy other than hormonal

The informed consent documents (including the assent form(s) if applicable) are prepared during protocol development but are maintained as separate document(s). Essential elements of the Informed Consent include:

- Statement that the study involves research
- Purpose of the study/research
- Sponsor of study
- Expected duration of the subject's participation
- Number of subjects
- Description of procedures
- Description of foreseeable risks and discomforts including death if appropriate
- Risks to the unborn; prescribed birth control for males and females
- Benefits to subject
- Benefits to others
- Alternative procedures or treatments
- Degree to which confidentiality of records will be maintained
- Clinicaltrials.gov language
- CIBMTR data collection language
- Record retention

- Inspection of records
- Certificate of Confidentiality Language
- Contact Name/Number for questions about research/study, subject rights and research-related injury
- Medical treatment for study/research-related injury
- Liability for study/research-related injury including that the sponsor (NHLBI/NCI will not pay)
- Participation is voluntary
- Refusal to participate will not be held against you
- Discontinue and/or terminate participation – by subject or others
- Compensation
- Costs and Reimbursements
- New findings
- HIPAA language
- Research samples (required and optional)

Specific language is required for the some of the elements as described below:

- Clinicaltrials.gov language must be inserted verbatim: A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that will identify you. At most, the Web site will include a summary of results. You can search this web site at any time.
- Certificate of Confidentiality language must be inserted verbatim in the section titled "Who will see my medical information": Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify you.
- CIBMTR Data collection language: Data regarding your clinical situation, including follow up after [insert number of years of protocol follow up] may be obtained by the BMT CTN from the CIBMTR, which captures information on all US transplants.

Other considerations generally include handling of laboratory samples and repository use issues, budget preparation/management and development of accrual plans (see below sections).

Early in the process, the Laboratory/Repository Manager, in collaboration with the Biomarkers Committee, works with the Protocol Team to identify biological samples that may be required to address the basic study question. Consultation with the Protocol Team will include discussions relevant to assessment of tests considered standard of practice versus those designated specifically for research.

Steering Committee feedback is requested to identify barriers to site participation and to recommend possible changes that may facilitate participation. The Steering Committee will review required clinical and laboratory assessments and compare to accepted standards of practice. Recommendations from the Steering Committee are discussed by the Protocol Team and incorporated into the Protocol as necessary.

3.3.3. Circulating Draft Protocol

The Protocol Coordinator, with the assistance of the Administrative Coordinator, prepares the Circulating Draft Protocol which includes a version number and date. The Protocol Team must approve the Circulating Draft Protocol prior to distribution to the Steering Committee for review and approval.

3.3.4. Steering Committee Approval

Two weeks in advance of Steering Committee review, two to three Steering Committee members are designated by the Steering Committee Chairperson to review the circulating draft protocol document prior to presentation to the Committee. These reviewers assess details within the document, complete a BMT CTN Reviewer Checklist (posted on the BMT CTN private website) and provide comments regarding significance, innovation, approach, investigator(s), environment and overall assessment of the study.

Following the presentation to the Steering Committee and subsequent discussion, committee members will accept, recommend changes, or reject the protocol. A two-thirds vote majority overrides anyone's right to veto, however the study team needs to take into account comments from Steering Committee. If comments are concerning enough, the Executive Committee may recommend re-review by Executive Committee. A Circulating Draft Protocol may require multiple presentations to the Steering Committee prior to final Steering Committee approval at which time "draft" is removed from the document.

Once the Steering Committee has approved the protocol, it is reviewed/edited by the Protocol Team and then preparation begins for PRC review and approval.

3.4. Activities Related to Protocol Development/Implementation

Once the Working Draft Protocol is available, other protocol specific matters may require coordination. These are as follows:

- External services
- Regulatory requirements
- Site identification
- Accrual initiatives
- Repository/laboratory compliance
- Protocol specific site training
- Participant materials
- Statistical Analysis Plan development

3.4.1. External Services

The Protocol Chair, Protocol Officer, Protocol Coordinator and Business Representative review a list of all study participant care measures and investigations that are included in the protocol to determine which, if any, aspects of the protocol require contracting with external service providers. Examples include centralized pharmacy for acquisition and distribution of study medications, research or other central laboratories, radiation quality control services, etc.

3.4.2. Regulatory Requirements

The Protocol Chair, Protocol Coordinator and the Protocol Officer are responsible for addressing regulatory requirements. These include the FDA requirements (if appropriate):

- Communicating with the FDA and other regulatory agencies identifying the need for IND or IDE (unless delegated to an industry sponsor)
- Coordinating the submission process with NHLBI and/or NCI/NIH/industry
- Completing an IND/IDE application if required
- Waiting 30 days after submission prior to releasing protocol to participating sites (to be assured that there is not a clinical hold)

3.4.3. Site Identification

The following steps, though usually performed in a logical sequence, represent processes that may occur throughout all protocol implementation phases, from development through accrual completion.

Once the Working Draft Protocol is available, the typical sequence is as follows:

- The protocol team completes a site selection assessment considering diversity of the patient population when determining sites to participate.
- A protocol synopsis is distributed to Core Centers surveying their interest in participation. If interested, the centers are asked to provide:
    - Contact information for PI and Key Contact
    - The numbers of patients they project to enroll annually
    - Number of competing protocols at their center, if applicable
- Affiliate Centers are identified (and contacted, if necessary) if they have previously enrolled large numbers of patients on other protocols or have a significant patient population that would be eligible for the study. Priority is given to sites with diverse patient populations. The majority of BMT CTN protocols require Affiliate Center participation.
- If even more sites are required, the Protocol Coordinator arranges for a notice to be posted on the BMT CTN public website along with the Protocol Synopsis announcing the potential study and requesting interested centers that meet the requirements to complete the *Application for Participation as a Affiliate Clinical Center in the BMT CTN* and to contact the DCC.
- If additional sites are still required, the Protocol Officer and Protocol Coordinator identify potential Affiliate Centers for direct contact by the Protocol Chair(s)
- If applicable, Central Operations Offices of NCI NCTN Groups are asked for a listing of their transplant centers
- Occasionally international centers or networks may request to participate in BMT CTN studies. Regulatory, activation and study logistics requirements for international centers may vary by study and country. In addition to the Protocol Team, international centers must be approved by NHLBI and receive U.S. State Department clearance.

During a Protocol Team conference call, the Protocol Team considers Affiliate Center participation based on protocol-specific criteria such as:

- Study sample size, study participant population (based on disease/disorder and racial and ethnic diversity) and type of transplant
- Need for special center training for study-specific procedures (e.g., graft manipulation)
- Prior experience with BMT CTN studies including accrual history and retention rates

The DCC Business Representative receives all submitted applications and provides each Affiliate Center written notification indicating their application has been accepted, not selected or placed on "hold" for future considerations.

If not selected as a Study Site, an Affiliate Center may appeal the decision to the Executive Committee. The decision of the Executive Committee regarding Center participation is final.

3.4.4. Accrual Initiatives

A critical challenge of the Network is timely accrual to all active protocols. Accrual is the highest priority of the Network. The Protocol Coordinator on behalf of the Protocol Team:

- Participates in the development and implementation of new trials
- Prepares an accrual plan for each new protocol prior to launch
- Sets and tracks activation target dates
- Monitors quarterly accrual reports
- Assists in identification of potential Affiliate Centers
- Coordinates and oversees patient accrual strategies
- Participates in resolving accrual problems
- Helps develop and participates in educational sessions for clinical center coordinators
- Assists in coordination of educational webinars

The protocol team considers initiatives to ensure target accrual milestones will be met and underrepresented patients will be included. These activities occur throughout the protocol development and accrual phases of the study and include:

- Assessment of accrual feasibility and target patient populations using the CIBMTR database
- Development of projected accrual timeline
- Development of an accrual plan which includes minority and pediatric patient accrual targets. BMT CTN provides double accrual credit for patients from underrepresented racial and ethnic groups on all studies; and double accrual credit for patients enrolled on rare disease studies (maximum two credits per patient). Other accrual bonuses may be requested by the protocol team for underrepresented patients.
- Development of study materials for healthcare professionals or patients and caregivers
- Monitoring of accrual and assessment of accrual barriers throughout the study

Throughout the process, a representative from the NMDP/Be The Match Patient Services is consulted if there are unique needs for study-related patient educational materials. This representative collaborates with the Accrual Coordinator and the Protocol Team in developing materials as needed:

- Educational materials
- A description of the study to be made available in brochure form and posted on the Network's public website (and other appropriate websites)
- Advertisements for study participant recruitment
- Web postings for study participant recruitment
- A series of "Frequently Asked Questions" (FAQs) for patients (vs. the FAQs developed for the PRC)
- Responses for the Patient Services staff to use when addressing queries regarding the study as it is publicized

All subject recruitment and educational materials are submitted to the NMDP IRB for approval with the final approved Protocol Document and Consent forms.

3.4.5. Protocol Review Committee (PRC) Review

The PRC is a standing committee appointed by the NHLBI (see Chapter 1). Prior to scheduled meetings, the PRC Executive Secretary provides the DCC with a roster of PRC members and NIH participants. The Protocol Chair(s), Protocol Officer and Statistician and senior members of the DCC represent the Protocol Team at the PRC meetings.

Protocol reviews are typically held by conference calls. Dates and times are coordinated by the Executive Secretary and the DCC. The PRC Chair and Executive Secretary prepare an agenda in consultation with the DCC. In general, the agenda includes:

- Short presentation of the study by Protocol Team representatives
- Open discussion between PRC members and Protocol Team representatives
- Closed executive session (limited to PRC members, the Executive Secretary and other NIH staff)
- Open session listing the PRC recommendations (subject to approval by the NHLBI Office of the Director)

Three weeks in advance of the meeting the DCC prepares the following materials for distribution to the PRC by the PRC Executive Secretary:

- Steering Committee approved protocol document
- "Frequently Asked Questions (FAQs)" document
- Accrual plan
- The PRC Reviewer Checklist to be completed by each reviewer and returned to the Executive Secretary prior to the teleconference regarding the study design and feasibility:
    - Importance of the question being addressed
    - Need for multi-center network to meet objectives
    - Merit of experimental design, including appropriate controls, treatment plan, study endpoints, and sample size
    - Study feasibility including appropriate per patient budget for network study and adequate resources including medications
    - Appropriate recruitment strategies
    - Adequacy of patient population and number of patients, including appropriate representation of minorities, women, and children

The PRC Executive Secretary is responsible for compiling the completed PRC Reviewer Checklists and distributing their comments to the DCC. The Protocol Coordinator will work with the Protocol Team representatives to prepare a written response for distribution by the Executive Secretary to the PRC members at least 24 hours prior to the scheduled meeting. The responses and any additional questions will be discussed during the Open Session of the PRC meeting. A closed session with the PRC members will be held to discuss the responses and determine if there are any remaining concerns. At the end of the teleconference, the PRC Chair will provide a verbal list of recommendations which are considered "unofficial" until approved by the NHLBI Office of the Director.

The PRC Executive Secretary prepares the final meeting minutes. After approval by the PRC Chair, the minutes of the PRC meeting are sent to the NHLBI Office of the Director for final approval. The Executive Secretary provides a copy of the Director-approved document to the DSMB Project Manager. The DSMB Project Manager provides the protocol recommendations to the DCC protocol representatives to share with the team.

If subsequent PRC reviews are required, revised materials are prepared and include:

- Revised or completed protocol document
- Protocol document noting substantive changes since prior review
- Protocol Team written response to the PRC recommendations/comments

After PRC approval, the Protocol Document with changes recommended by the PRC is prepared for submission to the DSMB for review.

In addition, the following Technical Committees review the protocol at this time.

- Biomarkers
- Clinical Research Associate
- Pharmacy, if applicable
- Special Populations (Pediatrics/Human Subjects)
- Toxicity and Supportive Care

3.4.6. DSMB Review

The DSMB is a standing committee appointed by the NHLBI (see Section 1.6.3). New protocol reviews are presented during the scheduled annual or monthly meetings. These are coordinated by the NHLBI DSMB Executive Secretary (DSMB ES) with assistance of the Emmes DSMB Project Manager (DSMB PM). The DCC prepares the agenda in consultation with NHLBI staff. In general, the agenda includes the following:

- Short presentation of the study by Protocol Team representatives
- Open discussion between DSMB members and Protocol Team representatives
- Closed executive session (limited to DSMB members, the Executive Secretary (ES) and other NIH staff, if appropriate)

Once it is determined that a protocol may be included in an upcoming DSMB submission, the Protocol Coordinator is to notify the DSMB PM for meeting planning purposes. Additionally, the DSMB PM should be notified of the presenter and others from the protocol team attending the meeting and the amount of time needed. A DCC project leader is expected to join for studies

being reviewed in addition to the Protocol Officer or Protocol Chair(s) presenting materials. The DCC project leader serves as the DCC representative on the call to ensure the presenter is familiar with the DSMB meeting format and to help facilitate progression through the agenda. Typically, someone from Emmes or NMDP is presenting the materials and no additional action is needed since they are part of the DCC and serve the role as DCC representative. However, if a protocol chair or another non-DCC individual presents, a DCC representative from Emmes or NMDP needs to be identified and attend.

Once a protocol is ready to be presented during the meeting, the DCC representative will briefly note what will be reviewed and who will present, ensure the presenter is on and ready, and then pass the meeting over to the presenter to begin. The DSMB PM will serve as a back-up for the DCC protocol representative in the event they have issues joining, etc.

3.4.6.1. DSMB Meeting Materials Preparation

The following materials are provided to the Emmes DSMB Team (bmtctndsmb@emmes.com) for submission to the DSMB three weeks prior to scheduled meetings. Final protocol team input must be provided by the end of day (EOD) 3 business days prior to the DSMB submission date to allow sufficient time for materials finalization, or earlier if requested by the DCC staff. Finalized materials must be provided to the Emmes DSMB team by 11am ET on the submission due date as materials must be uploaded by 12pm ET. If formatting and finalizing support is needed, contact bmtctndsmb@emmes.com a week in advance of the deadline to coordinate support.

- Memo summarizing the contents of the submission package
- Final PRC approved protocol document
- PRC recommendations/comments and Protocol Team responsesRed-line version of the PRC approved document if changes are made after PRC approval
- FAQs document (updated to address questions posed by the PRC if appropriate)
- Accrual plan
- Study drug or device information; e.g., Investigators Brochure, if relevant
- DSMB reviewer form for each draft document provided to collect comments, issues of concern, requests for additional information or clarification in the following areas:
    - Study objectives and feasibility
    - Study design and statistical approach
    - Study operations
    - Human subjects protection
    - Overall approval recommendation
    - Study drug or device information; e.g., Investigators Brochure

The DSMB PM will provide the following draft materials to the Protocol Coordinator and DCC project manager/lead for review and updates prior to the DSMB meeting:

- Pre-minutes (if input is needed)
- DCC summary memo
- Attendance list

The DSMB ES is responsible for compiling the completed DSMB reviewer forms and distributing their comments to the DSMB PM who then distributes to the Protocol Coordinator. The DSMB reviewer comments are provided 1 week prior to the DSMB meeting. If DSMB reviewer comments are received late, responses may not be able to be included in the response document, but they will need to be addressed in the meeting presentation. Protocol teams should schedule a meeting within 3-4 business days prior to the DSMB meeting to review DSMB reviewer comments and develop a response. Final team input on responses to reviewer comments must be received by EOD 3 business days prior to the DSMB meeting date to allow sufficient time for finalization.

The following materials are to be provided to the Emmes DSMB team by 11am ET 1 business day in advance of the meeting, as appropriate:

- Protocol Team response to DSMB reviewer comments (only applicable if DSMB reviewer forms were provided). The response must be reviewed by one of the DCC PIs prior to providing for submission to the DSMB.
- PowerPoint presentation to be provided after DSMB reviewer comment responses have been incorporated as appropriate. This may be provided closer to the time of the meeting to ensure all reviewer comments are addressed and included but must be provided prior to the start of the meeting.

If applicable, the protocol will also be submitted for FDA review at the time of the initial submission to the DSMB.

3.4.6.2. Post-DSMB Meeting Activities

Preliminary recommendations are not provided during the DSMB meeting. However, any significant concerns/safety issues and/or confirmation that the DSMB recommends the study continue will be communicated by the NHLBI Program Director (PD) to the DSMB PM via email after the meeting. The DSMB PM will then disseminate the preliminary recommendations to the team as appropriate.

The DSMB ES prepares the meeting minutes. After approval by the DSMB Chair, the DSMB meeting minutes are sent to the NHLBI PD for final approval. Once the minutes are approved, the NHLBI PD provides program notes summarizing the NHLBI-approved DSMB recommendations and/or an NHLBI PD signed IRB memo regarding the DSMB recommendations to the DSMB PM. The DSMB PM distributes the NHLBI program notes and/or IRB memo to the DCC project staff. The DCC project staff will then distribute only the recommendations to the Protocol Team; the NHLBI program notes may not be distributed outside of the DCC. If The DSMB approves the protocol, the NHLBI-approved IRB memo regarding DSMB recommendations will be provided to the IRB(s) and study investigators, as appropriate, by the DCC. If all protocol sites rely on the NMDP sIRB, the IRB memo regarding DSMB recommendations will be made available to sites on the study website, but no numbered memo will be distributed, as the DCC is responsible for providing the memo to the NMDP sIRB.

If subsequent DSMB reviews are required, revised materials are prepared and include:

- Memo including the Protocol Team’s responses to DSMB recommendations and a summary of submission package contents
- Revised or completed protocol document (clean and in tracked-changes versions)
- Protocol document noting substantive changes since prior review

- DSMB reviewer form for each amendment document provided for DSMB review

Receipt of the DSMB meeting NHLBI program notes is required prior to subsequent DSMB review submissions, unless an exception is granted by the NHLBI. The NHLBI-approved DSMB recommendations IRB Memo, FDA approval of the protocol, if appropriate, and NMDP IRB approval are required prior to releasing the protocol to the participating centers.

3.4.7. NMDP IRB Review

The NMDP IRB serves as the single IRB for all BMT CTN studies released after July 1, 2017. The members of the NMDP IRB are a diverse group of distinguished healthcare professionals, donor advocates, and patient advocates with expertise in bone marrow transplantation and hematology/oncology.

The DCC provides the following materials to the NMDP IRB three weeks prior to scheduled monthly meetings:

- NMDP IRB Initial Application Form
- Final DSMB (and FDA, if applicable) approved protocol document
- Informed consent and assent (if applicable) documents
- Subject recruitment or educational study materials and materials/instruments/forms to be completed by subjects, if applicable
- PRC and DSMB approval documentation
- Principal Investigator CV and documentation of protection of human research training
- Other materials, if applicable (e.g., Investigators Brochure, and patient materials such as quality of life surveys and recruitment advertisements)

The NMDP IRB informs the DCC if the study is approved, approved with stipulations, or not approved. If stipulations or resubmission is required, the DCC will prepare the response with input from the Protocol Team.

As a final step once the protocol is approved by the NMDP IRB, the Protocol Co-Chairs, Protocol Officer and Protocol Coordinator must review the protocol document for completeness and accuracy and complete a Protocol Team Reviewer Checklist. All the Protocol Co-Chairs and the Officer must sign the front page of the document indicating their approval of the document. If applicable, the IND sponsor may sign the Protocol Team Reviewer Checklist and the front page of the protocol document. Once complete, participating centers will be notified of the new NMDP IRB-approved protocol and informed consent documents by a Numbered Memorandum distributed via e-mail from the DCC. The protocol will be posted on the both the BMT CTN public website and the BMT CTN private website.

No changes to the protocol document by a participating center are allowed. The Informed Consent is posted as a Word document on the private website. The participating center may incorporate institution-specific boilerplate language to the Informed Consent and Assent documents. The center sends the modified consent and assent (if applicable) documents to the BMT CTN Protocol Coordinator for review prior to submitting to the NMDP IRB, to ensure that any inserted wording by the site is accurate in regard to the protocol and contract. Upon Protocol Coordinator approval, the center submits to the NMDP IRB and the IRB Administrator will review the consent document(s) to ensure added language is the same as the center's NMDP IRB approved boilerplate language on file. If approved, the final document(s) will be sent back to the center with NMDP

IRB approval recorded on the documents. If not approved, the center will be notified they need to revise and resubmit the documents following the process outline above. If the consent/assent documents are translated into another language, the translated version must be provided to the NMDP IRB along with translator certification documentation.

3.4.8. Statistical Analysis Plan Development

Within 3 months of the official release of protocol to sites, the Statistical Analysis Plan (SAP) will be developed by the study statisticians. Then it will go through review and approval by the BMT CTN statistical team, the protocol team and the sponsor as needed. The SAP will be finalized and approved within 6 months of protocol release. The SAP will include the detailed statistical methods and techniques that will be used for the data analysis for each of the study endpoints as defined in the protocol. The SAP will usually include the Table, Figure and Listing (TFL) shells to present the data. The SAP may also include other statistical considerations or clarifications for the final analysis which are not clearly stated in the protocol language. The SAP needs to be approved by the leading statistician, protocol chair or protocol officer and sponsor representative as necessary. The SAP may be amended if there is a significant protocol amendment impacting the statistical analysis but needs to be signed off no later than the final database lock.

3.4.9. Medical Monitor Assignment

The DCC assigns a Medical Monitor to each study when it is activated. Medical Monitors are transplant physicians, contracted by the NMDP, and familiar with the conduct of clinical research and regulatory requirements for safety monitoring and reporting. The Network's Medical Monitors hold teleconferences quarterly to ensure uniformity in assessing adverse events and to share updates on regulatory requirements. A Medical Monitor newsletter may be distributed in lieu of a quarterly call if there are no new updates or adverse events for discussion.

As a matter of policy and to avoid bias, these physicians are not assigned to a study activated at their facility. In some cases, a Medical Monitor may provide support to a study prior to their site's activation on a trial or when the Medical Monitor's position at an institution would not involve care for patients in a study on which they serve as a Medical Monitor

A primary and alternate Medical Monitor is assigned for each study. Should a study require a disease-specific Medical Monitor (e.g., HIV or sickle cell disease) per the discretion of the DCC, a primary transplant and disease-specific Medical Monitor will be assigned along with an alternate transplant Medical Monitor. The Medical Monitor has primary responsibility for reviewing safety issues, including protocol-specified safety provisions (e.g., assessment of stopping rules) and unexpected events. The Medical Monitor is a physician:

- Trained in transplant or the disease-specific area at an institution not participating in the study
- Trained in the protocol safety reporting requirements by the DCC
- Reviews reportable adverse events real-time and other safety concerns identified by the DCC
- Reviews safety data and identifies potential safety issues or trends in safety parameters across the study population

3.4.10. Rare Disease Designation

The BMT CTN Executive Committee reviews each new study to assess if it should be designated as a Rare Disease study. Considerations for designating a Rare Disease study include not only the overall frequency of the disease in the general population but the annual number of transplants for that disease as reported to the CIBMTR in the three prior years. Studies designated as Rare Disease studies are eligible for:

- Study start-up reimbursement
- Letter of support from NHLBI and/or NCI
- Waiver of the activation to first patient enrolled metric on the center performance report
- Waiver of the policy re: accrual of first patient within 6 months of activation
- Double accrual credit
- Authorship eligibility for the PI at each center that activates the study if they provide input to data review, analysis and/or manuscript

These and/or other special allowances deemed appropriate by the Executive Committee for each study will be communicated to sites via Numbered Memo or Welcome Packet.

3.5. Development of Medical Monitor Quality Review Plan and Protocol Endpoint Review Process and Charter

Protocol teams must determine whether Medical Monitor Quality Review and/or Protocol Endpoint Review will be incorporated.

The mission of the Medical Monitor Quality Review is for the study's Medical Monitor(s) to conduct a periodic review of the clinical data to identify outliers. The Medical Monitor Quality Review Plan should outline the Case Report Forms and data points to be evaluated. The plan must be aligned with the study protocol and the statistical plan and developed in conjunction with the Case Report Forms and Study Database (see Section 3.6). The plan should be reviewed by the Protocol Team on an annual basis.

The mission of the Protocol Endpoint Review is to conduct a review of the endpoints and assess subject eligibility and protocol compliance. When possible, the review should be done in a blinded manner. The Protocol Coordinator and Operational Statistician will prepare the review materials for the committee.

The Endpoint Review Committee (ERC) is nominated by the Protocol Chair(s). Typically, the Committee consists of:

- Protocol Chair(s)
- Two or more Investigators that contributed to the development and implementation of the protocol (measured by Protocol Team call attendance and/or center accrual) or Early Stage Investigators from high-enrolling centers
- Protocol Officer
- Operational Statistician
- Ad hoc members as deemed necessary by the Protocol Chair(s)

The members of the ERC are expected to attend a minimum of 70% of the ERC teleconferences and to provide their written review of cases prior to each call, including calls that they are unable to attend. Unsatisfactory participation may result in removal from the ERC.

The Protocol Team should include a description of the risk-based endpoint review process in the protocol and develop the Protocol Endpoint Review Charter if deemed necessary before the study is open to accrual. The charter should outline the primary and secondary endpoints to be evaluated and detail the endpoints to be adjudicated, process for adjudication, procedures for discrepancy resolution, and recording of results. The charter must be aligned with the study protocol and the statistical plan and developed in conjunction with the Case Report Forms and Study Database (see Section 3.6). The charter should be reviewed by the Protocol Team on an annual basis.

3.6. Development of Case Report Forms and Study Database

BMT CTN Case Report Forms (CRFs) development begins when the Working Draft Protocol is available. The Protocol Coordinator is responsible for the following items with regards to CRF and database development:

- Drafting the initial version of the BMT CTN CRFs based on the working draft of the protocol and the Endpoint Review Charter and identifying core forms to be used and required protocol-specific forms, if necessary
- Reviewing the draft forms with statistical staff or senior staff members to assess accuracy and comprehensiveness of collecting data for analysis of primary and secondary endpoints
- Reviewing the draft forms with the Protocol Team to assess accuracy and comprehensiveness of collecting data for analysis of primary and secondary endpoints
- Determining specific data to be provided by the CIBMTR and verifying that the CIBMTR data will meet the requirements of the statistical plan and Endpoint Review Charter
- Reviewing CRFs with the CRA Committee
- Drafting secondary versions based on Protocol Team and CRA Committee recommendations
- Piloting CRFs when necessary
- Obtaining statistical staff or senior staff member's approval of CRFs
- Finalizing CRFs and updating the data system

NOTE: Data collected by CIBMTR supplement BMT CTN data. The CIBMTR collects data at two levels: 1) Transplant Essential Data level and 2) Comprehensive Report Form level. The majority of BMT CTN studies require CIBMTR Comprehensive Report Form level data.

The methodology of the software industry, specifically the Software Development Life Cycle (SDLC), is employed when updating the data system for release of new or modified CRFs:

- Requirements are defined prior to the initiation of work on the data entry system and an implementation schedule/timeline is agreed upon by all involved staff
- The functionality is implemented by the Protocol Coordinator, a Systems Analyst and/or Programmer
- Validation and verification are performed on all work and all identified issues/defects are addressed before release to the transplant centers
- All work is documented to ensure compliance with industry standards and to provide a history of changes made to the data system

The use of Common Data Elements (CDEs) promotes the understanding and sharing of cancer research information. The comprehensive set of standardized metadata descriptors for cancer research data defined in the Cancer Data Standards Repository (caDSR) was utilized to review and analyze CRFs employed by the BMT CTN. The BMT CTN continues incorporation of CDEs to facilitate interoperability with other research trial efforts including data exchange with the NCI NCTN Groups.

3.6.1. Repository/Laboratory Compliance Considerations

The BMT CTN has invested substantial efforts into defining the critical scientific objectives related to the collection, biorepository storage and utilization of patient and donor biologic research specimens. A dedicated Laboratory/Repository Manager is a DCC staff member who coordinates these critical activities, some with in conjunction with the Biomarkers Committee:

- Participates on the Biomarkers Committee as ex-officio member
- Assists in establishing principles for specimen collection (including their use in Ancillary Studies)
- Reviews protocol drafts to identify specific study-related tests and required biospecimens, including those with potential as prognostic markers
- Prepares quarterly Laboratory Compliance Reports and makes recommendations to the Executive Committee for annual Center Performance Evaluations
- Assists participating centers in resolving specimen discrepancy problems
- Serves as a resource in the preparation of the protocol specific Laboratory Sample Information Guide

3.6.2. Protocol Specific Site Training

During the development of the Working Draft Protocol, the Protocol Chair(s), Protocol Coordinator and Protocol Officer will identify site training requirements for a specific study. This may be necessary for patient evaluations (e.g., grading GVHD), use of a new device (e.g., graft manipulation), specific stem cell lab procedures, or web-based CRF completion.

For areas requiring special training, the Protocol Coordinator will identify appropriate individuals to conduct the training. If related to a particular device, the manufacturer of the device will be considered as a potential source of training personnel. For web-based data collection issues, the Protocol Coordinator will coordinate the necessary training. Recorded trainings may be employed.

When such training requires contracting with outside organizations, the name, contact information and required activity will be forwarded to the DCC Business Representative (or designee) who will initiate subcontract discussions with the potential provider. In addition, the Business Representative will use this information when determining the study budget.

See additional information regarding training in Chapter 4.

3.7. Protocol Budget and Management of Contributions

3.7.1. Protocol Budget Preparation and Revisions

The DCC Finance and Contracts Department at NMDP/Be The Match (collectively referred to as the "Business Representative") are responsible for protocol budget development and coordination with the NIH regarding the management of the overall clinical care funds.

3.7.1.1. Protocol specific budgets

Budget Preparation: When a Working Draft Protocol is available, the Business Representative, Protocol Chair(s), Protocol Officer and Protocol Coordinator, as well as any other key parties if necessary, meet via teleconference to initiate budget preparation. The following materials (found on the BMT CTN private website in the "Budget and Contracts" folder) are reviewed during this meeting:

- Protocol Budget
- Study Drug Budget
- Laboratory Budget
- Product or Services

The Business Representative drafts a budget based on this information. Standard of care tests, medications, pharmacy costs, etc. are included in the budget.

The protocol draft budget includes the following assumptions:

- Projected enrollment
- Number and type of Clinical Centers (e.g., Core/Consortia Centers, Affiliate Centers, NCI-funded NCTN Groups, etc.)
- DCC labor projections (anticipated contributions, e.g., central laboratory, central pharmacy, packaging and shipping)
- Per-patient budgets (Clinical Center payment)
    - Labor hours for the physician, co-investigator, clinical research coordinator and/or data manager
    - Protocol specified non-standard of care assessments or procedures
    - Shipping costs and supplies used at the Clinical Centers
    - Specialized evaluations (such as MRIs, MRAs, neurocognitive tests, etc.)
    - Other considerations (e.g., studies done with NCI-funded NCTN Groups)

3.7.1.2. Budget review and approval process

The draft budget will be reviewed by the Protocol Chair(s) and the Protocol Officer. The Steering Committee must approve the budget prior to the protocol PRC submission. The final budget must be reviewed by the Business Representative and Protocol Officer prior to submission to the NHLBI and NCI for approval. When approved, a summary of the per patient fee will be posted on the BMT CTN private website.

The Business Representative completes the following budget-related actions after Protocol Officer approval:

- Proceeds with the request for proposals and contracts for centralized services
- Finalizes contributions
- Reviews the budget for any final revisions
- Executes contracts and Clinical Study Protocol Riders with the participating Clinical Centers and NCTN Groups

3.7.1.3. Budget revisions

If a protocol specific budget is adjusted due to contributions or a significant change in expenditures, a revised budget will be circulated and approved as described above. After approval, the revised per patient fee summary, if applicable, will be posted on the BMT CTN private website and the revised budget will be circulated to all appropriate parties by the Business Representative.

If protocol amendments occur, the Protocol Chair(s), Protocol Officer, Protocol Coordinator and Business Representative are responsible for reviewing the amendment to determine if modifications affect the budget. If budget adjustments are required, the procedures described above will be followed.

When all milestone payments of a protocol have been made or can be projected, the overall BMT CTN budget is adjusted to reflect the true cost of the study. Additionally, the DCC provides NIH (NHLBI and NCI) the budgeted and actual protocol costs.

3.7.2. Per Patient Fee

3.7.2.1. Basis of payment

The payment schedule shall be determined by the Protocol Chair(s) and the DCC and approved by NHLBI and NCI. Examples include:

- Entire payment upon enrollment
- Milestone basis:
    - 50% upon patient enrollment
    - 25% at study day 180 based on submission and approval of data
    - 25% upon receipt of complete and acceptable data for a study participant
- Other payment schedules as appropriate

The per-patient budgets are estimates of labor time effort, materials, etc. and used for budget development purposes. The centers may apply the per-patient funds however they deem appropriate to perform the protocol-specific tasks as BMT CTN does not govern the use of per-patient funds the clinical centers receive.

3.7.2.2. Payment guidelines for collaborative studies with NCI NCTN Groups

Consensus guidelines developed by NCI and NHLBI are followed for studies done in collaboration between BMT CTN and NCI NCTN Groups. Payment is consistent with these guidelines, NCI NCTN Group policies and BMT CTN policies.

- For BMT CTN led trials done in collaboration with the NCI NCTN Groups, the relevant Group (or as applicable the Cancer Trials Support Unit (CTSU)) contributes their standard per-accrual fee for patients enrolled from their sites
- For NCI NCTN Group led trials, the BMT CTN will pay its Network centers the NCI standard per-accrual Lead Academic Participating Sites fee for patients enrolled from a BMT CTN Center. Payment typically occurs at the time of patient enrollment.

3.7.3. Contributions

The Protocol Team may identify potential contributors. Once identified, the Protocol Chair or designee shall work with the DCC Business Representative to identify the best method of contacting the potential contributors. All third-party contributions must comply to the "Third Party Involvement in NHLBI-Supported Clinical Trials and other Population-Based Studies: Awardee/Contractor Third Party Related Issues" found at:

http://www.nhlbi.nih.gov/funding/policies/thirdparty.htm

The Business Representative informs the NHLBI Project Officer that contributions are being sought for a particular protocol and obtains permission to proceed.

The Business Representative prepares a Memorandum of Agreement (MOA) utilizing the NHLBI approved template if possible and negotiates the MOA with the potential contributor(s) in consultation with the Protocol Chair(s) or other designees. Upon completion of negotiations, but prior to execution of the MOA, the Business Representative completes the NHLBI checklist, and obtains appropriate DCC and government representative signatures. The MOA may then be executed with the Contributor(s).

3.7.3.1. Contributor Agreements

The MOA with a BMT CTN Contributor should reflect, at a minimum, the following:

- Contributor has no influence on the governance or conduct of the Study, or in the analysis, interpretation, or reporting of its results; except in limited circumstances when Contributor provides support in development of study design and study conduct activities, such activities will be reflected in the MOA;
- Contributor has no commitments with the study investigators that relate to the subject matter of the study as to intellectual or tangible property or to other issues that conflict with Public Health Service policy on grants or contracts;
- There is reasonable evidence that a Contributor's involvement will not create any conflict of interest issues with the study investigators, the National Institutes of Health (NIH) and its Institutes or employees, or any appearance of any such conflicts of interest;
- Language reflecting any resulting inventions must adhere to the "Bayh-Dole Act" - 35 U.S.C. § 200-212. In addition, the BMT CTN will recognize that:
    - Contributor owns rights to their inventions.
    - Any inventions made jointly by employees or agents of BMT CTN and Contributor will be jointly owned.
    - If a Contributor insists on language that the sites must adhere to, and the BMT CTN and government agrees, such language will be incorporated into the study specific CSPRs; and

- In exchange for financial or in-kind support, the BMT CTN, upon approval from the NHLBI, can provide reports on trial status, i.e., accrual reports, BMT CTN's Annual Report, manuscript review, etc. Requests for additional information must be approved by BMT CTN DCC leadership, NHLBI and NCI.

Financial contributions are held at the NMDP/Be The Match in a designated account, to be utilized for costs related to that protocol, unless otherwise approved by the contributor.

Questions regarding the budget and contracting process should be directed to bmtctn@NMDP.org.

3.8. Procurement Guidelines for BMT CTN

The DCC is responsible for procuring services as required by the clinical protocols such as correlative laboratory studies, storage of laboratory samples, drug acquisitions and distributions, etc. The DCC Business Representative is responsible for placing Requests for Proposals (RFPs) or Requests for Quotations (RFQs), negotiating pricing, terms, and conditions, and for placing contracts or purchase orders for the procurement of goods and services for the Network.

Two approaches to the procurement of services are used by the BMT CTN: i) full and open competition, or ii) limited competition (select or sole source). Open competition is the preferred method in accordance with 45 CFR 74.43, which states "All procurement transactions shall be conducted in a manner to provide to the maximum extent practical, open and free competition." Applicable procurement requirements, such as 45 CFR 74.40 through 74.48 are followed for both approaches.

When an open competition is used, the Business Representative will develop, issue, and manage RFPs/RFQs. The Protocol Chair or his/her designee will provide assistance with identifying potential suppliers, developing the statement of work, selecting experts to serve on the proposal review committee and establishing the technical review criteria. Persons involved in the procurement process will not disclose any information about the procurement to prospective offerors unless such disclosure is authorized by the DCC.

Under certain circumstances, using other than full and open competition (e.g., select or sole source awards) may be appropriate. Circumstances that may justify the use of other than full and open competition include: (a) the availability of only one or a limited number of qualified sources; (b) unusual and compelling urgency; and (c) the need to maintain an adequate base of suppliers.

Select or single source procurements over the simplified acquisition threshold (currently set at $150,000), must have sufficient documentation to justify the procurement. To initiate a select or sole source procurement, the Protocol Chair(s) or his/her designee must complete a Selected/Sole Source Justification form and contact the DCC Business Representative for review of the form. Next, the form is distributed to the BMT CTN Executive Committee for final approval or rejection. If approved, the DCC Business Representative proceeds accordingly. An RFP or RFQ will be issued to the selected source(s) or sole source, and in general, offerors will still be required to submit cost or pricing information.

Please direct questions regarding subcontracts or agreements for the BMT CTN to the Business Representatives at bmtctn@NMDP.org

CHAPTER 4

PROCEDURES FOR APPROVAL OF PROTOCOL AMENDMENTS

4. PROCEDURES FOR APPROVAL OF PROTOCOL AMENDMENTS

Approved protocols may require amendments to address issues that arise during study conduct (e.g., eligibility changes, toxicity review). In addition, new information may arise from other studies that affect the conduct of an ongoing study (e.g., new FDA or CDC guidelines). This chapter defines the steps for preparing amendments for approved and/or active protocols.

4.1. Proposal of a Protocol Amendment

Proposals for protocol amendments may come from the Protocol Team, DCC, Steering Committee, DSMB, NMDP IRB, participating clinical centers, NIH or the FDA. All proposals should be submitted to the Protocol Coordinator.

The Protocol Coordinator is responsible for:

- Recording the requested modification
- Contacting the submitting individual for any clarification
- Distributing the proposed amendment and/or document with proposed changes and the rationale to the Protocol Officer and the Protocol Team
- Assigning and maintaining protocol version numbers, copies of amendments and documents of changes in collaboration with the Administrative Coordinator

The Protocol Officer may contact the submitting individual to further discuss and clarify the proposed amendment. Additionally, changes recommended by the DSMB should be discussed with the NHLBI PD which can be coordinated by the DSMB PM.

4.2. Review of Proposal for Protocol Amendment

The Protocol Officer and Protocol Statistician will review the proposed amendment and the rationale and may discuss the changes with the Protocol Chair(s) and DCC Leadership. A decision regarding the need for a protocol amendment is the responsibility of the Protocol Officer in consultation with the Protocol Team.

Once approved by the Protocol Team, input may be solicited from the Steering Committee. If there is a disagreement regarding the protocol amendment, the Executive Committee will review the justification and rationale for the amendment and arbitrate. The decision of the Executive Committee to proceed with a proposed protocol amendment is binding.

4.3. Finalizing the Protocol Amendment

All proposed protocol amendments containing substantive changes must be reviewed by the DSMB, recommended for approval, and signed off by the NHLBI Office of the Director before submission to the NMDP IRB and distribution to Clinical Centers.

4.3.1. DSMB Review

Amendment proposals are uploaded via Secure Links on the DSMB website by Emmes and notification is provided to the DSMB via the DSMB Executive Secretary, or his/her designee, following the process for new protocol reviews. The following materials for a protocol

amendment are to be provided to the Emmes DSMB team (bmtctndsmb@emmes.com) for submission to the DSMB three weeks prior to scheduled meetings. Final protocol team input must be provided by EOD 3 business days prior to the DSMB submission date to allow sufficient time for materials finalization. Finalized materials must be provided to the Emmes DSMB team by 11am ET on the submission due date as materials must be uploaded by 12pm ET. If formatting and finalizing support is needed, contact the Emmes DSMB team a week in advance of the deadline to coordinate support.

- A memo summarizing the contents of the submission package and rationale for changes
- An indication of old and new version numbers
- A summary of protocol and informed consent changes (if any) with a detailed listing of changes, i.e., "change document"
- Revised protocol and/or informed consent
- Study drug or device information, e.g., Investigators Brochure, if relevant
- DSMB reviewer form for each draft document provided

The DSMB PM will provide the following draft materials to the Protocol Coordinator and DCC project manager/lead for review and updates prior to the DSMB meeting:

- Pre-minutes (if input is needed)
- DCC summary memo
- Attendance list

The DSMB Executive Secretary is responsible for compiling the completed DSMB reviewer forms and distributing their comments to the DSMB Project Manager who then distributes to the Protocol Coordinator. The DSMB reviewer comments are provided 1 week prior to the DSMB meeting. If DSMB reviewer comments are received late, responses may not be able to be included in the response document, but they will need to be addressed in the meeting presentation. Protocol teams should schedule a meeting within 3-4 business days prior to the DSMB meeting to review DSMB reviewer comments and develop a response. Final team input on responses to reviewer comments must be received by EOD 3 business days prior to the DSMB meeting date to allow sufficient time for finalization.

Additionally, the following materials are to be provided to the Emmes DSMB team in advance of the meeting, as appropriate:

- Protocol Team response to DSMB reviewer comments (only applicable if DSMB reviewer forms were provided). The response must be reviewed by one of the DCC PIs prior to providing for submission to the DSMB.
- PowerPoint presentation to be provided after DSMB reviewer comment responses have been incorporated as appropriate.

The DSMB ES prepares the meeting minutes. After approval by the DSMB Chair, the DSMB meeting minutes are sent to the NHLBI PD for final approval. The NHLBI PD provides program notes summarizing the NHLBI-approved DSMB recommendations and/or an NHLBI signed IRB memo regarding the DSMB recommendations to the DSMB PM. The DSMB PM distributes the program notes and/or IRB memo to the DCC project staff. The DCC project staff will then distribute only the recommendations to the Protocol Team; the DSMB meeting program notes may not be distributed outside of the DCC.

If the DSMB approves the protocol, the NHLBI-approved IRB memo regarding DSMB recommendations will be provided to the IRB(s) and study investigators as appropriate by the DCC. If all protocol sites rely on the NMDP sIRB, the IRB memo regarding DSMB recommendations will be made available to sites on the study website, but no numbered memo will be distributed as the DCC is responsible for providing the memo to the NMDP sIRB.

4.3.2. IRB Review

For BMT CTN studies under jurisdiction of the NMDP IRB, protocol amendments require NMDP IRB or IRB administrative review. Amendment proposals submitted to the NMDP IRB for review should include the following:

- NMDP IRB Request for Amendment form
- DSMB approval documentation
- Record of revision
- Protocol document, if revised
- Consent and assent (if applicable) documents, if revised

The NMDP IRB informs the DCC if the amendment is approved, approved with stipulations, or not approved. If stipulations or resubmission is required, the DCC will prepare the response with input from the Protocol Team.

4.3.3. Finalization and Distribution

As a final step once the protocol is approved by the DSMB and NMDP IRB (if applicable), the Protocol Chair(s), Protocol Officer and Protocol Coordinator must review the protocol document for completeness and accuracy and complete the Protocol Team Reviewer Checklist. All the Protocol Chairs and the Officer must sign the front page of the document indicating their approval of the document. Participating centers will be notified of the approved protocol amendment by a Numbered Memorandum distributed via e-mail from the DCC. Amendment documents may be included with the e-mail announcement and will be posted on the BMT CTN private and public websites. The documents will include:

- A summary and detailed listing of protocol changes
- A revised protocol with changes red-lined
- Revised Consent/assent forms with changes red-lined
- A clean second version with the changes fully incorporated into the document
- A rationale for changes may be provided
- NMDP IRB approval, if applicable

Other types of amendments containing non-substantive changes may be released to Centers or submitted to the NMDP IRB for NMDP IRB for administrative review before DSMB notification or deliberation with permission of the NHLBI Project Officer. These changes will be reviewed at the next regularly scheduled DSMB meeting. The DCC PIs will determine the appropriate review process in collaboration with the NHLBI Project Officer.

4.4. Regulatory Authorities and Documents

Protocols under an IND/IDE require formal submission of the amendment to the FDA. This is done before or simultaneously with the DSMB submission or NMDP IRB/institutional IRB submission. Centers will use their local IRB for BMT CTN protocols released prior to July 1, 2017 for the duration of the study. The NMDP IRB will be used for all BMT CTN protocols released after July 1, 2017 and also for centers participating in the BMT CTN 1501 and 1503 NMDP IRB Pilot Project.

Local IRB Review

For protocols released prior to July 1, 2017, participating Centers must obtain IRB approval of all protocol amendments for applicable protocols. After receiving IRB approvals, each Center must submit the IRB approval letter and approved consent form, if applicable, for the protocol amendment to the Protocol Coordinator. The Protocol Coordinator records the date of the protocol amendment approval, and consent if applicable, from each participating Center.

NMDP IRB Review

The DCC will distribute the NMDP IRB approval letter to participating centers via Numbered Memorandum. If the amendment included updates to the consent and assent (if applicable) documents, the Center must incorporate institution-specific language (as approved by the NMDP IRB, see Section 7.1) into the documents and submit to the DCC Protocol Coordinator for preview. Once approved, the Center sends the modified consent and assent (if applicable) documents to the NMDP IRB along with documentation of DCC Protocol Coordinator approval. If the consent/assent documents are translated into another language, the translated version must be provided to the NMDP IRB along with translator certification documentation. The NMDP IRB administrator will review the consent document(s), and if approved, send final document(s) back to the Center with NMDP IRB approval recorded on the documents and cc the Protocol Coordinator. If not approved, the Center will be notified they need to revise and resubmit the documents.

Implementation of Amended Informed Consent and Assent Documents

Sites must obtain NMDP IRB approval of their informed consent and assent documents and begin using the new document(s) within 60 days of the release date. If not implemented within this timeframe, the site must submit a written plan to the BMT CTN Executive Committee outlining the implementation timeline. The Executive Committee may require enrollment be suspended if the timeline is not acceptable.

Of note, if a significant safety risk is added to a new consent/assent document version, the NMDP IRB may (1) specify that no patients may be consented until the new version is approved; (2) request sites to expedite the new ICF through the approval process; and (3) require sites to re-consent patients that were consented via a prior version of the ICF with the new ICF.

4.5. Other Study Related Revisions

4.5.1. Case Report Form Revisions

Case Report Forms (CRFs) and the study data file may require modification as a result of a protocol amendment. The Protocol Coordinator takes the following steps regarding CRFs and/or study data file revisions:

- Reviews the final amendment to determine if any changes to CFRs are required
- Drafts changes to the CRFs
- Reviews changes with a DCC PI, Protocol Statistician or Protocol Officer and Protocol Team, if necessary
- Implements changes and coordinates a software release with the Clinical Systems Analyst and/or programmer

4.5.2. Protocol Budget Revisions

The Protocol Chair(s), Protocol Officer, and Protocol Coordinator, in consultation with the Business Representative, will be responsible for reviewing the protocol amendment to determine if any changes will affect the protocol budget. If changes are required, the Business Representative will draft a revised budget. The revised budget will be routed in accordance with Chapter 3. If the per patient fee is affected, the budget summary will be circulated to all appropriate parties and posted to the BMT CTN private website by the Business Representative.

4.5.3. BMT CTN Services Revisions

The Protocol Chair(s), Protocol Officer and Protocol Coordinator are responsible for reviewing the amendment to determine if any changes that have been made affect the use of additional BMT CTN Services. If changes are required, the Protocol Coordinator notifies the BMT CTN Business Representative who re-negotiates contracts with the service provider and revises the budget as required.

4.5.4. Other

Other materials must be reviewed and appropriately revised to address the protocol modifications. These items include the eCRF Completion Guidelines, Laboratory Sample Information Guide, Site Monitoring Plan, study initiation materials, various patient educational materials, study postings or Frequently Asked Questions (FAQs). DCC staff members such as the Protocol Coordinator, Protocol Officer and the Laboratory/Repository Manager, all share responsibility in revising relevant sections within these documents. When necessary, the Patient Services Representative is consulted to participate in preparing revisions to the Informed Consent. Senior DCC staff members, and the Protocol Team as required, will review any revised information or documents prior to their implementation.

4.6. Additional Site Training

The Protocol Coordinator reviews the protocol amendment to determine whether any additional center training is required. The Protocol Coordinator is responsible for all training related to protocol and CRF revisions. If other training requirements are identified, the Protocol Coordinator will work with the Protocol Officer to identify appropriate individuals to conduct the training. If related to a particular device, the manufacturer of the device will be considered as a potential source of training personnel. When such training requires contracting with outside organizations, the Protocol Officer will discuss with the DCC PIs, and forward the name, contact information and required activity to the Business Representative who will initiate subcontract discussions with the potential provider and determine the impact on the study budget.

4.7. Amendments for Collaborative Studies involving NCI NCTN Groups

These studies fall into two categories:

- Led by the BMT CTN
- Led by NCTN Group

For those studies led by the BMT CTN:

- Amendment materials are distributed by the Protocol Coordinator as early as possible to participating Centers and to the Central Operations Office of the appropriate NCTN Group
- Prior to release of the amended protocol, the NCTN Group follows their standard operating procedures for amendment review and approval

For those studies led by the collaborating NCTN Group:

- Amendment materials are provided to the DCC by the relevant Central Operations Office
- The Administrative Coordinator then circulates materials to all participating BMT CTN Clinical Centers per standard practice as noted above

Studies posted in the Clinical Trials Support Unit (CTSU) system will follow the CTSU amendment procedures.

CHAPTER 5

SITE MONITORING

5. SITE MONITORING

As part of the Quality Assurance plan and in full agreement with the NIH policy that states all clinical trials require monitoring to ensure the safety of study participants and the validity and integrity of the data (NIH Guide, NIH Policy for Data and Safety Monitoring, June 10, 1998), monitoring will be a continuous, ongoing, and multifaceted process. This includes external review by the DSMB and IRBs, as well as internal data quality control, review and evaluation. Site monitoring visits are central to this process and will include reporting to appropriate individuals with oversight responsibilities.

5.1. Initiation Site Visits

Prior to protocol implementation, the DCC Protocol Coordinator arranges either an initiation site visit or activation call with key center personnel to review all relevant materials and processes for implementation of the protocol. Multi-site activation calls may be held to ensure outreach to all appropriate personnel. A Protocol Officer or Protocol Chair in attendance on the call is optional.
Prior to study initiation, each clinical site, pharmacy, and laboratory will be assessed to ensure each facility possesses the following:

- Adequate facilities and equipment to conduct the studies
- Site personnel adequately knowledgeable and trained in protocol(s) requirements, study policies, procedures, and the data entry system
- Regulatory binder/file(s) have all required regulatory documents
- Adequate processes are established to protect the rights and safety of all study participants involved in the protocol

During the site activation call, the Protocol Coordinator will evaluate the pharmacy and clinical unit, patient record storage area, and computer facilities as well as ensure that adequate communication among all center staff is in place. Subsequent to the start of any study, all clinical sites will also be evaluated following these same procedures.

Laboratories will also be evaluated to confirm that the laboratory possesses the necessary professional certifications and licenses, and that laboratory operations quality assurance programs, assays, equipment, and staff meet study requirements.

Site activation calls specific to pharmacists, lab coordinators, and/or clinic coordinators may also be held in the event additional training is required.
Recordings of site activation calls may be provided to participating site staff that did not participate in the actual call.

5.2. Follow-up Monitoring Visits

The DCC will conduct on-site or remote monitoring visits periodically at the participating clinical centers, laboratories and pharmacies. The visits are conducted by Clinical Research Associate(s) CRA(s) from the DCC and may be accompanied, as appropriate, by other DCC or NIH representatives. The purpose of the site visit is to ensure compliance with protocol requirements, regulatory requirements, study treatment, laboratory procedures, sample acquisition, data submission and study policies and procedures. These visits are also used to exchange information regarding protocol adherence, review clinic, laboratory and pharmacy operations, provide training, check drug accountability, assess compliance with IRB reporting procedures for serious adverse

events and violations/deviations, and discuss any problems encountered regarding implementation or compliance with the protocol design. A data audit comparing source documents to submitted data is performed during these visits. In addition, an overall assessment of management, coordination, and communications of the study site is conducted. Consequently, information can be easily exchanged, mutual problems can be resolved, and study quality can be maximized.

On-site or remote monitoring visits are conducted at least once every three years for participating sites. Frequency of visits is dependent on accrual, site performance, number of patients enrolled, data quality, staff turnover and industry contributor and/or sponsor requirements. The purpose of the visit is to enhance data quality, ensure study integrity, satisfy regulatory requirements, and evaluate and improve site performance. An agenda for the site visit will be provided to the Principal Investigator(s) and site staff in advance of the visit.

The CRA(s) will hold a summary meeting, preferably at the end of the visit, with the Principal Investigator(s), the Lead Investigator and the site's CRA(s)/CRC(s) to discuss the CRA's observations, review any problems identified, and provide a preliminary summary of the visit to the site. In addition, a formal written report of the site visit is prepared by the CRA(s) and typically distributed within 30 days of the site visit. If site-specific problems of a serious nature are identified (e.g., failure to obtain informed consent, failure to have enrolled study participants sign the most current IRB-approved Informed Consent, enrollment of ineligible study participants, pharmacy or product administration errors, high data audit error rate), the Principal Investigator(s) may be requested to submit a corrective action plan for review by the DCC. Plans should be signed and dated by the appropriate study personnel implementing the plan. Any action items identified during the site visit will be tracked until resolution.

Industry-sponsored studies may have different monitoring requirements which will be defined in a study-specific MOP, as an addendum to the BMT CTN Administrative MOP, or in the study specific Site Monitoring Plan.

5.3. Data Quality Assurance

Database quality will be maintained through a variety of analyses that target anomalies, delinquent data and key entry errors. Reports summarizing anomalies found are transmitted to the transplant centers for resolution. They are also posted on the AdvantageEDC^{SM} and Advantage eClinical^{SM} web sites. The DCC also uses this process to analyze the frequency of errors according to type to determine if certain types of errors are recurrent. Modifications to the data entry system or re-training of centers' CRAs/CRCs will be employed for errors occurring frequently across transplant centers. If errors are localized within a transplant center, steps will be taken to resolve the problems by additional training to the center.

5.4. Data Review

The DCC Protocol Coordinator and/or Data Manager reviews data forms submitted by transplant center CRA(s)/CRC(s) for completeness, internal consistency, protocol compliance and adherence to the MOPs. In addition, "Missing Values Reports" and "Missing Forms Reports" are available through AdvantageEDC and Advantage eClinical and are dynamically updated. At minimum on a monthly basis, computer generated queries will be posted for each center. The queries will identify incomplete, questionable, or inconsistent data. Each center must either correct the data through

AdvantageEDC and Advantage eClinical or provide an explanation on the validity of the existing data to the appropriate DCC Protocol Coordinator.

Transplant center CRA(s)/CRC(s) are expected to carefully check all data for completeness and consistency. Numerical values, such as hematological values are cross-checked to ensure accuracy. Validation may be required from the site to verify data. This is further elaborated upon in Chapter 9.

5.4.1. Missing Forms

Delinquent forms in AdvantageEDC and Advantage eClinical will be identified and compared to an exception list. All missing forms will be identified by form type for each study participant enrolled in a protocol. The web-based data entry system, AdvantageEDC and Advantage eClinical, will provide a table that summarizes all forms submitted and past due forms listed by study participant. After a form is entered, the list of forms submitted, and outstanding forms is updated. A missing form will continue to be requested until the form is transmitted or until an exception is granted and entered into the missing forms exception file. Transplant Center CRA(s)/CRC(s) are required to review these tables for all study participants on a frequent basis.

Centers participating in BMT CTN trials must provide TED level data to the CIBMTR on all consecutive hematopoietic stem cell transplants performed at their institution during the period they are actively enrolling patients. Additionally, each center must then submit a Comprehensive Report Form for each patient participating on a BMT CTN trial (unless otherwise specified in the protocol) and follow the reporting requirements as outlined in the protocol-specific Form Submission Schedule. The BMT CTN Data Coordinator (located at the CIBMTR-Milwaukee campus), routinely works with transplant centers to obtain any missing and/or inconsistent CIBMTR data, including the collection of outstanding report forms.

5.4.2. Evaluation of Center Performance

The success of a multi-center network depends on high quality performance from the participating sites and careful coordination of effort. It will be the responsibility of the DCC to provide analyses and periodic reports on site performance with oversight from the NHLBI, NCI, DSMB, NMDP IRB and Steering Committee. The DCC is responsible for conducting site monitoring visits and for the administrative and statistical aspects of site evaluation. Reports are prepared and submitted to the NHLBI, NCI and Steering Committee according to specified guidelines. For the evaluation process to be successful, it is important to maintain open lines of communication among all parties, periodically review the common goals in order to maintain the highest degree of study integrity and ensure protection of human study participants within an environment that strives for continuous improvement of processes and operations.

Accrual reports for each protocol are prepared by the DCC, posted on the BMT CTN private website and updated nightly. Centers not meeting accrual goals will be contacted by the DCC and/or Protocol Team and Steering Committee Chairperson to determine the cause of slow accrual and if any corrective processes would improve accrual. The NHLBI and NCI will be informed of center-specific barriers to accrual.

The DCC will closely monitor accrual of new studies within the first six months of each center's activation date. If a center activates the study and does not accrue a patient within the first six

months, the DCC will request the center submit an action plan to address lack of accrual. If no patients are enrolled within the subsequent six months (i.e., within a year of center activation):

- The DCC will request the center close the study; and
- The center will be penalized on the Accrual metric on the annual center performance report.
- Additionally, if the center has a member on the protocol team, the member will be asked to resign from the team.

Centers may submit a written request to the Executive Committee to keep the study open after one year with no accrual. The Executive Committee will make the final determination. The DCC/Executive Committee will also assess each new protocol prior to activation. If they determine the protocol qualifies as a rare disease study, this accrual assessment plan may be modified or waived. A likely modification is there would be a longer observation period before an action plan would be requested.

Summaries of missing forms and days past due and data audit error rates, by center, will be provided to the DSMB at each annual data review meeting. The DCC will contact centers with serious delinquencies to resolve any training or staffing issues.

Periodic reports of center performance are provided to NHLBI and NCI. Serious violations, such as failure to obtain informed consent, enrollment of ineligible study participants, treatment or pharmacy errors, etc. will result in prompt notification to NHLBI and NCI. The DCC will analyze each serious violation to determine the impact of the error on study integrity. The issue will be discussed with the center and the center PI will be responsible for supplying a written explanation of the violation and corrective and preventative actions taken.

Remote Monitoring Activity

In addition to site visits, the DCC routinely monitors accrual reports, CRF completion, responses to queries, critical data reporting, distribution of data, AE/SAE trending, and incidence of protocol deviations/violations and occurrences. The Protocol Coordinator(s) has responsibility for identifying sites with problems in these areas and referring them to the Protocol Chair(s), Project Officers. The Protocol Chair(s) and Project Officer will determine whether corrective action is indicated. The corrective action may include, but not be limited to, discussion with the Principal Investigator, additional training of site personnel, a site visit, or referral to the Executive Committee.

Final Visit

For some studies, it may be appropriate to conduct final closeout visits, which occur after the study is completed and all data and finalized case reports are submitted. During this visit, the monitoring team determines study completion status. The review of regulatory compliance and documentation is done. The return of supplies and/or study medication(s) is also completed. After the visit, a final report, indicating the completion of the study, will be prepared.

The BMT CTN DCC records retention requirement policy is for sites to maintain patients' research charts for 5 years after the study closure memo date unless the sponsor's requirements differ. Site's institutional records retention policies should be followed if they exceed the requirements of the BMT CTN DCC.

5.4.3. Center Performance Reports

Effective scientific progress within the Network requires ongoing self-evaluation of BMT CTN procedures to maximize efficiency and enhance the scientific agenda. The BMT CTN provides Quarterly and Annual Center Performance Reports for each Core Center. The purpose of the report is to provide reward and encouragement for activities that further the BMT CTN goals; corrective advice for underperforming centers; and methods for recommending a Center's removal if their performance is not meeting the specified requirements. A copy of the Core Center Performance Evaluation Tool and Rating Schema is posted on the BMT CTN private website.

Evaluation of Center performance will include attention to both protocol-specific activities as well as intellectual and administrative participation in the Network. Recognition and reward of superior performance will be emphasized to encourage achievement as well as objective critique and discipline for inadequate participation.

Protocol-Specific Performance

The primary opportunity to advance the BMT CTN scientific agenda is timely and efficient opening of protocols and vigorous accrual of subjects for each study. Recognizing that centers of varying size may have differing patient base as well as institutional scientific commitments to other funded or developing studies, simple measures of periodic accrual may be insufficient.

The Annual Center Performance Report evaluates the following:

- Network Scientific and Administrative Participation

  Activities that directly foster the BMT CTN goals are recognized. Intellectual contribution to the Network can include participation as a Protocol Chair of a BMT CTN protocol; active membership on a Protocol Team including participation in team calls (for call participation credit), leadership or active participation on a BMT CTN Technical Committee, or ad hoc Task Force or special interest Committee; authorship or revision of components of the BMT CTN MOPs; election to a BMT CTN leadership position; and/or active scientific collaboration with the Network through study proposals, ancillary studies, scientific publications germane to BMT CTN protocols and supplemental grant applications and awards which extend the scientific leverage of Network projects and funding. Of note, a Protocol Chair or Team member cannot appoint another person as a substitute for Protocol Team calls. The member is responsible for reviewing the team minutes for a missed call upon receipt and indicate his/her understanding/agreement and stance via email.

- Protocol Initiation and Activation

  Protocol initiation, activation and enrollment will be monitored from the time of protocol release to submission of Informed Consent for preview; prompt preparation of needed revisions and approval; and time to open each protocol at the Center.

- Accrual

  Commitment of patients to each study will be determined by pre-initiation polling of each center. Quantitative measures of accrual at each center will be judged against the benchmarks of the pre-study commitment; the number enrolled per year; the percent of center's patients eligible who are enrolled adjusted as possible for the percent of patients who are not enrolled due to participation in a local, institutional competing trial. Accrual of at least one patient within six months of the site's activation will also assessed. Centers

are strongly encouraged to maintain commitment to each trial and avoid developing competing trials that directly reduce Network participation.

- Study Procedures

  Specific enumeration of protocol violations will be monitored. Major violations (e.g., enrollment of ineligible patient or serious deviation from protocol specified activity) will be reviewed on a continuous basis while minor violations (deviations from procedure that do not compromise the patients' safety or the study endpoint) will be tracked and reviewed semi-annually.

- Data Quality

  Overdue missing forms and data audit error rate will be quantified and reviewed semi-annually. Excess delay in data submission or data errors will be interpreted as reflecting insufficient staff training, supervision or commitment of the center PI to adhere to the Network goals.

- Laboratory Evaluation and Compliance

  Laboratory compliance, including sample collection, shipment and completion of appropriate CRFs are routinely monitored by the Laboratory/Repository Manager and support staff. The DCC provides complete instructional materials, training and educational opportunities for CRAs/CRCs to assist with the logistical procedures related to research sample collection, storage, testing and shipment.

Critique and Discipline

For Core Centers, minimum criteria for participation will include satisfactory performance in all the above categories. Data for each assessment will be collected by the DCC through the data tracking system that prospectively monitors each of these performance measures. Each center's performance will be reviewed annually by the BMT CTN Executive Committee. Inadequate performance will be documented and reviewed with the Center PI by the Steering Committee Chairperson and as needed, including one or more of the three BMT CTN DCC PIs. Failure to improve performance documented at a 6-month re-review may lead to recommendation that a Center be withdrawn from the Network.

Recognition and Reward for Superior BMT CTN Participation

Accrual over that expected, BMT CTN special projects and extraordinary efforts to enhance Network goals will be recognized and rewarded. Performance awards will be determined by the BMT CTN Executive Committee. Awardees can be nominated by Steering Committee members or directly recognized by the Executive Committee.

Participation will be recognized by one or more of the following:

- Added authorship on BMT CTN publications, primarily for added accrual or specific scientific augmentation of a study's progress
- Recognition of an Affiliate Center by making a representative an active voting member of the Steering Committee with travel support through the DCC for two years.
- Travel awards for Center research personnel (e.g., data managers, CRAs/CRCs, pharmacists) to attend either BMT CTN Steering Committee or Coordinator meetings, professional advancement meetings/courses, or the Tandem BMT meetings.

5.4.4. Protocol Violations and Deviations

Protocol violations and deviations are planned or unplanned departures from the IRB-approved protocol, informed consent and/or study materials. A protocol violation is a serious noncompliance that may affect the participant's rights, safety, or well-being or the completeness, accuracy and integrity of the study data. A protocol deviation is a less serious non-compliance.

5.4.4.1. Protocol Violation

A protocol violation is any change, divergence or departure from the IRB approved study protocol, consent document, or study materials that affect the subject's rights, safety, or welfare, or the completeness, accuracy and integrity of the study data. It may be a result of an error, fraud or misconduct and/or result in the exclusion of a patient from the study.

If the noncompliance meets any of the criteria below, it is considered a protocol violation. A single noncompliance may meet more than one criterion below. The list is not exhaustive.

- The noncompliance has harmed or posed a new, significant or increased risk of harm to the study participant:
    - The participant received an incorrect dose(s) or dosing schedule of the study drug that may pose increased risk to the participant
    - Unauthorized manipulation of the study product or its storage, handling or administration that may pose increased risk to the participant
    - The participant met the withdrawal criteria during the study but was not withdrawn and as a result may be subject to additional or increased risk
    - The participant received an excluded concomitant medication that may pose increased risk to the participant
    - The protocol's SOPs and/or required procedures were not followed resulting in the potential of increased risk to the participant
    - Study drug not held, reduced or discontinued as instructed by protocol
- The noncompliance compromises the scientific integrity of the data collected for the study:
    - The participant was enrolled/randomized but did not meet the eligibility criteria
    - The participant did not receive the study-prescribed treatment assignment
    - The participant was not treated per protocol procedures that specifically relate to primary endpoints/outcomes of the trial (e.g., a repeat biopsy was not conducted within the protocol-specified window prior to the patient beginning study procedures)
    - Key data and/or samples were lost
    - A serious adverse event was not reported within the appropriate timeframe
    - The participant's blinded treatment assignment was exposed to the participant and/or site staff without necessary approval for unblinding
    - The site stopped reporting data for a participant that did not specifically withdraw consent for data collection
    - The site stopped reporting data for a participant that did not meet the protocol requirements to do such
    - The investigator and/or the participant failed to comply with study requirements

  - Initiation of study treatment prior to enrollment
  - Any delay in study timeline, e.g., transplant delayed to donor availability
  - Using procedures different from those specified in the protocol for assessing critical endpoints such as disease stage, relapse, progression, engraftment, chimerism etc.

- The noncompliance is a breach of human subject protection regulations, policies or procedures, Good Clinical Practice, and/or or FDA regulations:

  - Lapse in IRB approval
  - Failure to obtain informed consent prior to initiation of study procedures
  - Collecting optional research samples who participants who did not provide consent for the samples
  - Inadequate informed consent process
  - Participant consented via an expired consent
  - Consent form not properly signed, initialed and or dated by patient, witness and/or guardian if applicable
  - Falsifying research or medical records
  - Performing tests or procedures beyond the professional's scope/credentials
  - Working under expired professional license or certification
  - Repeated deviations and minor deviations
  - Inadequate record keeping
  - Data breach in which participant's patient health information was exposed or risked exposure via unsecured email, database etc.
  - Failure to produce or maintain proper documentation
  - Any other deviation to the protocol that the DCC or Principal Investigator considers significant

5.4.4.2. Protocol Deviation

A protocol deviation is less serious non-compliance with the protocol, typically resulting from unforeseen circumstances or in the best interest of the patient. Some of the violations listed that do not pose increased risk to the participant may be considered deviations. Other examples of protocol deviations include, but are not limited to:

- The participant received an excluded concomitant medication that is believed not to pose additional increased risk
- Co-enrolling a patient another study without pre-approval from the BMT CTN

The BMT CTN does not require reporting of every protocol deviation to the BMT CTN DCC unless an industry sponsor requires such. Examples of deviations that do not require reporting to the DCC include:

- Missed assessments that do not compromise patient safety or a primary or secondary endpoint of the study
- Assessments completed outside of the protocol-specified date range that do not compromise patient safety or a primary or secondary endpoint of the study
- The participant missed <10% of the doses of the study drug that does not subject the participant to any increased risks

- Missed collection of laboratory sample (it will be documented in lab compliance reports)

BMT CTN studies do not allow planned deviations to eligibility criteria

5.4.4.3. Reporting of Protocol Violations and Deviations

Reporting of protocol violations and deviations follow the same procedures. The Principal Investigator or designee is responsible for reporting protocol violations and deviations to the BMT CTN DCC and IRB of record within 5 business days of days of knowledge of the occurrence. Both protocol violations and deviations must be reported on the Protocol Deviation/Violation Form in the clinical database (where available) or via phone or email to the DCC/ Protocol Coordinator for the study. At that time, the center will provide the DCC with a complete description of the deviation and a description of the plan to avoid similar deviations in the future. If applicable, the center and DCC will engage in a discussion to determine whether if the participant(s) impacted by the deviation will continue in the study. In addition, the Investigator will notify their IRB or the NMDP IRB according to the IRB-specific reporting requirements. Reporting of protocol deviations is discussed with centers during the site initiation call and documented in the pre-study initiation call report. Centers are instructed to keep documentation of all protocol deviations.

Industry-sponsored studies may have different requirements for the reporting of protocol violations and deviations. These requirements will be defined in a study-specific MOP or in a study-specific Protocol Deviation Reporting plan.

CHAPTER 6

ADVERSE EVENT REPORTING

6. ADVERSE EVENT REPORTING

6.1. Definitions

Adverse Event - Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of definite, probable, possible, unlikely, or unrelated).

Life-Threatening Adverse Event - Any adverse event that places the participant, in view of the investigator, at immediate risk of death from the reaction.

Serious Adverse Event (SAE) - Any adverse event that results in any of the following outcomes: death, a life-threatening adverse event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in any of the previous outcomes may be considered serious if they jeopardize the participant and require medical or surgical intervention to prevent any of the previously listed outcomes from occurring.

Unanticipated Adverse Device Effect (UADE) - Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO) - any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given the research procedures that are described in the protocol-related documents and the characteristics of the subject population being studied.
- Related or possibly related, meaning there is a reasonable possibility that the incident, experience or outcome may have been caused by participation in the research.
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unexpected/Unanticipated Adverse Event - Any adverse event, the specificity or severity of which is NOT listed in the study protocol, Investigator's Brochure, product inserts or informed consent document.

- For studies under IND utilizing an Investigator's Brochure, expectedness for regulatory reporting will be determined by the Investigator's Brochure. Other events NOT listed in the protocol, consent, product inserts or known to be events related to the underlying disease or transplant process, will be considered unanticipated.

Expected/Anticipated Adverse Event – Any adverse event that is listed in the study protocol, Investigator's Brochure, product insert or informed consent document as observed with the interventions being tested in the clinical trial. Additionally, expectedness for transplant treatment studies is associated with what is observed after a hematopoietic cell transplantation. For example: grade 4 neutropenia is observed in virtually all HCTs and included among the expected effects of the transplant.

- For studies under IND utilizing an Investigator's Brochure, the determination of expected event that would not require regulatory reporting will be made according to the Investigator's Brochure. Other events listed in the protocol, consent, product inserts or known to be events related to the underlying disease or transplant process, will be considered anticipated.

Attribution - The determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories:

Definite	The adverse event is ***clearly related*** to the study drug/device/procedure/ treatment(s).
Probable	The adverse event is ***likely related*** to the study drug/device/procedure/ treatment. *For BMT CTN studies: the adverse event is not likely to be caused by the subject's underlying medical condition or other concomitant therapy, and the nature of the adverse event or the temporal relationship between the onset of the adverse event and study drug/device/procedure/treatment administration lead the investigator to believe that there is a reasonable chance of causal relationship.*
Possible	The adverse event ***may be related*** to the study drug/device/procedure/ treatment(s). *For BMT CTN studies: the adverse event is not likely to be caused by the subject's underlying medical condition or other concomitant therapy, and the nature of the adverse event or the temporal relationship between the onset of the adverse event and study drug/device/procedure/treatment administration lead the investigator to believe that there is a reasonable chance of causal relationship.*
Unlikely	The adverse event is ***doubtfully related*** to the study drug/device/ procedure/treatment(s).
Unrelated	The adverse event is ***clearly NOT related*** to the study drug/device/procedure/ treatment(s). *For BMT CTN studies: the adverse event is most plausibly explained by the subject's underlying medical condition or other concomitant therapy, or the adverse event has no plausible biological relationship to study drug/device/ treatment.*

Common Terminology Criteria Adverse Events (CTCAE) – a descriptive terminology developed by the National Cancer Institute (NCI) for use in reporting adverse events. The CTCAE includes a grading (severity) scale for each adverse event term. Exhibits 6-1-1 and 6-1-2 provide reporting

requirements for BMT-related complex/multi-component events. A copy of the current CTCAE guidelines is located at https://ctep.cancer.gov/. Please note that CTCAE grading for laboratory values can vary from the descriptions below (i.e., a laboratory value can be CTCAE Grade 4, but not life-threatening).

Grade – Severity of the adverse event. Grades were developed using the following guidelines:

Grade 0 – No adverse event or within normal limits

1 – Mild adverse event

2 – Moderate adverse event

3 – Severe adverse event

4 – Life-threatening or disabling adverse event

5 – Fatal adverse event

6.2. Adverse Event Reporting Requirements

6.2.1. Unexpected/Unanticipated Adverse Events

For the purpose of continuity, any reporting requirements for Unexpected Adverse Events will also include Unanticipated Adverse Events and Unanticipated Adverse Device Effects (UADEs), unless a difference is explicitly stated. Timelines for reporting may vary (more conservatively) per study. If this is the case, the reporting timelines will be communicated in the safety reporting section of the protocol.

Exhibit 6-2-1 provides unexpected adverse event reporting requirements for study centers participating in a BMT CTN study.

Reporting requirements are calibrated to the severity or seriousness of the event and the perceived expectedness of the event to the study drug/device/procedure/treatment, irrespective of the attribution of the event to the study drug/device/procedure/treatment. Each protocol provides specifics on the type of unexpected events required to be reported (i.e., unexpected grade 3-5 AEs or unexpected SAEs). All reportable unexpected adverse events must be reported to the BMT CTN DCC in an expedited manner from the time of enrollment to the treatment segment, unless specified otherwise in the protocol.

Adverse events should be reported using CTCAE terminology and severity scales. In general, investigators should report adverse events as diseases or syndromes whenever possible, instead of reporting individual component symptoms, signs, laboratory abnormalities, and sequelae. Each reportable unexpected adverse event should have a single adverse event description. All reportable adverse events will be coded in the Medical Dictionary for Regulatory Activities (MedDRA) by the Safety Monitor or other applicable trained MedDRA coder.

Exhibit 6-2-1

REPORTING UNEXPECTED ADVERSE EVENTS ON A BMT CTN STUDY

SEVERITY GRADE	ATTRIBUTION	TRANSPLANT CENTER REPORTING REQUIREMENTS
5 - Fatal 4 - Life-threatening or Disabling	All attributions	Submit the Adverse Event form and a summary of the event to the DCC within 24 hours of the event. For Grade 5, also submit study death form to the DCC. Submit all completed AE forms to the DCC within 4 working days of learning of the event. For Grade 5, the summary should include potential contributing causes of death. Information reported for the adverse event must include: Name of adverse event, date of first onset, peak severity, relationship to study drug/device/procedure/treatment, resolution date, actions taken with respect to administration of study drug/device/procedure/treatment, and other treatment for the adverse event.
3 – Severe	All attributions	Submit the Adverse Event form and a summary of the event to the DCC within 3 working days of the adverse event. Submit all completed AE forms to DCC within 4 working days of learning of the event. Information reported for the adverse event must include: Name of adverse event, date of first onset, peak severity, relationship to study drug/device/procedure/treatment, resolution date, actions taken with respect to administration of study drug/device/procedure/treatment, and other treatment for the adverse event. Multiple recurrences of the same adverse event should be reported separately. These events are considered separate if they are considered recovered without active intervention for >24 hours.

6.2.2. Expected/Anticipated Adverse Events

For the purpose of continuity, any reporting requirements for Expected Adverse Events will also include Anticipated Adverse Events.

Exhibit 6-2-2 provides expected adverse event reporting requirements for study centers participating in a BMT CTN study.

All fatal (Grade 5) expected adverse events will be reported in an expedited manner to the DCC through submission of a Death Form. Deaths do not have to be reported within 24 hours for observational studies. Most protocol-specific life-threatening (Grade 4) and other non-fatal, non-life-threatening expected adverse events will be reported on study forms submitted on a defined forms submission schedule. Life-threatening (Grade 4) adverse events not collected on study forms should be reported in an expedited manner through the expedited AE collection process for that study.

In addition, each Protocol Team must develop an interim analysis plan using the CTCAE grading scale (or alternate grading scale if appropriate) to monitor protocol-specific expected adverse events. The plan will be included in the study protocol.

Exhibit 6-2-2

REPORTING EXPECTED ADVERSE EVENTS ON BMT CTN STUDIES

SEVERITY GRADE	ATTRIBUTION	TRANSPLANT CENTER REPORTING REQUIREMENT
5 – Fatal	All attributions	Submit study death form to the DCC within 24 hours of notification of the death. Submit death summaries and/or autopsy reports of the expected adverse event to DCC at the time of the report. The summaries should include potential contributing causes of death. Deaths do not have to be reported within 24 hours for observational studies.
4 – Life-threatening or disabling	All attributions	Submit study form(s) capturing data on the expected adverse event to the DCC at the form's scheduled due date (in the case of calendar driven forms) or event date (in the case of event-driven forms). If the event is not captured on a study from, report using the expedited AE reporting process.
3 – Severe	All attributions	Submit study form(s) capturing data on the expected adverse event to the DCC at the form's scheduled due date (in the case of calendar driven forms) or event date (in the case of event-driven forms)

Note: Selected Grade 3-5 events will be tracked and regularly monitored by the DCC and DSMB as specified in protocol-specific monitoring plans.

Any expected event that requires expedited reporting based on the reporting requirements outlined in the protocol should be reported under the same timelines outlined by grade for unexpected adverse event reporting. Reports of secondary primary malignancies (SPMs) if required by protocol should be reported within 3 business days.

6.3. Adverse Event Monitoring

6.3.1. Unexpected Adverse Events

Unexpected adverse events will be reported via a web-based AE system. The Safety Monitor will review daily all submitted unexpected SAEs. The Safety Monitor will forward the information to the Medical Monitor(s) for review within 1 business day.

All expedited reportable events will be reviewed by the Medical Monitor(s) at, or associated with the DCC, within 2 business days of receiving the summary of the adverse event from the Safety Monitor. If the Medical Monitor(s) requires additional information to make his/her assessment,

transplant centers will have 4 business days to respond to the request for additional information. The Medical Monitor will make a determination if the event is serious, unexpected/unanticipated, related and/or a UPIRSO. Based on the Medical Monitor's assessment, the Safety Monitor will report or facilitate reporting to the regulatory authorities, NHLBI, DSMB, and/or NMDP IRB as applicable.

The Medical Monitor(s) has medical expertise relevant to the study protocol and may request the participant's treatment assignment (if a blinded trial) when reviewing the adverse event. The DCC representative (Safety Monitor) is responsible for notifying the NHLBI Executive Secretary (with the NHLBI Project Officer in copy) via a password-protected report sent via email within 7 days for all reportable and/or Medical Monitor-confirmed unexpected SAEs or of any concerns regarding the frequency or type of adverse event(s) on a study or study treatment arm. The events sent to the NHLBI/DSMB will be decided prior to any participant enrollments through a review of this criteria by the DSMB and facilitated by the safety monitor. The reporting requirements may vary by study and will be outlined in the protocol. When an expedited report is sent, the NHLBI Executive Secretary is responsible for reviewing the adverse event materials to determine if the materials are complete. The NHLBI Executive Secretary will notify the DSMB Chair of the reportable event by forwarding the Chair the event report document(s). The DSMB Chair will review the adverse event materials, determine if the information is complete, determine if full DSMB review is required, and make recommendations to the NHLBI concerning continuation of the study. Full documentation of the procedures will be available at the DCC. If the DSMB requires additional information to make their assessment, the transplant center will have 4 business days to respond to the request for additional information. These queries will be communicated to the DCC Safety Monitor via the NHLBI Executive Secretary. The safety monitor will then facilitate query resolution with the site.

The Medical Monitor will review a cumulative line listing of all adverse events reported in an expedited fashion on a semi-annual basis (data will be reported in a blinded fashion when the protocol intervention requires blinding). The Medical Monitor will review the adverse events for safety signals identifiable when reviewing in aggregate. They will also review the cumulative listing for events required by protocol to make a recommendation of events to be removed from the active listing (i.e., events that are expected and not otherwise required to be reported by protocol). The Medical Monitor may seek additional guidance from one of the DCC Principal Investigators, based on the expertise required, for their assessments as long as the DCC Principal Investigator's institution is not participating in the protocol under consideration, and the DCC Principal Investigator is not considered to be otherwise in conflict by the NHLBI or by the Steering Committee. If there any concerns regarding safety, the NHLBI Project Officer will be notified immediately. The DCC Safety Monitor or the Medical Monitor will provide a written summary of the safety concern. In the event of dual Medical Monitors assigned to a study (a transplant and disease-specific Medical Monitor), the transplant Medical Monitor will provide the review.

In the event of a safety concern based on aggregate data identified by the BMT CTN DCC, the BMT CTN protocol team, or an individual site, the protocol statisticians at Emmes will compile the data. When further review is required, the relevant aggregate data, along with a summary of the noted concern, will be submitted to the Medical Monitor for review and recommendations. Based on the Medical Monitor's review and recommendation, the concern may be further escalated to the NHLBI and DSMB for review and recommendations. The safety concern may only be shared with the BMT CTN protocol team as directed by the DSMB.

The DCC will prepare at least annual summary reports of all reportable adverse events to be included in the annual DSMB data review report. The report is sent as a password-protected document via email or uploaded to the BMT CTN website via SecureLink.

6.3.2. Expected Adverse Events

The DCC will prepare annual summary reports of all expected adverse events for the NHLBI Project Officer and the DSMB. The summary reports will be included in the annual DSMB report. The report is sent as a password-protected document via email. Grade 3-5 expected adverse events will be reported as defined in the protocol. In general, the Network uses a Core Toxicity Form for all studies. In addition, each Protocol Team augments this with protocol-specific toxicities of interest. All events on the Toxicity Form are a subset of the CTCAE relevant to the particular study. The Toxicity Form is submitted at regular time intervals as defined by the Protocol Team.

The Medical Monitor will review events reported on the protocol-specific toxicity form, the GVHD forms and the infection forms annually, when forms are included as a part of the protocol. This review will assess whether there are safety concerns that should be referred to the DSMB. The Medical Monitor may seek additional guidance from one of the DCC Principal Investigators, based on the expertise required, for their assessments as long as the DCC Principal Investigator's institution is not participating in the protocol under consideration, and the DCC Principal Investigator is not considered to be otherwise in conflict by the NHLBI or by the Steering Committee.

In the event of a safety concern based on aggregate data identified by the BMT CTN DCC, the BMT CTN protocol team, or an individual site, the protocol statisticians at Emmes will compile the data. When further review is required, the relevant aggregate data, along with a summary of the noted concern, will be submitted to the Medical Monitor for review and recommendations. Based on the Medical Monitor's review and recommendation, the concern may be further escalated to the NHLBI and DSMB for review and recommendations. The safety concern may only be shared with the BMT CTN protocol team as directed by the DSMB.

Any concern regarding the type or frequency of a Grade 3-5 expected adverse event will be reported to the NHLBI Project Officer who will determine if referral to the DSMB is warranted. If required, data materials will be provided by the DCC. The DSMB Executive Secretary will arrange for review by the DSMB Chair. The Chair will determine if additional DSMB review is required and make recommendations to the NHLBI concerning continuation of the study.

The DCC will ensure that any additional reporting requirements defined by the NHLBI Project Officer, DSMB Chair and other oversight groups are identified and implemented.

The DCC in collaboration with the NHLBI Project Officer will determine the exact content of these summary reports and the reporting schedule.

6.3.3. Stopping Guidelines

The Protocol Coordinator, Safety Monitor and Emmes Statistician for each protocol will review the adverse events monitored for stopping guidelines on a regular basis to be specified in the protocol, but at least monthly. The Medical Monitor will provide a review annually but may be requested to the review the stopping guidelines more frequently in the event that the guidelines

approach the threshold. The Medical Monitor may request to have an expedited review of the trial by the DSMB based on this review.

6.4. Adverse Event Reporting and Management

Because all or most study participants in BMT CTN trials will be receiving potentially toxic preparative therapy, significant regimen-related toxicity is anticipated. Study CRFs are designed to capture information on these adverse events. Likewise, substantial mortality is anticipated and will be captured via filing of appropriate CRFs. In general, unexpected SAEs may require reporting until a protocol defined event within each protocol occurs (i.e., initiation of second intervention post-progression). Each protocol or other protocol material should be consulted for when adverse event reporting is no longer required. Any adverse event that occurs after the protocol defined event reporting period only requires reporting only if the SAE is felt to be related to the primary BMT CTN protocol study intervention.

6.4.1. FDA IND Reporting

If a study is under an FDA Investigational New Drug (IND), all suspected and unexpected fatal or life-threatening adverse events are reported to the FDA within seven calendar days after receipt of the information, following FDA guidelines. All other suspected and unexpected serious adverse events are reported to the FDA via a written report within fifteen days of receipt of the information (21 CFR 312.32). If the Medical Monitor assesses the event to be unrelated to the study, then the event will not require expedited reporting but will be included in a summary report issued annually. All expected/anticipated adverse events (i.e., those listed in the informed consent, product inserts, or study materials), including death and graft failures are reported to the FDA via annual reports.

The DCC is responsible for reporting to the FDA for studies under an IND on at least an annual basis.

6.4.2. FDA IDE Reporting

If a study is under an FDA Investigational Drug Exemption (IDE), all unanticipated adverse device effects will be reported to the DCC for assessment. Evaluation of UADEs will be communicated to participating investigators, all reviewing IRBs and the FDA within 10 days of the initial event notification to the DCC. If the Medical Monitor assesses the event to be unrelated to the device, then the event will not require expedited reporting but will be included in a summary report issued annually. All anticipated device effects are reported to the FDA via annual progress reports.

The DCC is responsible for reporting safety information to the FDA for studies under an IDE on at least an annual basis.

6.4.2.1. Guidelines for Reporting AE to IRBs and OHRP for NHLBI Sponsored Clinical Trials Network

6.4.2.2. Introduction

NHLBI guidelines on reporting adverse events on a clinical trial require that all IRBs associated with the trial be provided with the following information:

- A description of the DSMB procedures
- Identification of the DSMB members' areas of expertise, excluding names
- Feedback after each DSMB meeting

Guidelines note that the Office of Human Research Protection (OHRP), DHHS issued a memorandum dated May 22, 2000, Continuing Review of DSMB-Monitored Clinical Trials, which authorizes IRBs to rely on current statements from DSMBs that the DSMBs have reviewed study-wide adverse events, interim findings and any recent literature that may be relevant to the research.

For BMT CTN trials using the NMDP single IRB, the following procedures of identifying a UPIRSO should be followed:

- Individual site investigators are required to assess an event that occurred at their site as to whether the event meets the criteria of a potential UPIRSO or potential serious or continuing non-compliance. If the event meets the UPIRSO, the site must use the NMDP IRB system to complete the Reportable Event form. The site must submit notification to the BMT CTN Protocol Coordinator that the single event is being reported to the NMDP sIRB as a UPIRSO. The Reportable Event form asks that a copy of the notification to the BMT CTN DCC and any response(s) received back be attached to the form. The site will also be asked if the Medical Monitor assessed the event as a UPIRSO.
    - The Medical Monitor will make an assessment of whether the event is unexpected and related to the study protocol, as well as if there is a need to modify the protocol or consent based on if the research places participants or others at greater risk of harm than was previously recognized. The Medical Monitor's assessment serves as the network's assessment of whether the event is reportable to the NMDP sIRB. The site PI can use the Medical Monitor's assessment of the event to include with the Reportable Event Form as documentation. The DCC or designee will review the Medical Monitor's assessment and whether the site reported the event to the NMDP sIRB and if not, confirm that the site investigator did not assess the event as a UPIRSO.
    - If the report was submitted by the site, no further action will be required by the DCC for reporting the event as a UPIRSO.
    - In the event the report was not submitted by the site and the site investigator did not assess the event as a UPIRSO, the DCC Protocol Coordinator will complete the Reportable Event Form and submit to the NMDP sIRB.
- There may be events where the individual event does not qualify as a UPIRSO, but a series of the same event does qualify because it becomes unexpected in terms of frequency. For these cases, it is anticipated that the DSMB will review those events in aggregate and make a determination if the events in aggregate qualify as a UPIRSO. If the events qualify as a UPIRSO, the DCC will submit the Reportable Event Form to the NMDP IRB.

In the event that the Medical Monitor or DSMB identifies a UPIRSO for a trial not utilizing the NMDP sIRB (released prior to July 1, 2017), the DCC will prepare a summary report for submission to the OHRP. Once the DCC receives a response from OHRP, Principal Investigators will be notified by the DCC via a memo.

Of note, these procedures are in addition to local IRB's adverse event reporting requirements, which the individual sites are responsible for upholding.

6.4.3. Adverse Event Documentation

AE definitions and procedures for reporting and monitoring AEs will be documented in the study protocol and/or the MOP.

In addition, each Network study should have study-specific safety monitoring outlined in the protocol to ensure adverse events are reported and monitored in a timely manner. The protocol will be reviewed by the DSMB prior to implementation of the study and executed by the Network DCC following study initiation.

6.4.4. Providing Follow-up Information to Applicable IRBs

After the DSMB meeting during which data were reviewed, the NHLBI Director provides DSMB meeting program notes summarizing the NHLBI-approved DSMB recommendations and/or an NHLBI signed IRB memo regarding the DSMB recommendations to the DSMB Project Manager. The DSMB Project Manager distributes the program notes and/or IRB memo to the DCC project staff. The Protocol Coordinator will then distribute only the recommendations to the Protocol Team; the program notes may not be distributed outside of the DCC.

The NHLBI-approved IRB memo will be provided to the IRB(s) and study investigators as appropriate by the DCC. If all protocol sites rely on the NMDP sIRB, the IRB memo regarding DSMB recommendations will be made available to sites on the study website, but no numbered memo will be distributed as the DCC is responsible for providing the memo to the NMDP sIRB.

6.4.4.1. Gene Transfer Trials

Gene transfer trials have reporting requirements above and beyond those for trials of other interventions. They must follow the NIH Guidelines for Research Involving Recombinant DNA Molecules.

The NHLBI has a DSMB that oversees participant safety aspects of all gene transfer studies that it supports. Therefore, regardless of whether the individual study has its own data monitoring group, the NHLBI Gene Therapy DSMB will review all data.

Information on reporting adverse events and other data on gene transfer trials will be supplied by the NHLBI Project Office during development of the study protocol.

6.4.5. Requests from an IRB for Additional Information

If an IRB, whether for a data coordinating center or a clinic, requests information beyond what was agreed to at the beginning of the trial and beyond the above guidelines, the Protocol Officer will immediately inform NHLBI Leadership. Decisions as to how to handle each request will be made jointly, and will depend on the nature of the request, whether or not the DSMB had identified safety concerns, the kind of trial, the stage of the trial, and perhaps whether the IRB is for a coordinating center or a clinic. Possible options are:

- The NHLBI Project Officer will send a letter to the PI stating that the DSMB is carefully monitoring outcomes and adverse events and that if anything occurs that would alter the protocol or informed consent, each investigator and IRB will be informed promptly. The NHLBI Project Officer will ask the PI to discuss this letter with their IRB.
- For late phase trials, the IRB chairperson will be provided with adverse event data, without breaking down the information by treatment group. The IRB chairperson and one other member of the IRB would be authorized to see these data, in order to assure them that serious, unexpected events are infrequent. These data would be for the entire study, regardless of whether the IRB is for a coordinating center or a single clinic. (Note that for early phase trials, this information would generally already be provided to the IRBs.)

If neither of the above options is acceptable to the IRB, NHLBI Leadership will discuss whether to provide the data requested by the IRB. If it is decided that data will not be provided and the IRB still objects, participation of the center in the study may cease.

CHAPTER 7

HUMAN SUBJECTS PROTECTION AND REGULATORY PROCEDURES

7. HUMAN SUBJECT PROTECTION AND REGULATORY PROCEDURES

7.1. Institutional Review Board

Each transplant center requires IRB review and approval prior to participation in a protocol. Centers will use their local IRB for BMT CTN protocols released prior to July 1, 2017, for the duration of the study. The NMDP IRB will be used for all BMT CTN protocols released after July 1, 2017, and also for centers participating in the BMT CTN 1501 and 1503 NMDP IRB Pilot Project.

Local IRB

Documentation of the IRB review must be available at the transplant center and submitted to the DCC along with a copy of the IRB-approved Informed Consent prior to study initiation. Each center's IRB of record is responsible for reviewing the protocol for continuation on an annual basis or as defined by its IRB.

On an annual basis, or as defined by each center's IRB of record, the IRB will review the protocol for continuation. The status of annual IRB reviews will be maintained by the transplant center and a copy forwarded to the DCC. The DCC will provide a reminder letter to the transplant center at 60 days and 14 days prior to IRB expiration to facilitate timely renewal. In addition, a notification will be sent to the transplant center on the day of expiration, informing them that their enrollment is suspended until they receive IRB approval. A final reminder is sent 14 days post expiration, notifying centers that they will be de-activated if they do not receive IRB approval.

NMDP IRB

The NMDP will serve as the single IRB for all BMT CTN protocols released after July 1, 2017. All BMT CTN Core, Consortia and Affiliate Centers must enroll in the NMDP Single IRB prior to opening a new study. Enrollment steps are detailed in the NMDP IRB Manual for Local Institutions Using the NMDP IRB as a Single IRB. Study-specific requirements to be completed after enrollment for each new study are also outlined in the manual. Centers should contact NMDP Human Research Protection Program staff members for more information: NMDPSIRB@NMDP.org.

Documentation of current NMDP IRB review and approval must be available at the transplant center along with a copy of the NMDP IRB-approved institutional informed consent and assent (if applicable) documents prior to study initiation. The NMDP IRB annual review documentation will be distributed by the DCC via Numbered Memorandum.

7.2. Health Insurance Portability and Accountability Act (HIPAA)

It is the responsibility of each participating transplant center to understand their institution's requirements under the Health Insurance Portability and Accountability Act (HIPAA). This web site is an additional resource to provide guidance in assuring compliance: http://aspe.hhs.gov/admnsimp/.

7.3. Office of Human Research Protections (OHRP) Institutional Assurances

Each participating institution must have a current Federal Wide Assurance (FWA) on file with OHRP and provide documentation of this number to the DCC. Transplant centers that are identified as potential new participating sites and do not have a FWA, are required to obtain one from the Office of Human Research Protections, prior to site activation.

7.4. Participation of Women, Racial and Ethnic Minorities, and Children

NIH sponsored clinical trials and the Code of Federal Regulations state that study participants enrolled in clinical trials must include women, racial and ethnic minorities, and children to facilitate potential benefit to all persons at risk for a particular disease, disorder or condition under investigation (45 CRF 46).

Research sponsored by NIH must include children (individuals under the age of18) unless there are scientific and/or ethical reasons for exclusion. It is the responsibility of the Special Populations (Pediatrics/Human Subjects) Committee to review each BMT CTN protocol to ensure that children, women and racial and ethnic minorities are included to the fullest extent possible. Sites should make every effort to include these populations in subject recruitment activities.

7.5. Site Regulatory Documents

In order for a site to be activated for participation in a BMT CTN clinical trial that is under an IND or IDE, the following materials must be submitted to the DCC for entry into a regulatory tracking system by the Regulatory Coordinator:

- *Form FDA 1572* for IND studies or *Investigator Agreement* for IDE and non-IND/IDE studies - Statement of clinical center's Principal Investigator
- *Financial Disclosure* - provides information regarding the financial agreement between an investigator/institution listed on the Form FDA 1572 and/or contributor/collaborator for the trial
- *Curriculum Vitae* – a current CV for the Principal Investigator and Co- Investigator(s)
- *Medical Licenses* - current professional licenses for select personnel
- *Delegation of Authority Log* – the log documents the responsibilities assigned to the research team members and their dates of involvement in the project
- *Letter of Local IRB approval for each protocol, if applicable* - Sites will be required to submit an initial approval letter from the IRB prior to enrollment of any participation. In addition, sites will also submit annual documentation of IRB review and approval. For studies reviewed by the NMDP IRB, the DCC will distribute NMDP IRB review and approval documentation via Numbered Memorandum.
- *Local or NMDP IRB Approved Informed Consent Document* - must be submitted for initial approval of each protocol and all amendments thereafter
- *Federal Wide Assurance* number

Additional items are required for activation as described in Section 9.4.

7.6. IND or IDE Application

Filing of an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application with the FDA is required whenever clinical investigations of an unapproved new drug or biological product or new device are to be studied. In the BMT CTN, an industry contributor providing the product under investigation may request that the company or a BMT CTN Investigator serve as the IND or IDE sponsor. It is expected that the DCC will provide technical and administrative services to prepare, distribute, and track the IND/IDE application and assume the reporting obligations of the IND/IDE sponsor unless contractual arrangements specify otherwise. Similarly, the DCC will assume responsibility for coordination and review of annual IND/IDE reports to the FDA and maintain electronic copies of all correspondence.

CHAPTER 8

PUBLICATIONS, ABSTRACTS AND PRESENTATIONS

8. PUBLICATIONS, ABSTRACTS AND PRESENTATIONS

8.1. Policy Statement

Research activities of the BMT CTN are intended to contribute knowledge to the field of hematopoietic cell transplantation. Definitive contributions are made through publications in peer-reviewed literature. Abstracts, public presentations, electronic postings and data sharing also contribute to public knowledge, but do not substitute for peer-reviewed publications.

BMT CTN will comply with NIH public access policies including submission of study results and final manuscripts (e.g., clinicaltrials.gov, PubMed central, etc.). The BMT CTN will comply with all journal requirements (e.g., modified copyright transfer agreements, disclaimers, etc.) as consistent with NIH policy.

Types of BMT CTN papers include, but are not limited to:

- Primary report of data
- Report of protocol-defined ancillary studies
- Report of protocol-independent analyses from one or more studies
- Report of secondary analyses/Report of technical or administrative committee issues or analyses
- Presentations or abstracts

8.1.1. Oral Presentations Related to BMT CTN Studies

Oral presentations to local groups, which are limited to the design or rationale of the BMT CTN sponsored protocols, are exempt from the review policy described below. Material will not be recorded, published, or re-presented without Publications Committee approval.

8.1.2. Press Release Requirements

Press releases relating to any BMT CTN-led study activity, including but not limited to study activation, first patient enrollment, and study results, must be approved by the BMT CTN DCC leadership team (MCW, NMDP and Emmes Principal Investigators or their designees) and NIH. The approval process may take up to ten business days. The DCC will provide "About The BMT CTN" boilerplate language which must be included in the press release.

8.2. The Role of the Publications Committee

The Publications Committee is responsible for developing publication and presentation policies. All policies must be approved by the Steering Committee before implementation.

The Publications Committee reviews all proposed publications and presentations to assess scientific rigor and relevance to the BMT CTN mission. This review process ensures protection of proprietary information and study participant confidentiality and assesses the public impact of publication and/or presentation.

No participating institution, BMT CTN Technical Committee, Protocol Team or other individual may present or publish individual findings from work performed on study protocols or work related to BMT CTN meetings and conference calls without review of the Publications Committee,

NHLBI and NCI. This includes methodologic or position papers related to BMT CTN protocol development or operations.

8.2.1. Membership

Members are identified from a slate of candidates put forth by the Nominating Committee. The Steering Committee approves these selected individuals. At least one member should represent an Affiliate Center.

8.2.2. Amendments to Publication/Presentation Committee Guidelines

Changes to the review policies will be subject to review, amendment and approval by the Steering Committee.

8.2.3. Conflict of Interest

In the event a member of the BMT CTN Publications Committee is asked to review a manuscript, publication or presentation in which he/she is listed as an author, they should recuse him/herself from adjudicating the document.

If both the BMT CTN Publications Committee Chairs are included in the author list, they will take responsibility for re-assigning an Interim-Chair to review the manuscript, publication or presentation.

If more than three members of the Publications Committee are included in the author list, the Publications Committee Chairs will be responsible for assigning ad-hoc reviewers to review the manuscript, publication or presentation.

8.3. Review Timeline

Abstracts, presentations, and proposed publications relating to data obtained from BMT CTN protocols or to activities of BMT CTN Committees or Protocol Teams are to be submitted to the DCC Publications Committee Liaison. The Liaison will distribute abstracts, presentations and proposed publications to the Publications Committee for review. The Committee will have five (5) business days to make recommendations to the Corresponding Author concerning abstracts and presentations and ten (10) business days to make recommendations to the Corresponding Author concerning publications. If an expedited review is necessary, the Chairs may determine their review will suffice.

If Publication Committee members have concerns about the submitted materials and/or appropriateness of data, the Committee submits questions and/or recommendations within five days to the Liaison to forward to the Corresponding/Senior Author for resolution. The Committee, at its discretion, may choose to submit questions and/or recommendations to the Steering Committee for resolution if they determine that Steering Committee involvement is required. The Steering Committee is required to provide any responses to the Committee within ten (10) business days.

8.4. Primary Results Manuscript

Manuscripts reporting the results of each BMT CTN trial or BMT CTN methodologic or position papers are prepared and submitted in a timely manner. No clinical trial results are released, presented or published without review from the Publications Committee, NHLBI and NCI.

8.4.1. Data Analysis

The statistical analysis of trial data is performed by the DCC. Final decisions about patient outcomes and endpoints are the responsibility of the protocol team and/or Endpoint Review Committee and are documented in the Statistical Analysis Plan (SAP), if different from the protocol. Upon completion of the statistical analysis, the DCC issues the Data Analysis Report of the study. In general, the Data Analysis Report is available within two months of locking the trial dataset. The Protocol Chair(s) will monitor progress toward completion of the Data Analysis Report. The Protocol Chair(s) may ask the BMT CTN Steering Committee Chair to assist with addressing delays in the completion of the Data Analysis Report.

8.4.2. Writing Responsibilities

Completion of the primary study manuscript is the responsibility of the Protocol Chair(s) or designee(s). The first draft manuscript is completed within three (3) months of receiving the Data Analysis Report and necessary supplemental analyses. Co-authors shall have access to the study Data Analysis Report and shall be afforded ample opportunity to contribute to completion of the manuscript.

If the Protocol Chair(s) or designee is unable to complete the first-draft manuscript in a timely fashion, the DCC has the responsibility to address the delay. If necessary, the DCC Principal Investigator may ask the BMT CTN Steering Committee Chair to re-assign first-draft responsibility to another author who will become the Lead Author on the manuscript.

Upon completion, the Lead Author distributes the first draft manuscript to all co-authors. Author comments are used to generate subsequent drafts and the final manuscript. Authors should settle differences in interpretation by discussion and consensus whenever possible. If consensus cannot be achieved, the decision is made by majority vote. If necessary, the BMT CTN Steering Committee will adjudicate. In general, the time from completion of the first draft manuscript to the final manuscript submission should not exceed four (4) months.

8.4.3. Timelines

To ensure timely publication of study results, the timelines below should be followed:

- Dataset closure to Data Analysis Report – two (2) months
- Data Analysis Report to first draft manuscript – three (3) months
- First draft manuscript to submission –four (4) months

8.5. Secondary Manuscripts

Manuscripts arising from the study outside the primary trial endpoints are considered secondary manuscripts. These include:

- Reports of analyses of secondary or exploratory endpoints pre-specified in a protocol
- Reports of ancillary or correlative studies defined in the primary trial protocol
- Secondary analyses of one or more BMT CTN trials
- Independent ancillary studies not pre-specified in the primary trial protocol
- Methodological papers
- Position papers
- Other technical reports

For secondary analyses included in the protocol, the protocol team should develop a publication plan and establish authors for each paper using authorship guidelines below. All manuscripts must follow the same review process as a primary results manuscript as detailed in Section 8.4.

8.6. Manuscript Requirements

All manuscripts of the BMT CTN are subject to the following requirements:

- Titles
  - The manuscript title should include the words "Blood and Marrow Transplant Clinical Trials Network," if permitted by the Journal.
  - If not permitted in the title, manuscript text should include language such as "…. submitted on behalf of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)." The Methods section is the preferred section for this reference.
- Acknowledgments
  - General
    Other investigators not part of the authorship list but who have made significant contribution to the conduct of the study, as well as staff members from a Clinical Center, DCC or NIH, are noted. Each primary study manuscript must include a listing of all participating clinical centers and the responsible study physician at that center.
  - Government Sponsors
    Each manuscript must acknowledge all NIH funding sources for the study, including in every instance, funding from NHLBI and NCI to the DCC and the participating Clinical Centers using the following language: "The Blood and Marrow Transplant Clinical Trials Network is supported in part by grant #U10HL069294 and U24HL138660 from the National Heart, Lung, and Blood Institute and the National Cancer Institute."
  - Other Networks/Cooperative Group involvement
    - Manuscripts for BMT CTN-led studies involving collaboration with other Networks or Groups must acknowledge the Network/Group as specified by the Primary Network/Group Investigator and Publications Committee Contact involved with the study.
    - Manuscripts for studies endorsed by the BMT CTN but led by other Networks or Groups must acknowledge the BMT CTN appropriately. The DCC Business Representative will inform the Primary Network/Group Representative and Investigator of the procedure for publication review and acknowledgments. A final draft of the manuscript must be submitted to the BMT CTN Lead Author (see

below) and DCC Business Representative before submission to ensure appropriate acknowledgement is made.

- Non-government Support
  The Contributors must be acknowledged in concordance with the active Memorandum of Agreement (MOA). Generally, contributors are provided a draft copy of all publications and allowed at least thirty (30) days to review the information and provide comments as detailed in the MOA.

- The DCC Business Representative reviews materials in advance to confirm that contributors are accurately acknowledged
- Protocol-specific and Cooperative Group Publication Instructions are located on the BMT CTN public website: https://bmtctn.net/author-resources.

8.6.1. Approvals and Submission

- The First or Last Author are responsible for submission of the final manuscript and for obtaining written approvals from all authors as well as the representatives of the DCC, NHLBI and NCI. The DCC requires that First/Corresponding Authors complete internal abstract and manuscript review checklists for this purpose prior to submission of materials to assure that all required approvals are obtained and that contributors and/or sponsors are acknowledged accurately. These checklists are available on the BMT CTN public website: https://bmtctn.net/author-resources. In addition, the BMT CTN Lead or Corresponding Author will conduct final review of the manuscript to ensure accurate and complete acknowledgments. They will also keep co-authors informed of any revisions, replies to reviewer feedback, and re-submissions. For BMT CTN studies, the BMT CTN Lead Author is the First Author; for cooperative group led studies, the BMT CTN Lead Author will be assigned and may not be the First Author.

  The Lead Author is responsible for obtaining approval from all co-authors. In addition, the Lead Author should send all submission materials to the DCC for circulation to the following people 30 days prior to the planned manuscript submission (7 days for presentations/abstracts):

  - DCC co-PIs
  - Publications Committee
  - DCC Business Representative
  - NHLBI/NCI Program Officers
  - Primary Network/Cooperative Group and Publications Committee Contact representative, if applicable
  - Contributors, if applicable

- The Corresponding Author should ensure that each author and the DCC, NHLBI and NCI representatives receives a final copy of the submitted manuscript, abstract or presentation.

Review, correction and return of galley proofs are the joint responsibility of the Lead and Senior Authors and the Protocol Statistician. For collaborative studies led by the BMT CTN, the Primary Network/ NCTN Group and Publications Committee Contact representative should also review the galley proofs. For NCTN Group led studies, the BMT CTN Lead Author will provide BMT CTN acknowledgment requirements to the First Author and review the final manuscript proof, or

any deviations from the BMT CTN acknowledgment requirements, prior to manuscript submission. The final manuscript proof must also be provided to the DCC leadership team.

8.7. Authorship Guidelines

Authorship guidelines are based on fairness, inclusion and degrees of participation and compliance. Authorship recognizes a consistent focus on intellectual input and effort extended during the lifecycle of the trial. The Publications Committee is responsible for the development and modification of guidelines for determining authorship. Authorship guidelines are ratified by the Steering Committee prior to implementation.

Authorship on BMT CTN publications is a privilege commensurate with both personal and center contribution to the research being presented and the Network as a whole. The primary requirement for authorship of a BMT CTN publication is a substantive contribution to the research effort and is a recognition for many aspects of contribution including: (1) membership and active participation in the Protocol Team; (2) active accrual to the protocol; (3) timely and accurate reporting of data; and, (4) active participation in relevant Steering Committee activities. These activities may include participation in the following areas: hypothesis generation, concept development, protocol development, study implementation, subject enrollment, data collection, data analysis, and manuscript preparation and finalization. In most instances, contributions in several areas must occur, and in every instance, authors are expected to contribute to manuscript preparation and finalization.

The fundamental premise of authorship designation is the recognition of overall effort. First and senior authorship positions on manuscripts should be broadly shared among Protocol Team members. First and senior authorship on the primary paper does not imply the same position on any subsequent manuscripts resulting from the same completed protocol or related ancillary studies.

8.7.1. Authorship Eligibility Requirements

Each member of the Protocol Team has eligibility for authorship on the final primary manuscript from the study. In addition, each Clinical Center Principal Investigator whose center enrolls at least one subject in the study is eligible for authorship. Additional authors may be invited at the discretion of the Protocol Chair(s), in consultation with the Protocol Team, with approval of the Publications Committee Chairs or full Committee, if needed. Eligibility for authorship does not guarantee authorship. Eligible authors must still make substantive contributions, including careful review and contributions to the draft manuscript.

8.7.2. Establishing the Order of Authorship for Primary Results Manuscript

For each manuscript, the Protocol Chair(s) and Protocol Officer will recommend the co-authors and the order of authorship based on the Administrative MOP parameters. Any potential additional authors proposed outside the scope of the Administrative MOP should be reviewed and approved by the Publications Committee with documented reasoning. The Protocol Officer will also assess Protocol Chair authorship order based on accrual and participation metrics posted on the public website and get approval/adjudication from the Executive or Publications Committee if needed. If there are multiple Protocol Chairs, two Chairs may share first or last authorship, provided they meet the below requirements and the journal allows this practice. Authorship order may differ for

manuscripts and abstracts. The Publications Committee will adjudicate any disputes, approve any requests for exceptions for special circumstances, and may also recommend additional authors after review of accrual tables and based on justifiable, well-documented reasoning.

Approved requirements for author order are as follows.

- SENIOR (last) AUTHOR REQUIREMENTS
    - Protocol Co-Chair [for primary results manuscripts]
    - Attended majority of Protocol Team Calls
    - Author's center actively participated in the trial
    - Author's center showed commendable protocol compliance and data submission
- FIRST AUTHOR REQUIREMENTS
    - Same as above Writes the first draft of the manuscript
- AUTHORSHIP BASED ON PROTOCOL TEAM AND ENDPOINT REVIEW COMMITTEE (ERC) PARTICIPATION
    - The second and third authors should be the Protocol Officer or Primary DCC PhD Statistician. In special circumstances protocol team/ERC members may be selected as second and/or third authors for exceptional contributions (other than accrual). The order will be determined by the Protocol Chairs and will be reviewed and approved by the Publications Committee.
    - Each Protocol Team/ERC member will be an author, in order of accrual, if the following criteria are met:
        - Attended the majority of Protocol Team/ERC calls
        - Author's center actively participated in the trial
        - Author's center had satisfactory protocol compliance and data submission
    - If a center has more than one member represented on the Protocol Team/ERC, only one member is eligible to be an author under this criterion. The other Protocol Team member(s) may be eligible for authorship if they meet any of the additional authorship criteria.
- AUTHORSHIP BASED ON CENTER PARTICIPATION IN ORDER OF ACCRUAL
    - The top ten accruing centers will have a single author in order of accrual, and with meaningful contributions, the top two accruing Affiliate Centers. If the study involves international centers, the top five U.S. and top five international centers will each have a single author. In addition, if there are U.S. centers with significantly greater accrual than the highest accruing international centers, up to three U.S. centers will have an author included. If not included in this list, a single author from the center with the highest accrual from groups underrepresented in medicine will be invited.
    - If the First or Last Author is from one of these centers, a Second Author from that center may be added
    - Author identity should generally be the site PI, unless that person is an author based on other criteria, in which case the identify is determined by center PI
    - Author's center must have also had satisfactory protocol compliance and data submission

- BMT CTN PUBLICATIONS LIST ALL CENTERS THAT PARTICIPATED
    - Any center that has enrolled at least one patient will be acknowledged in the publication
- CONSIDERATIONS FOR ADDITIONAL AUTHORS
    - A physician can be named in acknowledgement of overall effort, exceptional accrual and/or supportive input throughout the lifecycle of the study
    - An additional author from a same center mentioned above can be named if he/she has shown exceptional accrual or intellectual input. These can be non-physicians, e.g.:
        - Nurses and advanced practice providers
        - Study coordinators
        - Pharmacists
- SPECIAL CONSIDERATIONS FOR TRIALS OF RARE DISEASES

  The BMT CTN acknowledges that some indications for transplantation are sufficiently rare that many centers must be activated, with the likelihood that some will not accrue any or many patients. Possibility of authorship is a good incentive for participation in trials that may be difficult to open and hard to maintain. In trials designated by the Executive Committee as Rare Disease trials, the PI at each center that activates the study is eligible for authorship if they provide input to data review, analysis and/or manuscript preparation.
- IF THE JOURNAL OR ABSTRACT GUIDELINES LIMIT THE NUMBER OF AUTHORS, AUTHORS WILL BE DELETED IN THE FOLLOWING ORDER:
    - Remove Protocol Team members and top accruing centers in reverse order of center accrual
    - Remove Secondary Statistician
    - Minimum author assignments will be First, Last, Protocol Officer and Primary Statistician

8.7.3. Establishing the Order of Authorship for Secondary Results or Ancillary Study Manuscripts

Secondary results manuscripts will follow similar authorship guidelines as described for primary results manuscripts. However, special recognition is given to those who were not considered for First and Senior Authors on the primary paper. Consideration as added co-authors is extended to other Protocol Team members such as DCC members, clinical research coordinators and Early-Stage Protocol Team members, especially those from centers with good accrual rates.

Protocol Chairs and Officers will assign, as soon as is feasible, writing committees for secondary results manuscripts. They should offer the opportunity to lead these analyses to site PIs, with a focus on early and mid-career investigators. Proposals for secondary results manuscripts will be reviewed by the Protocol Team and authorship appropriately assigned.

For secondary analyses or ancillary studies conducted outside the purview of a Protocol Team that is actively still meeting, the protocol team should be invited to participate and given the opportunity to be co-authors on the manuscript. For secondary analyses or ancillary studies conducted outside the purview of a Protocol Team that is no longer actively meeting, the Protocol

Chairs of the parent study should be invited to participate and given the opportunity to be co-authors on the manuscript for studies that are conducted within five years of publication of the primary results manuscript. In either case, authorship consideration should also be given to investigators from the highest accruing centers and/or centers that provided a significant proportion of biospecimens, if applicable. An exception to this policy is if the ancillary study uses biorepository specimens and/or clinical data from multiple studies and the analysis is not related to the parent study's specific design.

8.7.4. Removing Authors

An author may not be invited or may be removed from the final manuscript upon failure to make substantive contributions to the overall project. The Lead Author may request that another author withdraw from authorship. The Publications Committee Chairs, or at the Chairs' discretion, the Publications Committee shall adjudicate authorship disputes by simple majority rule. If an author is removed, another eligible author may be added.

8.7.5. Authorship on Joint Studies

These studies primarily involve the NCI NCTN Groups. The BMT CTN Steering Committee supports the approach that the two study chairs representing the collaborating groups hold the first and last author positions at the time of manuscript preparation; this should be decided in advance by the Protocol Team.

8.8. Abstracts, Public Presentations, Electronic Postings

8.8.1. General

Abstracts, public presentations of study data and electronic postings of study data generally follow the same processes outlined for primary publications as noted above but may not include all authors included in the final manuscript.

8.8.2. Abstracts

Abstracts focusing on study results should only be submitted to one meeting unless there are additional results to present or another cogent reason to re-present the results. If submitting the same abstract to a subsequent meeting, the authors must provide justification to the Publications Committee and BMT CTN DCC leadership. An exception is Trials in Progress abstracts, which may be submitted to multiple meetings.

All abstract authors must have made substantive contributions to the study. Acknowledgments of funding sources are not required in the abstract text but must be included in the presentation slides or poster materials, if the abstract is accepted. The BMT CTN PowerPoint or poster template must be used when presenting oral or poster abstracts of BMT CTN-led studies.

The first or last author is responsible for submitting the abstract. Proposals for abstract submissions should be initiated well in advance of the abstract submission deadline. The Publications

Committee prioritizes their review process in the following way: peer-reviewed publications receive higher priority than abstracts, public presentations, and electronic postings.

8.8.3. Public Presentations and Electronic Postings of Study Data

In general, a complete set of summary slides is prepared by the Lead and Senior Author and Protocol Statistician upon completion and analysis of each BMT CTN study. Individual investigators who wish to prepare additional slides for public presentation must utilize data from the final Data Analysis Report. Such presentations must also be submitted to the DCC for submission to the Publications Committee Chairs, their designee, or at the Chairs' discretion, the entire Committee, for review and approval. Each such presentation must also acknowledge the authors, funding agencies, contributors and the participating Core and Affiliate Centers. Electronic posting of study data must not occur prior to publication of the study's primary manuscript in a peer-reviewed journal.

CHAPTER 9

CLINICAL CENTER PROCEDURES

9. CLINICAL CENTER PROCEDURES

Each BMT CTN Clinical Center is staffed, at a minimum, by a Principal Investigator (PI) and a Clinical Research Associate (CRA) or Clinical Research Coordinator (CRC). There may be additional physicians designated as co-investigators, as well as other administrative and research-related personnel.

9.1. Functions of the Principal Investigator

The responsibilities of the PI, who is a physician with substantial experience in both HCT and the performance of clinical trials, are to:

- Direct the activities of BMT CTN personnel at the Clinical Center
- Coordinate the scientific and administrative operations of the Clinical Center
- Oversee data integrity and participate in quality assurance measures such as initiation, data audit and close-out site visits
- Ensure adherence by Clinical Center personnel to the procedures described in and required by BMT CTN Protocols, protocol-specific SOPs if appropriate, and the BMT CTN MOPs
- Spend sufficient time in the Clinical Center to adequately observe study procedures
- Assure the Clinical Center's fiscal responsibility in the disposition of BMT CTN funds
- Prepare budgets and annual reports
- Obtain Local IRB approval for BMT CTN Protocols, Consent and Assent (if applicable) Forms and study participant materials; or obtain NMDP IRB approval for Consent and Assent (if applicable) Forms.
- Ensure that unexpected Grade 3-5 adverse events are reported in an expedited manner
- Ensure that any expected adverse events that require expedited reporting based on the reporting requirements outlined in the protocol be reported in an expedited manner
- Review and address concerns related to Core Center Performance Reports

9.2. Function of Lead Investigator

The PI may designate a Lead Investigator at his or her center for any BMT CTN protocol. The responsibilities of the Lead Investigator, who is a physician with substantial experience in both HCT and the performance of clinical trials, are to:

- Oversee daily conduct and progress of the study
- Interact with the CRCs to ascertain any implementation difficulties including enrollment, data submission, laboratory procedures, etc.
- Oversee data and participate in quality assurance measures such as initiation and data audit site visits
- Spend sufficient time in the Clinical Center to adequately observe study procedures
- Ensure compliance with BMT CTN Protocols, protocol-specific SOPs if appropriate and the BMT CTN MOPs
- Communicate with the PI and alert the DCC of any issues regarding protocol implementation, compliance or emergent issues relating to subject safety

9.3. Functions of the Clinical Research Associate/ Clinical Research Coordinator

The CRA/CRC is responsible for supervising daily operations in the Clinical Center and serves as primary contact for the study participants as well as for the DCC. The duties of the CRA/CRC are to:

- Ensure that potential BMT CTN study participants receive appropriate information about the study, including the Informed Consent documents
- Register study participants in the BMT CTN using AdvantageEDC^{SM} (Electronic Data Capture) or Advantage eClinical data capture system
- Ensure that all active research study participants have signed and dated the most current IRB approved Informed Consent
- Schedule participant appointments
- Ensure regulatory compliance
- Handle communications with the DCC regarding participant enrollment, data entry, missing forms, missing values, data anomalies, field discrepancies and data queries
- Notify the DCC as well as the IRB of record if appropriate within 24 hours of a Grade 3-5 Adverse Event
- Notify the DCC as well as the IRB of record if appropriate any expected adverse events that require expedited reporting based on the reporting requirements outlined in the protocol be reported in an expedited manner
- Notify the DCC of changes or impending changes in the Clinical Center personnel, and any changes of address and/or telephone number(s) of the Clinical Center
- Maintain a file of correspondence with the DCC
- Maintain a current transplant center roster of personnel addresses, telephone and fax numbers, e-mail addresses and notify DCC of changes as they occur
- Obtain necessary information about deceased study participants (e.g., death certificates, autopsy reports)
- Ensure compliance with the BMT CTN MOPs, BMT CTN protocols, protocol-specific SOPs if any and Numbered Memorandum
- Ensure the site has the most recently amended and IRB-approved version of BMT CTN protocols
- Check data forms for accuracy and completeness
- Ensure that study participant names, initials, dates of birth, addresses, phone numbers, social security numbers, and any other personal identifiers are removed from all materials sent to the DCC or attached to CRFs in AdvantageEDC or Advantage eClinical
- Submit complete data to the DCC in a timely manner in compliance with the BMT CTN AdvantageEDC User's Guide, eClinical User's Guide and protocol-specific Forms Guides
- Respond to data queries from the DCC in a timely manner
- Ensure compliance with laboratory procedures
- Register patients with the CIBMTR by obtaining a CIBMTR Research ID for all patients
- Develop a training system to ensure that personnel performing BMT CTN procedures are properly trained and certified in AdvantageEDC, Advantage eClinical, and GlobalTrace, participate in scheduled conference calls with the Protocol Coordinator(s) and/or CRAs and secure access to the BMT CTN private website

- Meet with the Protocol Coordinator and/or DCC CRA during site visits at the Clinical Center
- Report irregularities or emergent problems that can affect the data quality to the PI and the Protocol Coordinator
- Perform other duties as defined by the Steering Committee or Technical Subcommittees

Each CRA/CRC will be given access to the AdvantageEDC User's Guide, eClinical User's Guide and protocol-specific Forms Guides to aid in completing data forms. Additionally, many protocol-specific items are distributed to the CRAs/CRCs including the protocol-specific Laboratory Sample Information Guide, Study Drug Manual etc. Materials may be stored electronically or in paper files.

9.4. Site Activation

Clinical Centers must be activated for enrollment by the DCC for each protocol. A protocol-specific checklist of required items for activation is distributed to Clinical Centers after the protocol has been released. The checklists typically include most of the following items:

- Lab normal values
- Most recent FACT, CAP and CLIA certifications
- FWA number
- Form FDA 1572 or Investigator Agreement
  The DCC recommends carefully reviewing FDA guidance so that only staff members making direct and significant contributions to the clinical study data are included on the study's Form FDA 1572 or Investigator Agreement and Delegation of Authority Log (see Numbered Memo CTN-177 for guidance)
- Roster for protocol personnel
- Delegation of Authority Log
- CV, Financial Disclosure and Professional License of select personnel
- Local IRB approval letter, if applicable
- DCC-approved institutional consent and assent (if applicable) documents prior to submission to Local or NMDP IRB
- Local or NMDP IRB approved institutional consent and assent (if applicable) documents
- AdvantageEDC, Advantage eClinical, and GlobalTrace online training attendance and completion of EDC practicum and GlobalTrace quiz by at least one coordinator
- Human Subjects Protection (HSP) training documentation for protocol personnel
- Good Clinical Practices (GCP) training consistent with principles of the International Conference on Harmonisation E6 (R2) for protocol personnel
- Signed Clinical Study Protocol Rider
- Clinical Site Contact Form for Central Pharmacies and/or Laboratories
- Pre-study site initiation conference call or visit; scheduled once the Clinical Study Protocol Rider is executed and informed consent documents are submitted to the NMDP IRB, unless otherwise specified by the DCC

Regulatory documents are required to be submitted (including training documentation) for these personnel prior to site activation:

- PI
- 60% of subinvestigators
- Primary site coordinator
- Pharmacist, if applicable to study
- Other required protocol-specific site personnel, as deemed necessary

Upon review and approval of these and protocol-specific items, if any, by the DCC, a site activation memo will be sent via e-mail to the study staff at the transplant center. This memo will contain information on accessing the study database, enrolling patients, and obtaining study-related materials. The memo will specify which specific personnel are activated.

9.4.1. Change in PI or Study Staff

If the site plans to add or replace the PI or other study staff after site activation, the Protocol Coordinator must be informed prior to the start date of the new staff member. For a PI change, the Protocol Coordinator should be notified at least 30 days prior to the change. Protocol Chairs' approval is required for any proposed PI change. The Protocol Coordinator will provide the list of items that need to be submitted, including updated Delegation of Authority Log and documentation of the staff member's GCP/ICH E6(R2) and Human Subjects Protection (HSP) trainings.

Additionally, if there is a new PI assigned to the study, they must submit documents including FDA Form 1572 or Investigator Agreement (as applicable), submission and approval from the IRB of record, and updated consent documents, CV, medical license, GCP and HSP training documents and protocol-specific training, protocol, and Investigator Brochure signature page (as applicable) and Financial Disclosure Form (if applicable). The PI should also communicate with the Protocol Coordinator to determine if any contracting changes are required. Once all required approvals and completed documents are in place, the Protocol Coordinator, or delegate, will issue written documentation to the site indicating review is complete and the site is approved to move forward with the change in PI. Failure to follow the process outlined above before a change in PI occurs can result in the participating center being put on hold until all required approvals and documents are obtained.

9.5. Recruitment

A recruitment goal will be established for each Clinical Center for every BMT CTN protocol. Each center will develop a plan in order to achieve this goal. The sites will track study candidates along with each study participant after enrollment. Each center should review this plan periodically throughout recruitment in order to determine the effectiveness of the plan. The plan must outline methods to identify and enroll minorities, women and children (if appropriate) , in strict adherence to NIH and DHHS policies. If the site is not achieving its recruitment goal in a timely fashion, the plan will be discussed with the DCC and modified.

Each Clinical Center must register study participants through the CIBMTR using the CIBMTR Research ID Assignment Form, which will be used to track both transplants and eligible transplant candidates to assist in meeting the recruitment goals and requirements of the BMT CTN.

Additionally, systematic evaluation of study participants transplanted or treated off protocol will identify potential barriers to accrual and possible protocol modifications to enhance accrual. Particular attention will be paid to differential enrollment rates for minorities, women and children.

9.6. Eligibility Screening

If a study participant appears to be eligible for a BMT CTN protocol, the following steps should be taken:

- The plan of the study should be reviewed with the potential study participant and any questions posed by the study participant should be answered completely
- Upon decision to participate in the study, the study participant must sign the Informed Consent form document *prior to enrollment and study specific procedures.* Remote consent sessions are acceptable as allowed by the study protocol and NMDP Single IRB policy.

Once a study participant has been assigned a registration number, the number remains associated with the study participant and will not be reassigned.

9.7. Scheduling Study Participant Appointments

When scheduling appointments, the various time windows must be kept in mind. Efforts should be made to avoid missed visits and to keep scheduled visits as close to the target date as possible.

In the event that a study participant is moving to an area that is not near the Clinical Center, staff should encourage the study participant to return to the Clinical Center for their scheduled or follow up visits. If a study participant is not planning to return to the Clinical Center for a follow-up visit, the CRC should make arrangements to obtain the necessary information through the study participant's primary physician. In addition, the center can make arrangements with the DCC to transfer the participation to another participating center that has IRB approval for the study (see section below). The DCC supports the center in all efforts to collect data in this situation. Upon transfer, the participant will need to sign the study consent at the destination center.

9.8. Preventing Dropouts and Missed Contacts

A primary objective of each protocol is to study the clinical course of study participants receiving protocol treatments and medications. To achieve this objective, it is essential that each patient be examined regularly at follow-up visits until the study is completed or until the patient expires. Missing information can bias the results of the study. Although occasional missed visits cannot be prevented, the study results could be invalid if there are many missed visits, numerous patient drop-outs, and/or missed specimen draws. When data are incomplete, it is difficult to predict the direction of any bias resulting from the incompleteness. The only correct way to deal with missing information is not to have any. Preventing dropouts and missed visits is a responsibility shared by the entire site staff.

Prior to registering a patient, a line of communication should be established between the site and the patient's primary care physician. The need for long-term follow-up and data collection should be explained and understood by the primary care physician.

9.9. Checking Completed Forms

Before submitting data to the DCC, the CRA/CRC should carefully check all data for completeness and consistency. The CRA/CRC must also ensure that study participant names, initials, dates of birth, phone numbers, addresses, social security numbers, and any other personal identifiers are

removed from all materials sent to the DCC or attached to CRFs in AdvantageEDC or Advantage eClinical.

Completeness and consistency: Every effort should be made to complete every field on each data form. Exception requests made be submitted for fields in which the data point will never be available at the center. Each form will be thoroughly reviewed at the DCC. Incomplete and inconsistent items will be queried by the DCC, and clarification requested.

Numerical values: Numerical values such as hematologic data have expected ranges defined in AdvantageEDC or Advantage eClinical. If a value is outside the expected range, then a message is displayed to the user at the time of data entry. This type of message is not necessarily evidence of an error, but simply a request to verify that the number is correct.

9.10. Transferring Study Participants

All follow-up reporting requirements of BMT CTN study participants are the responsibility of the Clinical Center that initially registers the study participant. In the event of study participant transfer, it is the responsibility of the CRA/CRC at the originating center to initiate communication with the destination center. A study participant may be transferred from the originating center to another center only if the destination center has the study IRB-approved. In addition, all missing forms and data discrepancies must be resolved. Copies of study participant charts, forms and BMT CTN information will not be forwarded to the destination center until the DCC receives confirmation of study participant transfer. The study participant must sign the destination's center IRB approved consent prior to undergoing any study specific assessments or procedures. After confirmation of the study participant transfer, data reporting requirements of transferred BMT CTN study participants become the responsibility of destination Clinical Center staff.

9.11. Review of Co-Enrollment Requests

BMT CTN encourages co-enrollment of research subjects in complementary studies if co-enrollment does not confound the analysis of individual study endpoints. The following considerations are provided to guide centers in decisions about co-enrollment:

- Differential enrollment must be avoided. That is, a secondary study where the intervention depends upon the randomization assignment of the primary study is not allowed.
- The DCC requests that the center submits a Trial Co-enrollment Form, the ClinicalTrials.gov NCT Number or study synopsis to the Protocol Coordinator at for each study where co-enrollment is contemplated.
    - The Protocol Coordinator will forward the information to the appropriate parties as determined by the protocol team and/or project plan.
    - Decisions will normally be provided within one to three business days and, unless otherwise indicated, would apply to all subsequent study candidates.
- The center should check the BMT CTN private website for co-enrollment requests submitted by other centers prior to submitting a Trial Co-enrollment Form or study synopsis. They are posted by protocol subweb in the "Co-enrollment" Folder under the Protocol Supporting Documents block

The Protocol Officer will review co-enrollment requests and will decide if the co-enrollment request is approved or not. A major consideration for approval is if the co-enrollment doesn't interfere with study endpoint analysis. If the Protocol Officer denies the request, the site will be informed. If the Protocol Officer approves the request, at least one Protocol Chair must also approve it.

If the Protocol Officer is unable to review the co-enrollment request, then the co-enrollment request will be sent to the Protocol Chairs. At least two Protocol Chairs must agree on the decision. In the event of a disagreement between the two Protocol Chairs, the co-enrollment request will be sent to the DCC PI/Co-PIs for final decision. The DCC will document the decision and notify the center of the final decision of the study leadership. The Protocol Officer and Chairs may not approve a co-enrollment request for their own patient.

In the case of enrollment of a BMT CTN study participant in a clinical trial for a **life-threatening condition that is deemed necessary for the safety of the BMT CTN study participant**, e.g., a COVID treatment trial for a subject on a ventilator, prior approval is not required. However, submission of a "BMT CTN Co-enrollment Notification/Request Form" is requested for tracking purposes.

CHAPTER 10

SHIPPING INSTRUCTIONS

10. BMT CTN SHIPPING INSTRUCTIONS USING FEDERAL EXPRESS

Samples are collected and shipped to repositories and central reference laboratories for many of the BMT CTN protocols. Protocol-specific Research Sample Information Guides are developed for each protocol that requires the collection and shipment of samples to a repository or central reference laboratory. These guides outline the procedure for collecting, processing, labeling, packaging, and shipping samples. The guides are posted on the BMT CTN private website.

Unless noted otherwise in the protocol-specific Research Sample Information Guide, all samples will be shipped via Federal Express (FedEx). The FedEx account number and BMT CTN protocol identifier (FedEx billing reference) will be provided to participating transplant centers to cover the cost of the shipment. The account number and reference code are listed in the protocol-specific Research Sample Information Guide. The account numbers may only be used for the shipment of samples to the protocol-designated repository or central reference laboratory. Unauthorized use of the account numbers is prohibited. Centers using the account numbers acknowledge that any unauthorized use will be subject to reimbursement.

10.1. Specimen Packaging Guidelines for BMT CTN Project

Specimen packaging and shipping guidelines are outlined in each protocol-specific Research Sample Information Guide. All specimens will be shipped in accordance with IATA regulations. See the IATA Dangerous Goods Regulations (59th edition, 2018) for detailed requirements.

Note: the requirements may change annually.

- IATA packaging 650 – Biological Substance Category B
- IATA 620 - Infectious Substance, affecting Humans
- IATA 202 – Liquid Nitrogen
- IATA 954 – Dry Ice
- IATA section 5 – Packing
- IATA section 6 Packaging Specifications and Performance Tests
- IATA Section 7 – Markings and Labeling
- IATA Section 8 – Documentation (Shippers Declaration)

The shipper (BMT CTN clinical sites) is responsible for ensuring that packages meet all the Regulations

- **Training Requirements** are defined in Section 1.5 of IATA Dangerous Goods Regulations and must be provided to staff who package specimens for transport.

The following guidelines are generic. Packaging styles may vary depending on the vendor providing the packaging or the commercial shipper used.

Specimen Types

Infectious substances are substances which are known or are reasonably expected to contain pathogens. Infectious substances are divided into the following categories:

A. **Category A:** An infectious substance which is transported in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threating or fatal disease in

otherwise healthy humans or animals. Refer to IATA Regulations for list of organisms, mostly cultures. These infectious substances must be assigned to UN 2814. The proper shipping name is **Infectious Substance, affecting humans**.

B. **Category B:** An infectious substance which does not meet the criteria for inclusion in Category A. Infectious substances in Category B must be assigned to UN 3373. The proper shipping name is **Biological Substance Category B**.

C. **Exemptions**

- Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.
- Dried blood spots, collected by applying a drop of blood onto absorbent material, are not subject to these Regulations.
- Patient specimens for which there is minimal likelihood that pathogens are present are not subject to these Regulations if the specimen is packed in a packaging which will prevent leakage, and which is marked with the words **Exempt human specimen.**

Packaging for Shipment		
Exempt Human Specimen	**Biological Substance, Category B (IATA 650)**	**Infectious Substance, affecting Humans (IATA 620)**
Routine blood samples that have no indication on medical history or suspicion from physical appearance that the donor would be positive for a pathogen. Examples: routine DR, CT, HR, Work-up, IDM Screening, research, etc.	Samples where there is knowledge of or suspicion of a pathogen. Examples: Samples being shipped for confirmatory testing from an IDM reactive screen, knowledge of an infectious disease from health history or confirmed positive test. Positive CMV result is not included.	Infectious substance which is capable of causing permanent disability, life-threating or fatal disease in otherwise healthy humans or animals if exposure occurs. Refer to IATA Regulations for list of organisms, mostly cultures.
Specimen Shipment Requirements:	**Specimen Shipment Requirements:**	**Specimen Shipment Requirements:**
1. Leak-proof primary receptacle. Example: plastic blood tube or sealable bio-bags.	1. Leak-proof primary receptacle. Example: plastic blood tube or sealable bio-bags. *	1. Leak-proof primary receptacle. Example: plastic blood tube or sealable bio-bags. *
2. Leak-proof secondary packaging. Example: sealable bio-bag or canister. ***Note:*** **Neither the primary nor the secondary packaging are required to meet the 95 kPa pressure requirements.**	2. Leak-proof secondary packaging. Example: sealable bio-bag or canister.* ***Note:*** **Either the primary or the secondary packaging must meet the 95 kPa pressure requirements.**	2. Leak-proof secondary packaging. Example: sealable bio-bag or canister.* ***Note:*** **Either the primary or the secondary packaging must meet the 95 kPa pressure requirements.**
3. Absorbent materials capable of absorbing the entire contents must be placed between the primary receptacle(s) and the secondary packaging.	3. Absorbent materials capable of absorbing the entire contents must be placed between the primary receptacle(s) and the secondary packaging.	3. Absorbent materials capable of absorbing the entire contents must be placed between the primary receptacle(s) and the secondary packaging.

Packaging for Shipment		
Exempt Human Specimen	**Biological Substance, Category B (IATA 650)**	**Infectious Substance, affecting Humans (IATA 620)**
4. Multiple fragile receptacles (example: glass blood tubes) must be wrapped in cushioning material to prevent breakage. *Note: Bubble wrap or cloth is an example of cushioning material.*	4. Multiple fragile receptacles (example: glass blood tubes) must be wrapped in cushioning material to prevent breakage. *Note: Bubble wrap or cloth is an example of cushioning material.*	4. Multiple fragile receptacles (example: glass blood tubes) must be either individually wrapped in cushioning material to prevent breakage or separated to prevent contact between them. *Note: Bubble wrap or cloth is an example of cushioning material.*
5. No contents list is required.	5. An itemized list of contents must be enclosed between the secondary packaging and the outer packaging.	5. An itemized list of contents must be enclosed between the secondary packaging and the outer packaging.
6. Outer packaging must be of adequate strength for its capacity, mass and intended use. At least one surface must have a minimum dimension of 100 mm x 100 mm (4 inches by 4 inches).	6. A ridged outer packaging must be used. At least one surface must have a minimum dimension of 100 mm x 100 mm (4 inches by 4 inches).	6. A ridged outer packaging must be used. The smallest external dimension must be not less than 100 mm x 100 mm (4 inches by 4 inches).
7. Outer packaging must be labeled with the words: “Exempt human specimen”.	7. Outer packaging must be labeled with the words: “Biological substance, Category B” in letters at least 6mm high (approx. ¼ inch). The UN3373 symbol must appear on the outer packaging adjacent to the wording.	7. Outer packaging must be labeled with the words: “Infectious substance, affecting humans” in letters at least 6mm high (approx. ¼ inch). The UN2814 symbol must appear on the outer packaging adjacent to the wording. An infectious substance hazard label meeting class 6 infectious substance label requirements is needed. Package must be marked durably and legibly on the outside of the package with the name and telephone number of a responsible person.
8. Notify FedEx for proper over pack shipping supplies and instructions for pick up.	8. Notify FedEx for proper over pack shipping supplies and instructions for pick up.	8. Notify FedEx for proper over pack shipping supplies and instructions for pick up.
9. A Shipper Declaration is not required.	9. A Shipper Declaration is not required.	9. A Shipper’s Declaration is required. See Section 8 of the IATA manual for instructions on filling out the Shipper’s Declaration documentation

Packaging for Shipment		
Exempt Human Specimen	**Biological Substance, Category B (IATA 650)**	**Infectious Substance, affecting Humans (IATA 620)**
	10. The package materials must be validated as a whole by the vendor to meet the requirements for strength under the **IATA 650** packaging instructions.	10. The package materials must be validated as a whole by the vendor to meet the requirements for strength under the **IATA 620**packaging instructions.
	11. See specific IATA requirements when shipping with other dangerous goods. Dry Ice see IATA954 Liquid Nitrogen IATA 202.	11. See specific IATA requirements when shipping with other dangerous goods. Dry Ice see IATA954 Liquid Nitrogen IATA 202.
	Note: This category had been called "Diagnostic Specimen" in the past. As of January 1, 2007, the verbiage must be *Biological substance, Category B.* If you require this grade of packaging, please clearly notify the vendor.	12. Packaging must meet requirements of 6.5 and must be marked as required by 6.0.6

<u>Important</u>! The inner packaging material <u>must</u> be compliant with the markings on the outer box. Do not use the Exempt human specimen inner packaging materials with a box labeled Biological substance, Category B even if the sample is actually exempt.

Special Shipping Considerations		
Refrigerated 2 - 8ºC (Frozen cooling packs or wet ice)	1. Place secondary packaging inside the outer box. 2. Place frozen cooling packs or wet ice between the secondary and outer box. 3. Support must also be provided to maintain the position of the secondary packaging as the ice or cooling pack thaw.	It is not recommended to use wet ice. If ice is used, the container for the wet ice <u>MUST</u> be leak proof. The primary and secondary packages must maintain their containment integrity at the temperature of the refrigerant.

Special Shipping Considerations		
Dry Ice **Reference IATA 954 packaging and labeling**	1. Place secondary packaging inside outer box. 2. Place dry ice between secondary packaging and outer box. 3. Support must also be provided to maintain the position of the secondary packaging as the dry ice dissipates.	1. Instructions for UN1845 apply. 2. The primary and secondary packages must maintain their containment integrity at the temperature of the refrigerant as well as pressure integrity if refrigerant is lost. 3. Dry ice when offered for transport by air, must be in packaging designed and constructed to permit the release of carbon dioxide gas and to prevent a build-up of pressure that could rupture the packaging.
	The net weight of the dry ice must be recorded on the outside of the package. 3. Class 9 Dangerous Goods label. 5. Dry ice UN 1845 symbol.	When a Shipper's declaration is not required, the following must be recorded in the "Nature & Quantity of Goods" box of the Air Waybill in the following order: • UN1845 • Proper Shipping Name(Dry Ice or Carbon dioxide, solid) • Class 9 Net quantity of dry ice in each package.
	Contact FedEx for proper shipment and forms.	
Liquid Nitrogen **Reference IATA 202 packaging and labeling** **NOTE:** Insulated packaging containing refrigerated liquid nitrogen fully absorbed in a porous material and intended for transport, at low temperature, of non-dangerous products are not subject to these Regulations provided the design of the insulated packaging would not allow the build-up of pressure within the container and would not permit the release of any refrigerated liquid nitrogen irrespective of the orientation of the insulated packaging. (Dry shippers)	Place secondary packages into appropriate nitrogen shipper.	1. Plastic primary and secondary containers must be capable of withstanding very low temperatures. 2. The primary and secondary packages must maintain their containment integrity at the temperature of the refrigerant as well as pressure integrity if refrigerant is lost.

Special Shipping Considerations		
	The package must be clearly labeled 1. “Do Not Drop-Handle With Care”. 2. Cryogenic Liquids symbol “Class 2 Non-flammable Gas (Division 2.2). 3. UN 1977 4. Upright Package orientation symbol = 7.4.4 or 7.4.5 in IATA manual.	
	Contact FedEx for proper shipment and forms.	

CHAPTER 11

ANCILLARY STUDIES

Management of Contracted Laboratories

Genetics Studies: NIH Data Sharing Considerations

11. ANCILLARY STUDIES

An **ancillary study** aims to investigate questions related to but outside the scope of the parent protocol. An ancillary study could entail the collection of additional data and/or specimens from study participants or the conduct of additional analyses of existing research materials for purposes outside the specific objectives of the primary study. Ancillary studies may also be characterized by:

- Requiring a separate informed consent form or an "opt-in" section in the parent protocol;
- Placing an additional burden on participants;
- Utilizing biospecimens previously collected for unspecified future research;
- Requiring additional data or biospecimen collection during the course of the clinical trial;
- Being funded by a separate funding mechanism or source.

Ancillary studies may be correlative, utilizing both biospecimens and data associated with the primary trial, or involve analysis of data only. Retrospective studies that utilize prospectively collected data from one or more clinical trials which do not require biospecimens are not considered ancillary studies and are discussed in Chapter 12 (Secondary Data Analyses) of this Manual of Procedures (MOP).

11.1. Classification of Ancillary Study Proposals

Ancillary studies are broadly classified as clinical or laboratory depending on whether they involve the collection and/or analysis of biospecimens. Ancillary studies within the BMT CTN are further classified in two categories:

- **Protocol-defined ancillary studies** that are included in the main clinical trial protocol and informed consent but are not essential for assessing the primary endpoint. These studies are reviewed and approved in concert with the review and approval of the protocol as a whole. The processes for developing these studies are discussed within the scope of the Protocol Team. The Procurement Guidelines outlined in Section 3.8 of the MOP set forth the guidelines for selecting a supplier to perform the study's sample testing.
- **Independent ancillary studies** that are not part of a primary protocol, but which will use samples and associated clinical data previously collected or to be prospectively collected in the course of one or more clinical trials or which involve approaching subjects on one or more trials for supplementary data.

11.2. Consideration of Independent Ancillary Study Proposals

Before an independent ancillary study is endorsed by the BMT CTN, independent ancillary study proposals must go through the review process described below (summarized in Figure 11-1) and be approved by the BMT CTN Executive Committee. A document summarizing the ancillary study proposal and review process detailed in the MOP can be found on the BMT CTN public website.

BMT CTN clinical trial datasets are transferred by the DCC to the custody of the NHLBI within a month of primary results publication in a journal. Data will be made available in Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) as a public research resource. Once a dataset is transferred, associated biospecimen collections may subsequently also be accepted and transitioned to an open public collection managed by the NHLBI/BioLINCC. All

inquiries regarding biospecimen and clinical data availability, and the subsequent submission of formal study proposals requesting such research materials, should be directed to the NHLBI (https://biolincc.nhlbi.nih.gov/home/) once the dataset and biospecimens are both made available in BioLINCC.

11.2.1. Correlative Study Planning

Since investigators interested in conducting correlative research might be unfamiliar with the specific BMT CTN trials or with the Network itself, general information to allow efficient understanding of the clinical trial specifics, study populations, and data available are posted on the public BMT CTN website:(https://bmtctn.net/study-proposals).

11.2.2. Process for Initiation, Review, and Approval

Ancillary study proposals must be presented in writing to the BMT CTN DCC and/or Protocol Team by investigators who are known to be qualified in their field or who provide evidence of qualifications relevant to the proposed research question(s). Written proposals must be prepared by using the BMT CTN Correlative Study Proposal form, which can be found on both the BMT CTN public and private websites. The investigator must describe potential sources of funding for the study and indicate whether funds are currently available or are being sought.

For ancillary studies involving one protocol, initial proposal review is conducted by the Protocol Team. An important factor in the review of ancillary study proposals is the determination that the objectives and implementation of the primary study are not compromised. Protocol Team members individually review ancillary study proposals and evaluate them for:

- Significance and appropriateness of the proposed research question;
- Design of the proposed research;
- Qualifications of the investigator(s) to conduct the research;
- Availability and source of funding;
- Availability of biospecimens and requested clinical data, if required for the study.

Protocol Team member proposal scoring will be captured using the BMT CTN Ancillary Study Proposal Reviewer Checklist that can be found on the private BMT CTN website. This checklist can be used for both retrospective laboratory studies and for prospective studies proposed to be conducted in parallel to the primary trial. If the proposal involves collection and/or analysis of biologic specimens, the Protocol Team comments may be summarized and forwarded along with the proposal to the BMT CTN Biomarkers Committee for an additional review.

Biomarkers Committee review offers a second level of proposal evaluation, focusing on laboratory aspects of the proposed study in terms of feasibility and scientific merit and putting the proposal in the context of other laboratory studies approved or ongoing on BMT CTN clinical trials. The Biomarkers Committee sends its evaluation back to the Protocol Team for their review. The Protocol Team may amend its evaluation of the proposal based on this critique. Once the Biomarkers Committee review is complete, the proposed study is submitted to the BMT CTN Executive Committee for approval.

An ancillary study proposal involving a parent protocol for which the primary trial manuscript has been published at least five (5) years prior and for which no other ancillary study requests have

been received within the preceding two (2) years is eligible for expedited review; this mechanism allows a proposal to be directly evaluated by the Executive Committee without review by the Protocol Team and/or Biomarkers Committee.

For ancillary studies involving biospecimens from several protocols, primary proposal review is conducted by the Biomarkers Committee which then presents its recommendations, together with those of the various Protocol Teams, to the BMT CTN Executive Committee for final approval.

Substantive changes to an approved proposal, such as those impacting science or scope, must be approved by the Executive Committee.

Any ancillary study requiring a separate informed consent must also be reviewed and approved by the BMT CTN Data and Safety Monitoring Board (DSMB).

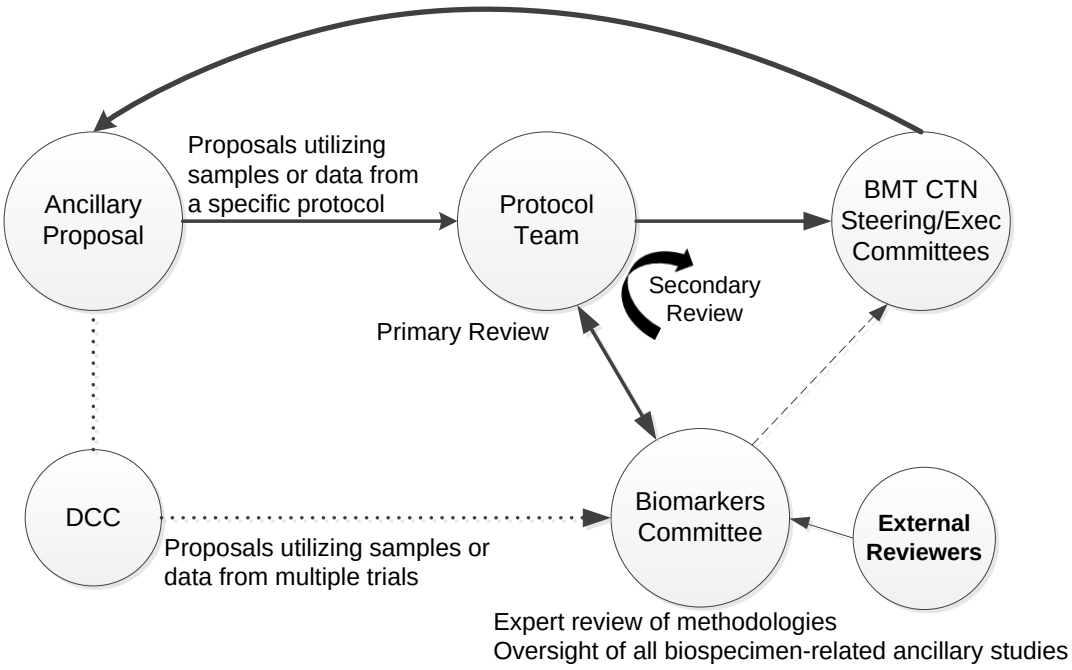


Figure 11-1: Overview of Ancillary Study Proposals Utilizing Biospecimens

11.2.3. Study Implementation

Once approved by the BMT CTN Executive Committee (and DSMB, if necessary), the ancillary study principal investigator (PI) will be notified of the endorsement by the DCC. Ancillary studies outside the main trial are generally voluntary for individual patient or institution participation. The BMT CTN DCC may elect to assess interest in study participation from centers in order to obtain a sample size matching that of the parent clinical trial.

11.3. Ancillary Studies Requiring the Collection of Clinical Data

Ancillary studies that require only clinical data are implemented as a "clinical" studies; they require real time supplemental data collection from patients being enrolled on BMT CTN clinical trials who are undergoing scheduled evaluations according to the protocol. Ancillary studies that require the collection of additional data during the course of the clinical trial require a separate informed consent. Examples of such ancillary studies include quality of life assessments and other functional assessments that are not part of the main clinical trial. Ancillary studies funded by the BMT CTN DCC and/or studies leveraging Network data that are not part of the primary trial protocol require a signed agreement between the study PI's institution and the NMDP/Be The Match (acting on behalf of the BMT CTN). This agreement will outline the responsibilities, data handing, publishing rights and other pertinent details and must be signed before the study data are distributed.

11.4. Ancillary Studies Utilizing Biospecimens and Associated Clinical Data

Ancillary studies using biospecimens are classified as "laboratory" studies; these studies generally require the use of corresponding clinical data. These studies will be implemented in slightly different ways depending on the categories described below:

- Studies utilizing previously collected samples that have been stored at the NMDP/Be The Match Biorepository (i.e. independent ancillary studies)
- Studies requiring real time supplemental sample collection during the course of the clinical trial (i.e., protocol-defined ancillary studies)

Prior to distribution of samples and associated clinical data, study PI must sign the applicable contractual document (Research Materials Distribution Agreement) with the NMDP/Be The Match (acting on behalf of the BMT CTN). Changes to the ancillary study, including but not limited to addition of authorized users, requests for additional research biospecimens or clinical outcomes data and/or data elements/variables, and changes to scope or science outlined in the approved study proposal must be captured via amendment of the RMDA; approval by the Executive Committee might also be required as described in Section 11.2.2.

11.4.1. Retrieval of BMT CTN Biologic Samples from NHLBI Biorepository/BioLINCC

The NHLBI Biorepository/BioLINCC currently stores and manages biospecimens associated with several BMT CTN protocols for which further protocol-defined research is not planned. All pertinent NHLBI policies and procedures must be followed to access these samples. All inquiries surrounding the availability of and requisition procedures for these "open" or public research biospecimen collections and associated clinical outcome data should be directed to the NHLBI(https://biolincc.nhlbi.nih.gov/studies/).

11.4.2. Retrieval of Biologic Samples from NMDP/Be The Match Research Biorepository

The NMDP/Be The Match Biorepository also stores and manages biospecimens collected from several early, recent, and ongoing BMT CTN protocols on behalf of the BMT CTN. These biospecimens are available to all qualified investigators with BMT CTN-approved ancillary laboratory studies. For the more recent protocols, biospecimen collections are often associated with protocol-defined or Protocol Team planned correlative laboratory studies; these collections

will be first made available to meet the requirements of planned studies and then offered to the larger BMT community to support future BMT CTN approved ancillary laboratory studies. All pertinent NHLBI policies and procedures will also be followed to access these BMT CTN biospecimens.

The process for formally requesting BMT CTN samples from the NMDP/Be The Match Repository is summarized below.

11.4.2.1. Pre-submission Requirements

Those submitting an ancillary study request must first contact the BMT CTN DCC and parent study Protocol Team to initiate a discussion regarding the evaluation/approval of planned studies as previously described.

11.4.2.2. Formal NMDP/Be The Match Sample Request Submission Process Overview

- Once the parent study and BMT CTN oversight committees have approved the ancillary study request, the study PI is provided a summary of the biospecimens available for their study by a BMT CTN DCC representative who will coordinate sample distribution with the NMDP/Be The Match Research Repository.
- The PI will approve the list of samples to be distributed and provide the information necessary for facilitating the proprietary study request, including administrative and contact information and shipping details. If an investigator prefers to use their own FedEx account for sample shipment, this information must also be provided.
- On behalf of the PI, the BMT CTN DCC representative submits a formal BMT CTN sample request to the NMDP/Be The Match Research Biorepository. The formal request package will include:
    - Confirmation of the study's approval by the appropriate BMT CTN oversight committees
    - Research plan summary (i.e., the Ancillary Study Proposal)
    - An electronic manifest generated by the NMDP/Be The Match Research Biorepository listing the biospecimens that the PI approved for distribution
- Selected samples are reserved and a BMT CTN Research Material Distribution Agreement (RMDA) is provided to the PI's institution
- Once signed by all parties, the RMDA is sent to the NMDP Biorepository to be stored with the sample/data request application.
- The NMDP/Be The Match Biorepository will notify the BMT CTN DCC representative once review of selected sample inventory is completed. to the BMT CTN DCC representative will then provide final approval for removing these samples from the biospecimen inventory for shipment to the PI.

11.4.3. Distribution of Sample Information and Associated Clinical Outcome Data

The BMT CTN assigns each study subject with two unique subject identifiers.

- The first identifier is the ***Project ID***, which uniquely identifies the subject within the context of a single BMT CTN study (e.g., 0702). This is the primary subject identifier that

is used in conjunction with the clinical data that is captured throughout that same single BMT CTN study. This subject identifier is used behind the scenes to uniquely identify protocol-specific clinical data that were collected for that subject.

- The second identifier is the ***Patient ID***, which uniquely identifies the subject in the context of any BMT CTN study. This is the primary subject ID that is associated with both the AdvantageEDC data collection forms and any biological research samples that are collected in any BMT CTN study and entered into the GlobalTrace application. In the context of research biospecimens processed and stored by the BMT CTN Repository, the biospecimens will be associated with this unique *Patient ID*.

If a subject is enrolled on more than one BMT CTN protocol (e.g., 1101 and 1202), the ***Patient ID*** will be used for both clinical data and biologic samples being collected throughout the study. Behind the scenes, protocol-specific ***Project IDs*** will also be assigned each subject, which will unambiguously identify the protocol-specific clinical data collected from each study.

Biospecimen specific information will be provided by a DCC representative to the ancillary study investigator in the form of an electronic Excel shipping manifest. The sample manifest will contain a listing of the unique sample identifiers along with all pertinent sample-related information (e.g., collection date, sample type, volume, etc.) including the unique ***Patient ID*** associated with each sample. Associated clinical data sets provided to the investigator for the ancillary study (usually in the form of a SAS file) will contain both the unique ***Project ID*** and the unique ***Patient ID*** for each subject. The later identifier will serve as the data element link between the biospecimens listed in the sample manifest and the associated protocol-specific clinical data set.

11.4.4. Ancillary Studies with Real Time Sample Collection

Approved studies requiring real time collection during the course of the clinical trial are implemented concurrently with the primary clinical trial. While transplant center participation in integrated ancillary studies may be voluntary, patient participation is always considered voluntary. If not included within the primary clinical trial protocol and consent form, the PI is required to develop an ancillary protocol and informed consent that will be reviewed by the NHLBI DSMB and clinical site or by the NMDP single institutional review boards before implementation. Additionally, the ancillary study PI must sign an agreement with the NMDP/Be The Match, acting on behalf of the BMT CTN, outlining responsibilities, shipping and handling of samples, publishing rights among other details pertinent to the study prior to receiving any samples.

11.5. Funding for Ancillary Studies

Funding for Ancillary Studies may be from Network resources, an institution, private sources, or the NIH. The Steering Committee may recommend submission of a competitive supplement application to the NIH, in which case the application will be reviewed through the traditional peer review mechanism. If NIH funding is to be sought, the BMT CTN will provide a letter of endorsement signed by the Executive or Steering Committee Chair or a DCC Leadership member.

The available funding or grant application budget for all ancillary studies must include support for the BMT CTN DCC for reimbursement of costs associated with clinical dataset provision and the selection and shipment of biospecimens. If DCC support with study statistical analysis is sought, additional costs will be incurred and must be budgeted. BMT CTN DCC costs will vary depending

on the complexity of the ancillary study. The DCC will provide an approved budget for DCC costs for all approved studies and any other sub-contractor forms required by a prospective funder.

Any funding received from government agencies or third-party funders, outside of the primary BMT CTN grants, shall be reported to the BMT CTN for inclusion in the tally of total contributions to the BMT CTN.

11.6. Ancillary Study Manuscripts

Please refer to Chapter 8 (Publications, Abstracts and Presentations) of the BMT CTN MOP.

11.7. Management of Protocol-Defined Contracted Laboratories

The BMT CTN has partnered with numerous university-based investigators and commercial laboratories in the U.S. to provide laboratory testing services to support protocol-defined laboratory studies. Many of the laboratories were selected in response to the release of a competitive request for proposals (RFP), while others were selected specifically by Protocol Teams for their unique capabilities, investigator expertise, and/or documented scientific contributions to the field of BMT research. The BMT CTN DCC has developed and implemented procedures for executing lab service agreements that detail the scope of work required and other responsibilities and considerations related to the services the project laboratories are providing. Ensuring high quality services are provided that will effectively meet the requirements of each correlative laboratory study is of utmost importance. To this end, the BMT CTN DCC has developed and implemented procedures that are summarized below that serve to develop a productive partnership and effectively support quality monitoring of the testing and final results submitted for analysis in our laboratory studies.

- At project initiation, a BMT CTN DCC representative meets with the laboratory project staff to review the scope of work associated with the lab service agreement. The team discusses the collection and distribution of samples, receipt and processing (when necessary) of samples, and the analytical testing that is to be performed by the laboratory. Finally, invoice submission procedures for reimbursement for testing services are reviewed.
- Communication procedures are established between the project laboratory and a DCC representative, establishing a single point of contact for the submission of general questions and technical issues that need to be reviewed and resolved.
- Test result content and formatting is discussed, and a final result template is developed. The final result template must be reviewed and approved by the protocol PI.
- Within the first few weeks of research sample testing, completed test data, in the agreed upon format, is submitted to the DCC representative for review and approval by the protocol PI. Any inconsistencies, omissions or quality concerns are resolved before additional testing is performed.
- Project laboratory performance is monitored periodically throughout the course of the project and reports are provided to the protocol PI.
- Review of test data is performed periodically throughout the project and at the completion of all planned testing.

11.8. Genetic Studies: NIH Data Sharing Considerations

When combined with clinical and other phenotypic data, analysis of whole genome information offers the potential for increased understanding of basic biological processes affecting human health and for improvement in the prediction of disease and treatment options. To advance this field of research, the NIH has established expectations for the sharing of genetic (e.g., SNP data) and phenotype (e.g., information about disease status, outcomes, and subject characteristics that are not individually identifiable) data obtained through NIH-funded Genome-Wide Association Studies (GWAS). The NIH GWAS data sharing policy ("GWAS policy") mandates that GWAS data obtained with NIH support be shared through a central repository when such data sharing is compatible with the consent provided by the participant. The NIH policy can be found online (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html).

Many of the ongoing and recently opened BMT CTN studies, as well as future studies currently in development, have incorporated the collection and storage of research biospecimens. It is the desire of the BMT CTN (and NIH funding agencies) that these biospecimens be suitable for either protocol-defined laboratory studies or for unrestricted future research (including GWAS or whole exome sequencing (WES) studies) in conjunction with the clinical outcome data associated with the parent study. As such, all BMT CTN protocol consents from trials in which biospecimens are collected include language facilitating NIH data sharing compliance efforts, allowing the Network to provide biospecimens that are available for the widest range of possible research opportunities.

The BMT CTN informed consent process and document inform participants that DNA isolated from certain stored biospecimens (e.g., whole blood, PBMC, isolated DNA, marrow aspirates, stem cell product) and associated clinical data might be selected for use in a future NIH-funded or conducted GWAS or WES study. The resulting de-identified genotype and phenotype data will be shared for research purposes through the deposit of both the genotype and phenotype data in the access-controlled public NIH Genotype and Phenotype database (dbGaP) managed by the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/gap).

CHAPTER 12

SECONDARY DATA ANALYSES

12. SECONDARY DATA ANALYSES

12.1. Definition of Secondary Data Analyses

This chapter outlines procedures and policies for secondary data analyses using BMT CTN study data. These data may be accessed through the BMT CTN DCC before it becomes available in NHLBI's BioLINCC as a public data resource for future studies. After the Proprietary Period as expired, BMT CTN clinical trial data are transferred to BioLINCC within 1 month of publication of primary trial results in a journal. Once the data are released by NHLBI, data requests and proposals for secondary data analyses must be submitted directly to NHLBI through BioLINCC for facilitation (https://biolincc.nhlbi.nih.gov/home/).

A "secondary data analysis" is defined as a study that uses previously-collected clinical data to address objectives that are outside the scope of the BMT CTN parent trial from which the data were obtained. This chapter does not address "ancillary studies", defined as analyses using additional data collected prospectively in the course of a BMT CTN study, nor does it apply to studies using biologic material from BMT CTN studies to address secondary questions; these are described in Chapter 11 (Ancillary Studies). This chapter also does not apply to secondary objectives already outlined in the protocol. Studies that use exclusively CIBMTR clinical data have their own mechanism for review and approval though the CIBMTR working committees. This chapter's discussion pertains to studies that use at least some data from one or more BMT CTN trial.

12.2. Rationale for Conducting Secondary Analyses

The rationale for encouraging secondary analysis of BMT CTN data is to leverage the large number of resources devoted to conducting the clinical trials towards the greatest increase in knowledge. BMT CTN studies generally share a common set of case report forms (CRFs), a standardized process for reviewing key data elements through data review committees, and careful monitoring procedures. Almost all BMT CTN studies require completion of the CIBMTR full length comprehensive report forms, which can be linked to BMT CTN data through the CIBMTR CRID (a unique number given to each transplant recipient) to provide additional data for analysis. For studies that can address important hypotheses through the analysis of BMT CTN data, the efficiency of having the data already collected and available is a great strength. From a Network perspective, the ability to conduct high quality secondary analyses further leverages the NIH resources provided and illustrates the value of the Network.

12.3. Information to Plan Secondary Analyses and Determine Feasibility

Since investigators interested in conducting secondary data analyses might not be familiar with specific BMT CTN trials or the with the Network itself; to encourage secondary data analyses, general information to allow efficient understanding of the clinical trial specifics, study populations, and data available are posted on the public BMT CTN website (https://bmtctn.net/study-proposals). These resources are organized in a way that allows ease of access and maximizes utility, including:

1. BMT CTN protocols, and synopses for completed and open trials (https://bmtctn.net/bmt-ctn-studies).
2. CRFs for completed BMT CTN protocols (https://bmtctn.net/protocol/data-reports) BMT CTN CRFs are labeled with actual variable names to allow unambiguous communication about variables of interest.
3. Listing of the primary manuscripts from completed studies (https://bmtctn.net/publications).

12.4. Submission and Adjudication of Secondary Clinical Data Analysis Study Proposals

To propose a secondary data analysis, investigators must download and complete the BMT CTN Correlative Study Proposal Form found on the public BMT CTN website (https://bmtctn.net/study-proposals). The study proposal provides a thorough yet concise description of the preliminary data and background, primary hypotheses, patient population, associated BMT CTN protocol number(s), necessary clinical information, source of funding or potential funding, and whether a BMT CTN or non-BMT CTN statistician will be performing the analysis. The completed study proposal is submitted to designated BMT CTN DCC contacts and is initially reviewed by DCC staff and statisticians for completeness and non-overlap with any previously-approved secondary data analyses or any planned secondary analyses in the primary study protocol. Following this initial review, the study proposal is provided to the parent study Protocol Team by the assigned BMT CTN statistician and together they adjudicate the proposal for feasibility and scientific merit. The BMT CTN statistician(s) must determine whether the requested data elements are available and whether they are necessary to address the study objectives outlined in the proposal. The study proposal, along with Protocol Team/BMT CTN statistician comments and recommendations, are then provided to the BMT CTN Executive Committee for final review and an approval. If the parent Protocol Team is not active, or if the secondary analysis involves more than one protocol, the assigned BMT CTN statistician will submit the proposal directly to the BMT CTN Executive Committee to discuss and adjudicate the scientific merit and feasibility of the study. The investigator submitting the proposal may be invited to present the study to the Protocol Team and/or Executive Committee, or the assigned BMT CTN statistician may do this. Questions are discussed with the investigator and addressed in the study plan in an iterative process throughout the course of the scientific review of the study proposal. Approval of the proposal will be documented on the Parent Study and BMT CTN Leadership Approval BMT CTN Biospecimen and Clinical Data Resources Form.

The BMT CTN DCC statisticians include Emmes and CIBMTR statisticians. The roles and responsibilities for supporting the secondary data analysis will be outlined in a guideline document for BMT CTN DCC Statistical Support and the collaboration efforts will be reviewed on a regular basis for specific tasks.

12.5. Funding for Secondary Data Analysis Studies

Funding for secondary data analysis studies may come from Network resources, an institution, private sources, or the NIH. If NIH or other grant funding is to be sought for an approved study, the BMT CTN will provide a letter of endorsement signed by the Executive or Steering Committee Chair or a DCC Leadership member.

The available funding or grant application budget for all secondary data analysis studies must include support for the BMT CTN DCC to cover the development of the requested data file, the review of all data elements, the delivery and support related to the use of the dataset by the investigators. Missing data may need to be addressed and potential supplemental data elements may also need to be considered. In order to perform tasks related to the development, QA and delivery of study data sets, DCC statistician time and effort needs to be reimbursed as part of the cost of conducting the study. BMT CTN DCC costs will vary depending on the complexity of the secondary data analysis study. If the investigator has requested BMT CTN statistician support to perform the study analysis, the number of statistical hours must also be included in the study budget. The DCC will provide an approved budget for direct and indirect DCC costs for all approved studies and any other sub-contractor forms required by a prospective funder.

Any funding received from government agencies or third-party funders, outside of the primary BMT CTN grants, shall be reported to the BMT CTN for inclusion in the tally of total contributions to the BMT CTN.

Any proposal or request to obtain study data from the DCC after the data are available in BioLINCC must be agreed upon by BMT CTN DCC and have available funding to support the development of the requested data file, the review of all data elements, the delivery and support related to the use of the dataset by the investigators.

12.6. Conducting Approved Secondary Data Analysis Studies

Upon approval of the secondary analysis proposal, a BMT CTN Research Materials Distribution Agreement (RMDA) must be executed before data will be distributed by the BMT CTN DCC. This agreement shall be signed by The NMDP/Be The Match on behalf of the BMT CTN, the principal investigator (PI) and the PI's institution. During the transfer of de-identified data from the BMT CTN to a local institution for analysis, the institution will abide by all rules established in the data agreement. Local IRB approval for data receipt may be required by the investigator's institution. IRB approval is not required by BMT CTN, but documentation of IRB approval or a waiver is required before the data are released. If the BMT CTN DCC will be analyzing the data, and no data will be released to the PI or to the PI's Institution, an RMDA is not required.

The BMT CTN strongly recommends that approved study PIs consider the inclusion of a BMT CTN statistician on the study team, as they are already familiar with the data being provided for the study. The parent trial PI or other key members of the parent Protocol Team could also be considered for study team inclusion. Their intimate knowledge of the primary protocol, the content and quality of the clinical data, and their previous work with the analysis of study outcomes and endpoints would likely be of considerable value to the study team.

If a non-BMT CTN statistician will be conducting the analysis, involvement of a BMT CTN statistician in a consulting role is highly recommended since the BMT CTN will need to review the analysis prior to presentation or publication.

The secondary analysis study team creates a timeline for completion of the secondary analysis and ensures the timeline is met. This timeline must be agreed to by the BMT CTN statistician creating the dataset and the team conducting the analysis since there are several key milestones that need to be considered over the course of the study.

12.7. Publications Guidelines

Please see Section 8 (Publications, Abstracts and Presentations) which addresses BMT CTN publication policies. Please note that the BMT CTN Publications Committee and NHLBI/NCI program officers must review all manuscripts before submission. See Section 8.6 for guidelines regarding how to reference NIH funding support for the parent study(ies).