CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program®/Be The Match® and Medical College of Wisconsin
Progress Report
January – December 2014

Milwaukee Campus
Medical College of Wisconsin
9200 W Wisconsin Ave, Suite C5500
Milwaukee, WI 53226 USA
(414) 805-0700

Minneapolis Campus
National Marrow Donor Program
3001 Broadway St NE, Suite 100
Minneapolis, MN 55413-1753 USA
(612) 884-8600

www.cibmtr.org
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1.0 OVERVIEW OF THE CIBMTR

The CIBMTR® (Center for International Blood and Marrow Transplant Research®) collaborates with the global scientific community to advance hematopoietic cell transplantation (HCT) and cellular therapy research worldwide. The CIBMTR is a research collaboration between the National Marrow Donor Program (NMDP)®/Be The Match® and the Medical College of Wisconsin (MCW) that facilitates critical observational and interventional research, which has led to increased survival and enriched quality of life for thousands of patients.

These research activities are made possible by the participation of a large network of transplant centers and the expertise of the CIBMTR Coordinating Center. Support for this program is provided by the National Institutes of Health (NIH) grants # 5U24CA076518 and # 5U10HL069294, Health Resources and Services Administration (HRSA) contract # HHS250201200016C, and other supplementary sources. This funding has resulted in the successful completion of hundreds of studies that positively impact clinical practice.

The CIBMTR is now in its tenth year of a robust, collaborative, and outcomes-focused research endeavor. The Coordinating Center spans two campuses and is committed to supporting the highest level of clinical research. This Progress Report covers the period from January 1 through December 31, 2014. Unless otherwise noted, all reported data are effective through December 1, 2014.

1.1 VALUE OF THE CIBMTR AS A RESOURCE

HCT is a sophisticated, resource-intensive therapy that is increasingly used to treat malignant and non-malignant diseases. HCT may use cells from healthy donors (alloHCT) or from patients themselves (autoHCT). Assessing HCT outcomes is challenging. Individual indications for HCT are uncommon, sources for grafts are diverse, the early HCT period is characterized by multiple competing risks, and technologies evolve rapidly. There is need for long-term follow-up of recipients since some HCT effects, e.g., therapy-related cancers, occur many years after treatment.

The CIBMTR maintains a large outcomes registry focused on HCT donors and recipients. Its network includes approximately 350 transplant centers across the globe, including almost all US centers, which share data on HCT outcomes; its database has information for more than 390,000 HCT recipients. The CIBMTR also provides statistical support for analyses of those data, making it an invaluable resource for assessing use and effectiveness of HCT. The CIBMTR originated in 1972 as the International Bone Marrow Transplant Registry (IBMTR). In 2004, the IBMTR program joined with the NMDP / Be The Match’s research program (established in 1987) to form the CIBMTR. Consequently, the program has well-established processes for collecting, sharing, and analyzing data resulting from 40 years of collaboration with investigators in the field. The productivity of the resource stems from this successful collaboration. Our goal as a resource is to facilitate research by sharing data as well as statistical and scientific expertise with clinical and basic scientists to allow them to better address important scientific and clinical issues. These investigators bring a broad range of expertise to the CIBMTR studies thus allowing our state of the art resource to be used to support research in many domains.

Outcomes registries like the CIBMTR’s facilitate understanding of treatment outcomes by addressing questions not amenable to randomized trials or single-center series. These include descriptions of use and results in various disease states and patient groups, determining prognostic factors, defining
inter-center variability in diagnosis, practice and outcome, evaluating long-term outcomes, and developing new analytic approaches. Outcomes registries can also be an asset in planning clinical trials by identifying the most promising questions (hypothesis generation), by providing realistic estimates of baseline outcome rates and of availability of patients under varying eligibility criteria, and by allowing simulation of statistical designs. Additionally, repositories of biologic samples linked to registry data, as is available through the CIBMTR, can facilitate unanticipated new areas of investigation as science advances. The value of outcomes registries in assessing treatment effects is not restricted to HCT and is increasingly recognized in many areas of medicine. While this type of endeavor is not inherently innovative, the CIBMTR incorporates innovative components in its operations and analytic strategies. The CIBMTR’s unique Resource of data and expertise in statistics, immunobiology, bioinformatics, and clinical HCT along with our collaboration with many investigators in diverse fields have led to successful completion of hundreds of studies with important impacts on clinical practice.

1.2 GOALS

Resource Development: The CIBMTR seeks to provide the biomedical community a high-quality clinical database and state-of-the-art statistical support to address important issues in HCT and related fields through continued enhancement of data collection and management technology and procedures, expansion of the Resource to include patient-reported outcomes, gathering and dissemination of data necessary for health services research and data on some non-HCT patients, development and application of novel statistical techniques, and collaboration with national and international networks in HCT and related fields. Additionally, the CIBMTR makes available a repository of paired donor / recipient specimens linked to clinical data.

Resource Utilization: The CIBMTR is committed to increasing use of the data, statistical, and biospecimen resources maintained by the CIBMTR; to supporting studies with important clinical and policy implications; and to enhancing Working and Advisory Committee and Coordinating Center processes to prioritize and complete these studies.

1.3 RESEARCH STRATEGY

Resource Development Plan (Section 2):
1. Optimize and enhance the quality and scope of the database.
2. Provide state of the art technology solutions and develop collaborative agreements to share data for research.

Scientific Resource Utilization Plan (Section 3):
1. Enhance processes for review, prioritization, and implementation of proposed studies.
2. Optimize the timeline for moving a study proposal to publication.
3. Utilize data from observational studies to support decisions regarding design of prospective clinical trials and/or amendments of such trials.
4. Assist in long term follow-up of patients participating in clinical trials.
5. Link outcomes data to immunologic data available from the NMDP / Be The Match sample repository.
6. Provide novel observational studies in malignant and non-malignant blood and other disorders, including use of genetically engineered cellular products.
7. Optimize the data analysis process through enhanced biostatistical approaches.
8. Facilitate health services research in HCT.

1.4 ORGANIZATIONAL AND RESEARCH PROGRAM STRUCTURE

The CIBMTR represents a large network of approximately 350 participating transplant centers (Appendices B1 and B2) that submit transplant-related data for patients. Centers submit data at two levels: a Transplant Essential Data (TED) level, which captures basic data, and a Comprehensive Report Form (CRF) level, which captures more detail. The CIBMTR Coordinating Center, staffed by approximately 185 employees (Appendices C1-C3), provides data acquisition, management, and statistical support for analyses of these data.

The Chief Scientific Director is responsible for all administrative and scientific operations. The Associate and Senior Scientific Directors assist in overseeing operational aspects of the CIBMTR Coordinating Center. The CIBMTR committees (Section 1.5) provide input and advice to the leadership team, ensuring the continued support of both the needs and priorities of its scientific and medical communities.

As identified in Figure 1.1, CIBMTR research involves five major programs:

- Clinical Outcomes Research;
- Immunobiology Research;
- Health Services Research;
- Statistical Methodology Research;
- Clinical Trials Support;
  - Blood and Marrow Transplant Clinical Trials Network (BMT CTN);
  - Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT).

1.5 COMMITTEE STRUCTURE

The CIBMTR committee structure ensures that research within each of the program areas is conducted responsibly and efficiently. The Joint Affiliation Committee provides executive oversight. The Advisory (Section 1.5.2), Executive (Section 1.5.2.1), and Nominating (Section 1.5.3) Committees manage administrative issues, including policy making and organizational development. The Consumer Advocacy Committee (Section 1.5.2.2) provides patients’ perspectives to all aspects of CIBMTR activities. The Scientific Working Committees (Section 1.5.4) manage clinical outcomes research activities and statistical analyses. The Immunobiology Steering Committee (Section 1.5.5) and Clinical Trials Advisory Committee (Section 1.5.6) provide scientific oversight for the Immunobiology Working Committee and RCI BMT (Section 3.3.2), respectively.

1.5.1 Assembly

The CIBMTR Assembly is the organization’s voting membership. A representative from each CIBMTR center that submits CRF-level data serves on the Assembly, which elects members of the CIBMTR Advisory Committee, Nominating Committee, and Clinical Trials Advisory Committee. The Assembly meets annually during the BMT Tandem Meetings and is regularly updated on CIBMTR activities through periodic e-newsletters (Section 4.3.7).
Figure 1.1. Organizational Structure for Scientific Oversight

- **Joint Affiliation Committee**
  - Executive Director: J. Chell, MD

- **National Marrow Donor Program**

- **Executive Committee**

- **Senior Research Advisor**
  - D. Weisdorf, MD

- **Associate Scientific Director for CIBMTR Minneapolis**
  - D. Confer, MD

- **Senior Scientific Director for SCTOD**
  - D. Rizzo, MD, MS

- **Senior Scientific Director for Research**
  - M. Eapen, MBBS, MS

- **Medical College of Wisconsin**

- **CIBMTR Assembly**

- **Advisory Committee**

- **Chief Statistical Director**
  - M.J. Zhang, PhD (Interim)

- **Chief Scientific Director**
  - M. Horowitz, MD, MS

- **Scientific Working Committees**
  - Advisory role

- **Steering Committees**

- **Clinical Trials Support Program**
  - M. Pasquini, MD, MS
  - TBD

- **Blood and Marrow Transplant Clinical Trials Network (BMT CTN)**
  - M. Pasquini, MD, MS

- **Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI BMT)**
  - TBD

- **Statistical Methodology Research Program**
  - M. Pasquini, MD, MS
  - M. Pasquini, MBBS, MS

- **Clinical Outcomes Research Program**
  - M. Eapen, MBBS, MS

- **Health Services Research Program**
  - Linda Burns, MD

- **Immunobiology Research Program**
  - S. Lee, MD, MPH

- **Clinical Trials Support Program**
  - M. Pasquini, MD, MS
  - TBD
1.5.2 Advisory Committee

The Advisory Committee (Appendix D1) provides oversight for CIBMTR policies and scientific agenda and also partners with the Working Committees to prioritize scientific studies. Members are elected to three-year terms by the CIBMTR Assembly and must be from qualifying CRF centers. The Advisory Committee also includes appointed representatives from donor centers (1), collection centers (1), the patient community (1), the business community (1), the bioethics field (1), and cord blood banks (1) as well as ex-officio members from the National Cancer Institute (NCI); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Allergy and Infectious Disease (NIAID); HRSA (4); and the CIBMTR Coordinating Center (7).

The Advisory Committee holds an in person meeting annually at the BMT Tandem Meetings. Additionally, the Committee meets quarterly and additionally, as needed, by teleconference. All Advisory, Executive, and Nominating Committee terms begin on March 1.

1.5.2.1 Executive Committee

The CIBMTR Executive Committee (Appendix D2), a subcommittee of the Advisory Committee, ensures that the organization carries out its mission and adheres to CIBMTR policies and procedures; it also provides advice and counsel to the CIBMTR Coordinating Center between meetings of the Advisory Committee. Members include the Advisory Committee Chair, Chair-Elect or Immediate Past Chair, four Vice-Chairs (each representing a geographic region), appointed members of the Advisory Committee, and senior Coordinating Center staff members who also serve on the Advisory Committee. The Executive Committee meets four times annually by teleconference and is responsible for:

- Providing scientific and policy advice to the Chief Scientific Director and Coordinating Center;
- Reviewing audit results and making recommendations for improvement;
- Appointing a CIBMTR Co-Chair and additional CIBMTR representatives to the BMT Tandem Meetings Scientific Organizing Committee for the annual BMT Tandem Meetings.

1.5.2.2 Consumer Advocacy Committee

The Consumer Advocacy Committee (Appendix D3) was created in 2005 as a subcommittee of the Advisory Committee to communicate CIBMTR research results and data to the non-medical community and to provide patient and donor perspectives during the development of the CIBMTR research agenda. Many members have personal experience as a donor, recipient, or family member of a recipient.

Co-Chairs serve on both the Advisory Committee and the Clinical Trials Advisory Committee (Section 1.5.5), and members also participate in Working Committees. The nine members meet in person at the annual BMT Tandem Meetings and by periodic conference calls.

The Consumer Advocacy Committee oversees the translation of published research articles into lay summaries. Committee members determine which research articles are most meaningful to patients and family members, and the lay summary is created collaboratively with the CIBMTR’s Medical Writer, the first author of the research article, committee members, and members of the NMDP / Be The Match Patient Services Writing Team. In 2014, 3 summaries were added to the CIBMTR Patient Resources webpage at www.cibmtr.org, bringing the total number of available summaries to 25.
1.0 OVERVIEW OF THE CIBMTR

1.5.3 Nominating Committee

The Nominating Committee (Appendix D4) consists of five members elected by the CIBMTR Assembly and meets by teleconference(s) each fall. Following an annual call for nominations, the Nominating Committee prepares a slate of candidates for open positions on the Advisory, Nominating, and Clinical Trials Advisory Committees. Elections are held annually by confidential electronic ballot.

The Nominating Committee also makes recommendations to the Advisory Committee for open Working Committee Chair and other leadership appointments, seeking recommendations from the CIBMTR Assembly, Advisory Committee, and incumbent Working Committee Chairs.

1.5.4 Scientific Working Committees

To ensure broad input into the research process and efficient use of resources, the CIBMTR facilitates 15 Working Committees focused on specific research areas:

- Acute Leukemia;
- Autoimmune Diseases and Cellular Therapies;
- Chronic Leukemia;
- Donor Health and Safety;
- Graft Sources and Manipulation;
- Graft-versus-Host Disease;
- Health Services and International Issues;
- Immunobiology;
- Infection and Immune Reconstitution;
- Late Effects and Quality of Life;
- Lymphoma;
- Pediatric Cancer;
- Plasma Cell Disorders and Adult Solid Tumors;
- Primary Immune Deficiencies, Inborn Errors of Metabolism, and Other Non-Malignant Marrow Disorders;
- Regimen-Related Toxicity and Supportive Care.

Total Working Committee membership exceeds 1,700 researchers. While most of these individuals are HCT clinicians, statisticians and basic scientists also participate. PhD statistical faculty and Master’s-level statisticians from the CIBMTR Coordinating Center provide their unique expertise in data analysis. Basic scientists investigating human leukocyte antigen (HLA), immunogenetics, pharmacogenetics, stem cell biology, and other areas related to HCT provide essential expertise in their respective research areas. The Working Committee structure encourages a collaborative but rigorous methodological approach to all CIBMTR activities, including:

- Designing and conducting relevant studies that use CIBMTR data, statistical resources, networks, and/or centers;
• Setting priorities for clinical outcomes studies that use the CIBMTR Research Database, including evaluating study proposals to ensure they are relevant to their subject area and will produce meaningful results;
• Assessing and revising CIBMTR data collection forms as needed;
• Planning and conducting workshops at CIBMTR meetings.

Working Committee membership is open to any researcher willing to take an active role in developing and conducting studies that use CIBMTR data and/or resources. Each Working Committee is staffed by at least one MS-level Statistician, a PhD Statistical Director, and an MD Scientific Director from the CIBMTR Coordinating Center. Each also typically has three to four Co-Chairs who are appointed by the Advisory Committee to non-renewable five-year terms. Working Committee Co-Chair appointments are made each fall, with terms commencing at the close of the BMT Tandem Meetings each year. Terms are staggered to facilitate succession and maintain continuity. Individuals may serve as Co-Chair more than once but not consecutively for the same committee. Co-Chairs participate in the nomination process for replacement positions and give special consideration to promising junior investigators, thus promoting ongoing leadership for the work of the CIBMTR. A list of Working Committee leadership can be found in Appendix D5.

Working Committee Co-Chairs provide subject matter expertise in autologous and allogeneic transplantation as well as understanding of CIBMTR organization and procedures. They must be members of CIBMTR centers that submit CRFs and that are compliant with Continuous Process Improvement (CPI) standards for data submission (Section 2.1.3.1), unless an exception is granted by the Advisory Committee. Co-Chairs are occasionally selected from outside these guidelines for their specific scientific expertise, for example, a scientist who directs a histocompatibility laboratory, apheresis center, or donor registry, who is committed to the CIBMTR and to the field of HCT.

Co-Chairs monitor and facilitate the progress of studies in their Working Committee’s portfolio. They communicate with Principal Investigators to address barriers and/or delays and participate in weekly CIBMTR Coordinating Center study critiques when studies in their portfolios are being discussed. In addition to chairing annual Working Committee meetings, Co-Chairs meet by teleconference every four to eight weeks with their committee’s Scientific Director and biostatisticians to review the progress of study proposals and ongoing studies. Co-Chairs lead the annual Working Committee meeting and, using input from that meeting, prioritize studies for the following year.

In August 2014, the CIBMTR Nominating Committee submitted recommendations, which the Advisory Committee approved, for 12 open Working Committee Co-Chair positions. New Working Committee Co-Chairs will assume their roles in March 2015 after conclusion of the annual BMT Tandem Meetings.

The CIBMTR Advisory Committee encourages each Working Committee to develop clinically relevant and meaningful studies. To that end, Working Committees review proposals for CIBMTR clinical outcomes studies. Proposals are formally solicited each fall but may be submitted at any time throughout the year. Proposals are reviewed by the Coordinating Center and then discussed in-depth at the appropriate Working Committee meeting at the annual BMT Tandem Meetings. The Chief Scientific Director, in consultation with the Chief Statistical Director and the Associate Statistical Director, allocates statistical resources to each Working Committee. Working Committee Chairs establish a work plan for the ensuring year that is consistent with available resources. See Section 8.
for a list of current Working Committee studies. An abbreviated listing, updated biannually, can also be found on the www.cibmtr.org website.

1.5.5 Steering Committees

Two CIBMTR Steering Committees, the Immunobiology Steering Committee (Appendix D6) and the Clinical Trials Advisory Committee (Appendix D7), provide an additional level of oversight for the use of certain resources.

The NMDP / Be The Match Histocompatibility Advisory Group also serves as the CIBMTR Immunobiology Steering Committee, which consists of appointed members and liaisons from the CIBMTR, NMDP / Be The Match, American Society for Histocompatibility and Immunogenetics, NMDP / Be The Match Cord Blood Advisory Group, HRSA, and C.W. Bill Young Marrow Donor Recruitment and Research Program. This committee reviews and approves the use of donor-recipient specimens from the NMDP / Be The Match Research Repository in CIBMTR studies and meets in person twice annually, in summer and at the annual BMT Tandem Meetings.

The Clinical Trials Advisory Committee assists in the review, approval, and oversight of proposals and protocols for Phase I and Phase II clinical trials submitted to the RCI BMT (Section 3.3.2). Its 10 members represent transplant physicians, non-physicians with experience in patient and donor issues, consultants, and representatives from the CIBMTR and RCI BMT. The committee meets in person during the BMT Tandem Meetings and by teleconference as needed.

1.6 TRAINING

The CIBMTR is committed to staff training and development for both Coordinating Center staff and participating transplant center professionals. A formal training program was established in 2012, and a Training and Development Specialist was recruited at that time. In 2014, the CIBMTR established a Training Steering Committee with the vision to “Deliver educational / training resources that enhance the quality of CIBMTR research.” One goal of the committee is to better integrate operational training across all functional areas and provide enhanced training opportunities that are appropriate for both internal and external audiences. New and continuing training initiatives offered in 2014 are described in this section.

1.6.1 Internal Training Initiatives

- **All-staff Meetings.** The CIBMTR holds quarterly staff meetings to share information between the two campuses and provide updates on ongoing operational projects, new key initiatives, and organizational objectives and measures. Staff accomplishments are also highlighted.

- **Data Operations Staff Annual Meeting.** Held in September 2014, this meeting incorporated training on good clinical practices, customer service, and business modeling.

- **Immunobiology Research Lunch and Learn Sessions.** The Immunobiology Research team, in collaboration with the Bioinformatics team, prepared and delivered several training sessions to internal CIBMTR and NMDP / Be The Match staff throughout the past year. Training topics included the role of transposons in killer-cell immunoglobulin-like receptors (KIR) recombination, a summary of population genetic talks from the American Society of Human Genetics annual meeting, and staff presentations providing overviews of their projects.
• **Information Technology (IT) Sessions.** IT provided monthly trainings to staff on project management, business requirements, and leadership as well as opportunities to attend lunch and learns with topics such as data warehousing, business intelligence, and business modeling. IT has purchased licenses to encourage regular individual training as well, with access to two types of online training libraries that include a broad range of technical and management skill training.

• **Statistical Training.** The CIBMTR maintains a formal training program for master (MS)-level statisticians to ensure uniform procedures in the coordination of Working Committee and research study implementation. A comprehensive educational manual is provided to each statistician for their personal reference, and a code library is maintained on both campuses. The educational manual is updated periodically and used primarily as a resource tool for the MS-level statisticians while in training and thereafter. As part of the MS-statistician continuing education training program, statisticians attend annual CIBMTR data management meetings, the annual BMT Tandem Meetings, and short courses on statistical techniques that can be applied to the field of HCT. To increase the MS-level statistician’s awareness of organizational and research changes, tools available, onboarding and ongoing training updates, the MS-level statistician’s training manual is continually enhanced to support better communication and knowledge. Training program initiatives for 2014-2015 include:
  - Statistical workshop led by Senior Biostatisticians, PhD Statisticians, and HCT physicians;
  - Bi-weekly Senior Biostatistician meetings with junior staff to provide mentoring and answer questions;
  - Monthly Senior Biostatistician meetings to discuss future projects;
  - MS-level Statisticians meetings to discuss updates on Working Committee management, study issues, SAS codes, policies and procedures, data, and other issues as needed.
Finally, to assess the MS-level statistician’s project management skills, a survey is planned to measure their current understanding and skills. Results of this survey as well as specific project management materials will be incorporated in the MS-level statistician’s training manual.

• **Biostatistics Graduate Student.** In 2014, one third-year doctoral student in the biostatistics program at MCW worked on CIBMTR projects. His training is focused on a sound theoretical understanding of statistical principles, research in the development of applied methodology, and collaborative research with biomedical scientists and clinicians. The student works closely with PhD-level biostatistical faculty members, particularly the CIBMTR Interim Chief Statistical Director, as well as physician faculty members. He meets regularly with his primary mentor, with whom he created an individual development plan.

• **Medical Students.** In 2014, the CIBMTR hosted three medical students during the academic year as well as two in a summer research program that allows first-year medical students the opportunity to explore a career in biomedical research and academic medicine and gain research tools applicable to clinical practice.
• **HCT Clinical Research Fellowship.** In 2014, one physician participated in the HCT Clinical Research Fellowship, which provides participants with coursework, data for research projects, and clinical experience as well as mentoring and an individual development plan. The fellow’s plan was developed with his primary mentor, the CIBMTR Senior Scientific Director for Research, who is a member of the fellow’s mentoring committee along with another physician faculty member and a PhD-level statistical faculty member. The fellow meets weekly with his primary mentor to discuss coursework as well as research progress and obstacles and to ensure the individual development plan is guiding the fellow’s training and providing him with the necessary experience to achieve his career goals.

1.6.2 External Training Initiatives

• **BMT Tandem Meetings.** With 2,950 attendees, the 2014 BMT Tandem Meetings included 5 plenary sessions, 11 concurrent sessions, 102 oral abstracts, 2 poster sessions, 4 corporate-supported symposia, and 3 product theaters. Continuing Medical Education (CME) and Continuing Education credits were issued through MCW to US physicians and allied health professionals. In addition to the extensive scientific agenda, many educational opportunities focused on young investigators and other allied health professionals:
  o **Clinical Research Professionals / Data Management Conference.** With almost 200 attendees, this conference provided forms training, which increases the accuracy with which CIBMTR forms are completed.
  o **BMT CTN Coordinators and Investigators Meetings.** With approximately 100 and 300 attendees, respectively, these meetings focused on data collection; the biology of diseases and the immune system; and processes, such as protocol activation, as well as specific clinical trials.
  o **IT Forum.** With almost 100 attendees, this forum discussed various aspects of the CIBMTR Data Life Cycle, including data collection through FormsNet, AGNIS, and data sharing through the Data Back to Center (DBtC) application and information requests. The Forum provides a unique opportunity to obtain input from the BMT community regarding future initiatives in data collection and data sharing.
  o **BMT Center Administrators Conference.** With approximately 165 attendees, this conference focused on payor strategies, performance improvement, data quality, caregiver challenges, and other management and leadership issues.
  o **BMT Pharmacists Conference.** With almost 200 attendees, this conference presented the latest research and best practices with a focus on specific diseases and populations.
  o **Transplant Nursing Conference.** With almost 500 attendees, this conference presented the latest research as well as disease-specific information and case studies.
  o **BMT Clinical Education Conference.** This conference is designed for Nurse Practitioners, Physician Assistants, Fellows, and Junior Faculty. With more than 300 attendees, the conference focused not only on the biology of diseases and clinical treatments but also quality improvement and patient interaction.

• **Data Matters Training Newsletter.** This data management-focused newsletter is published monthly via email and contains updates on projects, announces training opportunities and manual updates, and provides answers to frequently asked questions. Newsletter content is developed as a collaborative effort among several internal departments.
• **E-Learning Modules for Network Data Professionals.** E-Learning Modules were first released in October 2013. At this time, a total of 10 modules have been completed. These include an introduction to the e-learning module, an overview of the revision process for recipient forms, modules on HLA, lymphoma, and plasma cell disorders, and a training module on FormsNet3 for donor centers. The next E-learning modules will focus on the essential form series for new data managers, including CRID (2804), Recipient Module FormsNet3 Application, Data Back to Center Overview, Pre-TED (F2400), Baseline (F2000), Infusion (F2006), and IDM (F2004) forms.

• **Learning Management System (LMS).** Implemented in 2014, LMS is the infrastructure that securely registers courses, houses instructional content for online access, and tracks progress towards meeting organizational goals by individual and by center. Courses located in the LMS include HLA [Introduction to HLA, Basic Biology of HLA, Advanced Biology of HLA and HLA Reporting (Form 2005)], Essential Form Series (Form 2400 Pre-TED module), and Disease Specific Series (including Plasma Cell Disorders and Lymphoma). Use of the individual account registration was promoted through the Data Matters Training Newsletter and Clinical Research Coordinators (CRCs).

• **Data Management Manual.** The manual provides information detailing the forms completion process, SCTOD reporting requirements, data management protocols, and the consent process as well as instruction manuals for the Pre-TED (2400), Post-TED (2450), CRF forms (2100, 2200, 2300), and some disease forms. In 2014, one new manual section was published on the CIBMTR website, and an additional 11 manual sections have been written and will be published as soon as review is completed.

• **Center Reference Guide.** The Center Reference Guide includes information about participation in CIBMTR research, center membership, data submission, data manager education, mentor program, and the forms submission process as well as many useful tips and links.

• **Clinical Research / Outcomes Educational Track at the NMDP / Be The Match Council Meeting.** The CIBMTR Immunobiology Research team maintains responsibility for this educational opportunity. The 2014 program included the following workshops:
  - Globalization of HCT;
  - Weighing the risks and benefits of HCT for sickle cell disease;
  - New cellular therapy approaches: CARS and BIKES;
  - Out of the freezer: CIBMTR research using Research Repository samples;
  - Treating disease relapse after alloHCT;
  - Umbilical cord blood expansion: an alternative to HCT.

1.6.3 **Staff Continuing Education**

During 2014, 93% of staff members at both the Milwaukee and Minneapolis campuses attended various training programs in operations, CME, leadership development, and change management. See Appendix E for a list of specific training and professional development activities.
2.0 RESOURCE DEVELOPMENT PLAN ACCOMPLISHMENTS

2.1 QUALITY AND SCOPE OF THE RESEARCH DATABASE

Committed to optimizing and enhancing the quality and scope of the Research Database, the CIBMTR collects data for approximately 20,500 new transplant recipients annually as well as a continually increasing volume of follow-up data on previously reported recipients and donors. Figure 2.1 shows cumulative accession of transplants since 1970 when the IBMTR began collecting these data.

Figure 2.1. Accession of Transplant Recipients Registered with the CIBMTR

![Graph showing cumulative accession of transplants since 1970.](image)

2.1.1 Stem Cell Therapeutic Outcomes Database (SCTOD)

The CIBMTR administers the SCTOD for the HRSA-sponsored C.W. Bill Young Cell Transplantation Program, established by the Stem Cell Therapeutic and Research Act of 2005. Continued support for the SCTOD is provided through the Stem Cell Therapeutic and Research Reauthorization Act of 2010. The program has several goals:

- Collecting, analyzing and reporting outcomes data for all allogeneic transplants and other therapeutic uses of blood stem cells;
- Publicizing information about HCT to patients, families, health care professionals, and the public;
- Defining better processes for identifying unrelated matched marrow donors, peripheral blood stem cell (PBSC) donors, and cord blood units through one electronic system;
• Increasing availability of unrelated adult volunteer donors and cord blood units;
• Expanding research to improve patient outcomes.

Annually, the CIBMTR publishes HCT volumes and demographic data by transplant center and provides public access to this information available on the Program website (http://bloodcell.transplant.hrsa.gov).

As part of the contract to operate the SCTOD, the CIBMTR is required each year to perform a center-specific survival analysis comparing the one-year survival rates among US centers. The report contains transplants from both related and unrelated donors. The most recent report was finalized in November 2014 and contains information on all first allogeneic transplants performed in US centers from January 1, 2010, through December 31, 2012.

The CIBMTR has conducted four Center Outcomes Forums to engage relevant stakeholders in the center-specific outcomes reporting process. The most recent meeting was held in June 2014.

The Cellular Therapies for Regenerative Medicine (CTRM) data repository is also an SCTOD activity that tracks alternate uses of stem cells. The SCTOD contract mandates data collection on uses of cells found in bone marrow, peripheral blood, and umbilical cord blood for alternative therapeutic applications including regenerative medicine. The CTRM repository captures uses of cells for the treatment of diseases without the intention of replacing the recipient’s hematopoietic function. These therapies include, but are not limited to, treatment of infectious, cardiovascular, rheumatologic, neurologic, musculoskeletal, and endocrinologic diseases with the intent to improve organ function. The CIBMTR anticipates that the expansion of cellular therapy field with use of not only hematopoietic derived cells, but also cells from other tissues, will only increase and is expanding the capability and flexibility of data collection in this area.

Two working groups provide oversight specific to SCTOD:

• **Cord Blood Data Working Group.** This group reviews and makes content suggestions for the cord blood outcomes reports which, utilizing CIBMTR data, help banks meet regulatory requirements and understand product quality.

• **HRSA Blood Cell Transplant Website Working Group.** This group reviews and makes content suggestions for the C.W. Bill Young Cell Transplantation website (http://bloodcell.transplant.hrsa.gov). The CIBMTR provides the HCT data for this website.

### 2.1.2 Research Data Life Cycle

The Research Data Life Cycle (Figure 2.2) describes the track that data make as they are transformed from data to information and knowledge from the point of capture to its ultimate use in reporting and analysis. Activities along the Research Data Life Cycle are grouped in three general areas: Data Collection; Extraction, Transformation, and Load; and Data Sharing.

The process begins at data collection when transplant centers enter the data in one of the applications we offer to enable electronic data capture. Most centers will enter data in FormsNet, a web application now in its third generation. Centers that have implemented local or third party systems can also capture and submit data electronically using AGNIS (A Growable Network Information System) service. An overriding goal of these solutions is to ease data capture burden on the centers.
The CIBMTR collects data at two levels: TED and CRF. The TED data set is an internationally accepted standard data set that contains a limited number of key variables and is required for all consecutive transplant recipients. The CRF captures additional patient, disease, and treatment-related data. TED-level data, with some additional details of donor and graft characteristics, comprise the obligatory data to be submitted to the SCTOD by US transplant centers.

Following data collection, data are pulled four times per month from FormsNet to an Oracle staging environment that starts an Extraction, Transformation, and Load (ETL) program. During ETL, data are rigorously validated for consistency, completeness, and uniqueness using custom logic and standardized and encoded for optimal statistical analysis. ETL culminates in the loading of validated data to the Research Database.

Data Sharing completes the cycle, providing data for analysis that have been collected and curated to generate research value. These data are extracted from the Research Database in periodic retrievals to serve a range of research and stakeholder needs. The data retrievals provide the basis for research study data files, reports, and externally-requested datasets. TED-level data are also directly available to centers through use of the DBtC application (Section 2.2.2.2).

2.1.3 FormsNet

FormsNet is the CIBMTR’s web-based application for electronic submission of transplant outcomes data. The application was updated in 2014 to provide key enhancements supporting operational efficiencies. Monthly form maintenance releases began in January 2014 to update key form
validations, which save time as well as improve user experience and accuracy for CIBMTR staff and FormsNet users. Additional improvements to FormsNet in 2014 include:

- **Upgrades.** The Donor module was upgraded to the FormsNet3 platform to provide autopopulation, improved navigation / validation, and overall improved user experience.
- **Enhancements.** Recipient, Donor, Clinical Trials, Audit, Forms Definition Manager, and Monitoring applications were enhanced to provide improved support and operational efficiencies.
- **Auditing support.** Enhancements were made to the applications for auditing FormsNet data against source documents at centers.
- **Monitoring support.** The Monitoring application was enhanced to provide monitoring support for an additional clinical trial.

### 2.1.3.1 Continuous Process Improvement

Robust data collection is critical to the success of the CIBMTR. The CPI program ensures timeliness and completeness of data forms submissions (Appendix F). Transplant centers receive CPI reports three times per year (January, May, and September), listing the number of follow-up forms that were due in the previous trimester and the number and percentage of each submitted within the trimester. A form is not officially submitted until all errors are resolved and all applicable information is submitted and approved.

To be compliant, centers must submit at least 90% of forms due for the trimester, for all unrelated donor transplants and for related donor transplants that have occurred since December 3, 2007 (Table 2.1). As of September 1, 2014, 95% of US transplant centers were in compliance. The few remaining non-compliant centers enter a forms-due remediation procedure. If a center does not have current Institutional Review Board (IRB) approval information on file with the CIBMTR, it will not pass CPI even if the forms submission requirements are met.

<table>
<thead>
<tr>
<th>Table 2.1. CPI Form Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Form</strong></td>
</tr>
<tr>
<td>Pre-TED or Form 2000, required disease forms and/or Infection Forms</td>
</tr>
<tr>
<td>Post-TED or Form 2100, required disease forms and/or Infection Forms</td>
</tr>
<tr>
<td>Post-TED or Form 2200, required disease forms and/or Infection Forms</td>
</tr>
<tr>
<td>Post-TED or Form 2300, required disease forms and/or Infection Forms</td>
</tr>
</tbody>
</table>

In addition to the CPI recipient forms program, there are CPI regulations for donor forms. The Donor Data Management Team oversees submission of these forms from NMDP / Be The Match donor, collection, and apheresis centers. Donor CPI reports are generated four times per year (January, April, July, and October). To be compliant, centers must submit 100% of the forms required for that CPI period.
2.1.4 Research Database

Once collected in FormsNet, submitted data goes through computerized completeness and quality checks before being added to the CIBMTR Research Database. The latter now contains information on more than 390,000 transplant recipients going back to transplants performed in 1968. The distribution of patients in the database is displayed in Table 2.2 Mandatory submission of outcomes data for alloHCTs in the US ensures we capture almost all US transplants.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Allogeneic</th>
<th>Autologous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TED</td>
<td>CRF</td>
</tr>
<tr>
<td>Acute myelogenous leukemia</td>
<td>36,196</td>
<td>26,012</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>19,374</td>
<td>15,771</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>13,572</td>
<td>14,751</td>
</tr>
<tr>
<td>MDS / mucopolysaccharidosis</td>
<td>11,458</td>
<td>9,250</td>
</tr>
<tr>
<td>Plasma cell disorder</td>
<td>1,922</td>
<td>1,360</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10,137</td>
<td>5,991</td>
</tr>
<tr>
<td>Other malignant diseases(^1)</td>
<td>5,551</td>
<td>3,527</td>
</tr>
<tr>
<td>Severe aplastic anemia</td>
<td>5,667</td>
<td>6,403</td>
</tr>
<tr>
<td>Immune deficiencies</td>
<td>2,197</td>
<td>2,711</td>
</tr>
<tr>
<td>Inherited erythrocyte disorders(^2)</td>
<td>5,687</td>
<td>6,673</td>
</tr>
<tr>
<td><strong>Graft Source</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>44,705</td>
<td>55,183</td>
</tr>
<tr>
<td>Peripheral Blood</td>
<td>53,814</td>
<td>26,561</td>
</tr>
<tr>
<td>Cord Blood</td>
<td>4,336</td>
<td>7,124</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>111,761</strong></td>
<td><strong>92,449</strong></td>
</tr>
</tbody>
</table>

1. Includes other leukemias (n=8,629) and solid tumors (n=40,821).
2. Includes inherited erythrocyte disorders (n=8,078), inborn errors of metabolism (n=2,348), histiocytic disorders (n=1,321), autoimmune disease (n=606), and other non-malignant diseases (n=873).

In July 2014, the CIBMTR completed integration of Part I Forms Revision updates to the Research Database, including changes to pre-TED, baseline, product, and pre- and post-transplant disease forms for five major diseases that went live in FormsNet in October 2013. The scope of this effort encompassed the integration of 211 forms pages and more than 2,875 FormsNet field changes in the Research Database, ETL program, and SAS data retrievals that support CIBMTR research.

- **SAS Retrieval.** CIBMTR biostatisticians perform most analyses using third-party SAS software applications for clinical data analysis and reporting. To simplify study datasets, the CIBMTR creates SAS datasets of the most commonly analyzed data fields and the most commonly used computed variables. The data are extracted from the Research Database and formatted to be SAS-compatible. Four different datasets are created eight times per year, as shown in Table 2.3.
### Table 2.3. Study Datasets

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Description</th>
<th>Number of Variables</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>TED</td>
<td>All patients and transplants, regardless of reporting track</td>
<td>1,743</td>
<td>446,303</td>
</tr>
<tr>
<td>Research: Allogeneic</td>
<td>Patients on CRF track who had an allogeneic transplant and a follow-up form was submitted</td>
<td>15,984</td>
<td>105,713</td>
</tr>
<tr>
<td>Research: Autologous</td>
<td>Patients on CRF track who had an autologous transplant and a follow-up form was submitted</td>
<td>11,676</td>
<td>42,690</td>
</tr>
<tr>
<td>Study</td>
<td>Patients accrued to specified studies (generally prospective studies – e.g. KGF, RCI BMT trials)</td>
<td>16,208</td>
<td>14,535</td>
</tr>
</tbody>
</table>

#### 2.1.5 Data Quality

##### 2.1.5.1 Verification and Validation

When data are entered into FormsNet, a series of entry level validation checks takes place to ensure the data are valid. This process flags certain errors at the time of entry and allows the CIBMTR to contact the center data manager so errors can be corrected immediately while source documents are readily available. If a data field does not pass the FormsNet validation checks identified below, an error comment is generated, and the data manager is navigated to an error review page to review, resolve, or override the unresolved errors. Lastly, an error report is generated that lists any unresolved errors as well as errors that have been overridden. FormsNet validation checks include:

- **Mandatory field validation.** Certain fields on the forms must be completed for all recipients (e.g., primary questions that lead into secondary questions). Other fields must be completed depending on how a primary question is answered (e.g., ‘yes’ to ‘developed acute graft vs host disease (GVHD)’ makes all acute GVHD questions mandatory). The validation process checks that all mandatory fields are completed.

- **Range validation.** The validation process checks all laboratory values, drug doses, heights, and weights against established upper and lower limits. Additionally, the validation process ensures dates fall within an appropriate time frame.

- **Cross form consistency.** For certain data fields, the validation process checks for consistency between data reported on the current form and related data reported on a previous form. For example, on all forms, the contact date is validated against the HCT date.

- **Within form consistency.** The validation process also checks each form for consistency between related data reported on the same form. For example, all dates are validated against the ‘date of last contact’ or ‘date of actual contact’.

- **Core field validations.** The validation process checks against certain core data fields. For example, some questions are optional for international centers and required for domestic centers, so based on the location of the transplant center, a question may be optional or required.

Data extracted from FormsNet and loaded to the Research Database each month undergoes even more comprehensive validation and verification via an Extraction, Transformation & Load (ETL) process. These data are then more rigorously validated for consistency, completeness, and uniqueness.
using business rules created in custom logic for the categories provided below. Finally, the CIBMTR Data Quality Team reviews ETL errors and works with transplant centers to correct data.

- **Fields that cannot be null.** Business rules conduct structural validations to ensure data is complete and to limit the level of missing values in the data that may compromise its research utility.
- **Cross form consistency.** Additional rules are applied to ensure consistency across forms for a given patient on unique identifiers, key dates, and key values. This ensures the patient is uniquely defined across the database and there is no double counting.
- **Longitudinal consistency.** Several data specific rules are applied to ensure data is associated with the correct transplant records, especially for patients who receive multiple lines of therapy.
- **Logical relationships.** These rules ensure that logical dependencies between data are enforced. A simple example is that the date of transplants must occur after the patient’s date of birth.

Rules across these categories were updated and tested as part of the recent Forms Revision. Currently, the rate of form rejection is less than 2%, which is attributed to recent enhancements in transplant center education as well as to validations built in at the point of entry into FormsNet.

### 2.1.5.2 On-Site Data Audit Program

On-going data audits are performed at all CIBMTR participating transplant centers as part of the CIBMTR’s overall data quality assurance program. The audit compares data in source documents maintained at the transplant center with data contained in the CIBMTR Research Database. Currently, six Clinical Research Associates perform the on-site transplant center audits, spending three to four days at each center reviewing original source documents. The overall audit process is as follows:

- **Audit cycle.** Each domestic and international center that has submitted data for at least 20 HCTs is audited once within the 4-year audit cycle.
- **Recipient selection and eligibility requirements.** If a center has performed more than 20 HCTs during the audit period, recipient records are randomly selected for audit.
- **Forms and data fields.** All TED and CRF data are subject to data audit, and essential critical data fields are audited for each recipient.
- **Methodology.** Auditors compare the data submitted to the CIBMTR Research Database with the data in the source documents. Errors are reviewed with the data coordinator. CIBMTR auditors make all data corrections to the database, and the transplant center is provided with a record of all changes made to the TED forms and/or CRFs.
- **Audit analysis, reports, and corrective action.** Transplant centers receive a detailed audit report evaluating the results of their audit. Centers are required to submit a Corrective Action Plan following the audit in response to a critical field error rate above 3%, any systemic errors, consent issues requiring correction, or outstanding missing documentation issues.

In calendar year 2014, 51 centers were scheduled for audit (47 domestic, 4 international). As of December 1, 2014, 40 centers have been notified of their final audit results, including requested corrective action follow-up. Of those centers that have been sent reports, 80% passed with fewer than 3% critical field errors. Of the eight centers that did not pass the audit, four have completed all
required corrective action; the remaining four centers are in the process of completing requested corrective action.

2.1.6 Transplant Center Visits

The CIBMTR continued a program of transplant center visits in 2014 with the goal of understanding user needs, providing better data sharing solutions related to consolidation of data from disparate data sources, reducing time, and improving access to and delivery of data. Fifteen visits were conducted in 2014; the business needs gathered during these site visits will be incorporated into future enhancements to data sharing capabilities.

2.1.7 Data and Information for Statistical Center Operations (DISCO)

DISCO is the enterprise contact management system, deployed in Salesforce.com application software, and used by the CIBMTR to maintain key operational information, as follows: organization and contact information for transplant centers; Executive, Advisory, and Working committee administration; and membership data. Throughout 2014, DISCO was enhanced to more effectively track and manage the process flow of data related to Committee administration as well as Working Committee studies, from proposal to publication. By the end of 2014, the system will have completed its seventh release, furthering its ease of use and capabilities as a single point of access to administrative information and management reports.

2.1.8 Human Subjects / HIPAA Compliance

The CIBMTR is committed to the ethical conduct of research. All Coordinating Center personnel maintain Collaborative IRB Training Initiative certification. The NMDP / Be The Match IRB, which is fully accredited by the Association for the Accreditation of Human Research Protection Programs, reviews all human subject research conducted by the CIBMTR, and the CIBMTR maintains compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. CIBMTR rules requiring the registration of all consecutive HCT recipients ensure the inclusion of women, minorities, and children. For additional information, see Appendix G.

2.1.9 Information Security and Data Privacy

The SCTOD federal contract requires appropriate risk management in the form of minimum security controls, policies, and standards. The CIBMTR’s data systems are maintained in accordance with the Federal Information Systems Management Act of 2002, with information security guidance provided by the National Institute of Standards and Technology (http://www.nist.gov). In accordance with National Institute of Standards and Technology Special Publication 800-18 (http://csrc.nist.gov/publications/PubsSPs.html), and supervised by HRSA’s Office of Information Technology, the CIBMTR maintains a System Security Plan to address information security by implementing measures including management, operational, and technical controls.

Since December 2008, the CIBMTR holds an Authority to Operate from the Chief Information Officer of HRSA. The certification was renewed in December 2011, and annual security audits were performed in 2012, 2013, and 2014 to ensure compliance. The NMDP / Be The Match also holds an Authority to Operate from HRSA; ensuring similar standards of information security are applied to all CIBMTR and NMDP / Be The Match systems, including the FormsNet data collection system.
These controls maintained by the CIBMTR and NMDP / Be The Match represent robust information security risk management beyond those outlined by HIPAA.

### 2.2 TECHNOLOGY SOLUTIONS FOR SHARING DATA

It is key to the mission of the CIBMTR to provide state of the art technology solutions and develop collaborative agreements to share data for research. The CIBMTR leverages its federal funding to support a broad array of research programs in a cost-effective manner through its expert staff of physicians, statisticians, immunologists, and clinical research and IT professionals. The organization has become a respected leader in HCT research by providing a unique resource of information and expertise to the medical and scientific communities. CIBMTR studies have changed clinical practice and helped to improve survival and quality of life for patients undergoing or being considered for this complex procedure.

The CIBMTR Data Sharing Initiative focuses on improvements to provide fast, easy, and flexible access to data. In 2014, the CIBMTR supported the research of 44 principal investigators by providing datasets from the Research Database.

#### 2.2.1 Data Sharing Initiative

Thousands of hours of voluntary efforts from physicians and scientists spent using data from the CIBMTR Research Database to address important issues in HCT and other cancer treatments validate the need for this unique resource. The inclusive nature of the CIBMTR and its data access policies make these research data available to many through facilitation of studies in each of the research programs, standard CIBMTR reports, summary slides, and datasets. This year, the CIBMTR reviewed and updated its policies for clarity regarding expectations as well as obligations of users of CIBMTR data.

In 2014, the CIBMTR formalized its commitment to data sharing by creating a program to coordinate activities and effort to provide quality research data, information, and knowledge to meet the diverse needs of its stakeholders. The CIBMTR launched and completed a Data Sharing Assessment to evaluate the CIBMTR’s current IT resources and capabilities for data sharing, document the business needs and data uses of our stakeholders, and develop a roadmap for the future that leverages CIBMTR strengths as well as industry best practices. The Data Sharing Roadmap provides an evolutionary approach to create a unified Data Warehouse that leverages the existing work and design of the CIBMTR Data Warehouse as a foundation and is further expanded with the domain intelligence that already exists in the Research Database.

#### 2.2.2 Applications for Sharing Data

##### 2.2.2.1 A Growable Network Information System (AGNIS)

To assist transplant centers in collecting data for internal research, patient care requirements, and reporting purposes, the CIBMTR and NMDP / Be The Match BioInformatics created AGNIS. AGNIS supports secure data sharing across diverse database systems. It is an open-source web service developed with tools from the NCI caBIG® effort and other well-established projects, such as the Globus Toolkit. AGNIS software, distributed under a public license at www.agnis.net, is available to any interested center.
AGNIS allows participating centers to collect and share data with the CIBMTR as well as others who link to AGNIS. Data are entered once and then distributed and synchronized among databases. Data elements transmitted via AGNIS are curated using the metadata repository operated by the NCI Center for Biomedical Informatics and Information Technology, known as the Cancer Data Standards Registry and Repository (caDSR). This repository is compliant with government standards for electronic data transmission.

In the caDSR, common data elements for FormsNet database fields are compiled into Form Builder reports, which convert CIBMTR format into caDSR format and which centers use to submit data automatically to FormsNet via AGNIS. To date, common data elements have been created for more than 14,235 FormsNet database fields. This represents those database fields associated with 99% of the forms submitted via FormsNet. In addition, 28 Form Builder reports have been released in the caDSR. An additional 49 Form Builder reports have been created and are pending quality assurance testing and release in AGNIS. Between January 1 and December 1, 2014, a total of 18,109 forms were submitted through AGNIS.

### 2.2.2.2 Data Back to Center (DBtC)

The DBtC application provides users the ability to download CIBMTR TED level data variables. The data has been validated and processed in the CIBMTR Research Database and can be downloaded in a comma-separated value format. These data are reviewed and refreshed quarterly. A data dictionary is provided for each field and value in the datasets. Legacy IBMTR data is available for download as far back as 1964, and some legacy NMDP / Be The Match data is available as far back as 1987. These data can be downloaded by authorized users of a transplant center in a comma-separated value format. Between January 1 and December 1, 2014, 951 unique, non-CIBMTR visitors viewed 2,332 DBtC pages and downloaded data 486 times.

- In June 2013, DBtC access was extended to two cooperative registry groups (Asia-Pacific Blood and Marrow Transplant Group & Canadian Blood and Marrow Transplant Group) to obtain data submitted to the CIBMTR by their transplant center members. Access to a transplant center’s data is only provided in cases in which the transplant center has signed a data transmission / sharing agreement form with their respective registry. In 2014, the CIBMTR continued discussion with other international registries to put in place formal agreements to use CIBMTR data as their primary data source.
- In July 2014, DBtC underwent major enhancement to include all pre-TED and post-TED form version 4 changes introduced in FormsNet3 during the Forms Revision release in October 2013.

### 2.2.2.3 Center Volumes Portal

The Center Volumes Portal allows centers to preview; correct, if necessary; and approve center volume data published annually to the HRSA Blood Cell Transplant website (http://bloodcell.transplant.hrsa.gov). Under contract to HRSA as part of the C.W. Bill Young Transplantation Program, the CIBMTR provides information regarding transplants performed at US transplant centers.

The CIBMTR uses its portal site to give centers access to display and download the previous five years (2009-2013) of volume data as well as the current year under review (2013). For 2013, 59 of 215
centers have submitted approval to publish their center volume data. The review of the Center Volumes Portal will be ongoing through December 2014, and we anticipate the number of centers that agree to have their data published will increase significantly. During 2014, there were 5,081 pages viewed by 707 unique, external visitors to the portal site, and, of those, 1,668 pageviews were of the Center Volumes Portal.

2.2.2.4 Patient One-Year Survival Calculator – Allogeneic Transplants

In July 2014, the CIBMTR launched the Patient One-Year Survival Calculator for Allogeneic Transplants by deploying the calculator to the portal site for access by medical directors. This calculator represents the first of several online application tools planned by the CIBMTR that leverage data submitted by centers to support decision-making and research. The intent of this online survival calculator is to provide centers with a tool to predict one year survival for individual allogeneic HCT recipients. Data taken from the CIBMTR Center-Specific Survival Report for 2013 is used to calculate the “expected” probability of one-year survival for individual recipients of first allogeneic HCT in the US. Patient, disease, and transplant characteristics of allogeneic HCT recipients at US HCT centers between 2009 and 2011 are used to generate these estimates. The calculator will be updated annually to reflect new information contained in future center outcomes analyses.

2.2.2.5 BRIDG

BRIDG (Biomedical Research Integrated Domain Group) is a collaborative effort engaging stakeholders from four organizations: Clinical Data Interchange Standards Consortium; HL7 Regulated Clinical Research Information Management Work Group; NCI, including the caBIG project; and FDA. The goal of the BRIDG group is a common view of data exchange. The BRIDG model balances the concerns of the larger health care community while being specific enough to apply to a particular subject area, such as HCT. Common data elements for certain standard CIBMTR forms have been extracted and associated to one of three contexts: recipient, donor, or stem cell product. Future expansion of the BRIDG model will add HCT content as the basis for a physical database model. This physical model will help remove barriers that transplant centers experience in electronic transfer of HCT data to the SCTOD by providing a foundation upon which to develop their own in-house data systems and eventual development of electronic medical record integration engines to submit data to the CIBMTR Research Database.
3.0 SCIENTIFIC RESOURCE UTILIZATION PLAN ACCOMPLISHMENTS

3.1 PROCESSES FOR PROPOSED STUDIES

In its ongoing efforts to enhance processes for review, prioritization, and implementation of proposed studies, the CIBMTR provides many opportunities to conduct research in the Clinical Outcomes Research Program and encourages both senior and junior investigators to participate. Scientific Working Committees provide an opportunity for investigators to collaborate with leaders in the field and leverage the unique resources of the Research Database. The CIBMTR ensures that data from the Research Database are used for scientifically and clinically relevant research by engaging the scientific community and providing investigators with the statistical and scientific support necessary to perform studies that adhere to rigorous methodological standards.

To ensure Working Committee studies have notable impact on the field and effectively utilize CIBMTR resources, a number of processes took place in 2014:

- **Advisory Committee Oversight.** The CIBMTR Advisory Committee reviewed Working Committee work plans and progress in February (before the BMT Tandem Meetings), March (after the BMT Tandem Meetings), and July.

- **Communication Plan.** The CIBMTR developed and distributed a communication plan for Working Committee leadership in November. This plan articulated best practices for communication among the collaborating parties in their respective roles: principal investigators, writing committee members, Working Committee Chairs, MS statisticians, and Scientific Directors.

- **Working Committee Chair Meeting.** The CIBMTR conducted a meeting for all Working Committee Chairs at the BMT Tandem Meetings in February to discuss best practices and the role of an active Working Committee Chair.

- **Working Committee Scientific Director Meetings.** Working Committee Scientific Directors met bi-monthly to discuss best practices.

- **Working Committee Leadership Meetings.** Each Working Committee’s leadership team conducted monthly phone conferences to monitor study progress, discuss new proposals, prioritize activities, and refine study goals.

- **Statistical Team Meetings.** All MS statisticians met monthly to discuss best practices and implement enhanced collaboration tools across the statistical team.

- **MS Statistician Meetings.** The Associate Statistical Directors met with each MS statistician individually on a regular basis to assist with task prioritization and ensure work plan goals were met.

In 2014, the Clinical Outcomes Research Program achieved the following milestone accomplishments:

- **Studies.** Among the 15 Scientific Working Committees, 209 studies were in progress at the end of December.

- **Proposals.** The following numbers of proposals were submitted to Working Committees to be considered for presentation at their meetings, which occur during the BMT Tandem Meetings:
  - For the 2014 Working Committee meetings, the CIBMTR received 156 study proposals; 88 were presented, and 40 were accepted.
  - For the 2015 Working Committee meetings, the CIBMTR received 156 study proposals.
3.0 SCIENTIFIC RESOURCE UTILIZATION PLAN ACCOMPLISHMENTS

• **Publications.** In 2014, 48 Clinical Outcomes Research Program papers were published in peer-reviewed journals, including early electronic publications and printed publications.

• **Presentations.** Clinical Outcomes Research Program investigators presented the following abstracts at annual scientific meetings:
  - At the 2014 BMT Tandem Meetings, 16 abstracts (13 oral and 3 posters) were presented.
  - At the 2014 American Society of Hematology Annual Meeting, 16 abstracts (9 oral and 7 posters) were presented.

For a list of 2014 Clinical Outcomes Research Program (Scientific Working Committee) publications, see Appendix H. For a list of all CIBMTR presentations, see Appendix I.

3.2 MOVING A STUDY PROPOSAL TO PUBLICATION

In order to optimize the timeline for moving a study proposal to publication, the Clinical Outcomes Research Program study development cycle (Appendix J) involves a number of steps. Efficiently moving a study proposal to publication is a multi-faceted effort. In 2014, the following groups accomplished the specified activities.

**Working Committee Chairs:**

- Limited the number of studies in progress, emphasizing making greater progress on fewer studies.
  - Investigators submitted 156 proposals to be implemented in 2014; 88 were presented during the Working Committee meetings at the 2014 BMT Tandem Meetings, and 40 were accepted by Working Committee Chairs for implementation.
- Encouraged and provided support to study principal investigators to ensure study progression.

**Coordinating Center Staff Members:**

- Reviewed studies in the manuscript preparation phase during weekly Coordinating Center Statistical Meetings to identify those not meeting established timelines for submission.
- Provided ongoing reviews pertinent to data consistency and quality, shortening the timeline for dataset preparation.

**Advisory Committee:**

- Instructed Working Committee Chairs to only accept proposals for high priority studies that were immediately actionable.
- Monitored Working Committee progress on specific metrics to support and encourage Chairs and assist them, when needed.

3.3 SUPPORT OF CLINICAL TRIALS

Using data from observational studies to support decisions regarding design of prospective clinical trials and/or amendments of such trials, the CIBMTR Research Database provides an important resource to the Clinical Trials Support Program for the determination of feasibility and study planning. This program consists of the BMT CTN and RCI BMT, which conduct multicenter clinical trials, and data from the Research Database are used to design, monitor, and analyze these trials. Additionally, long-term follow-up data of patients enrolled in BTM CTN and RCI BMT trials are
obtained through routine CIBMTR data collection processes, resulting in considerable cost-savings. The CIBMTR Coordinating Center provides expertise and other resources that support both large and small trials in several ways:

- **Trial planning.** Investigators planning clinical trials in HCT use the Research Database to determine which patient populations may be available for trials. With the aid of CIBMTR Coordinating Center staff, they can estimate how changing eligibility criteria will affect patient accrual. The Research Database provides a more precise, less biased estimate of the baseline outcomes of interest than literature reviews, expert opinions, or personal experience at a transplant center. The database can identify the most common supportive care and other practices in potentially eligible patients so that clinical protocols can be written that are acceptable to most transplant centers. The CIBMTR routinely makes this information available to BMT CTN and RCI BMT protocol teams and provides it to other investigators upon request.

- **Data collection instruments.** The CIBMTR has an open policy for sharing data collection forms and database structures. The forms are freely available on the CIBMTR website and are the basis for data collection in many clinical trials. These forms reflect the knowledge and expertise not only of Coordinating Center personnel but also the many transplant experts on Working Committees who evaluate and revise the data collection forms.

- **Statistical consultation.** Coordinating Center personnel have provided statistical review of several HCT clinical trial protocols and are considered expert resources. CIBMTR faculty members serve as protocol statisticians for the BMT CTN and RCI BMT.

- **Trial interpretation.** The Research Database is a valuable tool for evaluating results of clinical trials, especially single-arm studies. Using the database, the Coordinating Center can provide matched controls for patients treated in single and multi-institution studies of transplant strategies, thus allowing more accurate estimation of treatment effects after controlling for patient characteristics. The BMT CTN uses this approach to evaluate Phase II data before embarking on large Phase III trials.

### 3.3.1 BMT CTN

The BMT CTN is the US national trials group charged with developing and conducting multicenter phase II and III clinical trials focused on HCT. The CIBMTR is the lead institution for the BMT CTN Data and Coordinating Center, which it runs in collaboration with NMDP / Be The Match and the EMMES Corporation, a contract research organization based in Rockville, MD. The BMT CTN’s accomplishments over the past year include:

- Opened one new trial to accrual, bringing the total number of launched trials to 34;
- Accrued 1,316 patients to trials, increasing the total number of accrued patients to 7,303;
- Managed 11 open protocols with overall accrual for open studies at about 175% of projections;
- Published 10 peer-reviewed manuscripts, including 5 primary results manuscripts;
- Presented 10 abstracts of study results at national and international meetings.

This year’s BMT CTN publications are listed in **Appendix H**, and all CIBMTR presentations are listed in **Appendix I**. A complete list of BMT CTN protocols is provided in **Appendix K1**.
3.3.2 RCI BMT

The Coordinating Center developed the RCI BMT in 2005. This resource conducts prospective research within the CIBMTR, providing researchers in the field of HCT with infrastructure and expertise in HCT clinical trial conduct and analysis. The RCI BMT’s goal is to help investigators generate data allowing novel and innovative ideas to move into the larger Phase II or Phase III setting into such groups as the BMT CTN or the national cancer cooperative groups. This year the RCI BMT’s accomplishments include:

- Published two manuscripts in peer-reviewed journals;
- Managed 5 open protocols, which accrued 2,477 patients;
- Completed analysis and submitted abstracts, which were accepted, for 12 protocols;
- Completed accrual on 3 protocols;
- Managed 2 Food and Drug Administration (FDA) investigational new drug protocols for Be The Match Operations: PBSC Procurement and Cord Blood Access, which accrued 2,174 and 548 subjects, respectively;
- Continued the development of three other protocols;
- Supported five studies involving unrelated donor data or sample collection for investigators.

A list of 2014 RCI BMT publications is provided in Appendix H, and a complete list of RCI BMT clinical trials is provided in Appendix K2.

3.3.2.1 Survey Research Group

The Survey Research Group, a team within the RCI BMT was created to assist HCT researchers in developing and conducting research involving questionnaires, direct subject interviews, and patient reported outcomes. The group is responsible for collecting high quality, scientifically valid data from donors, patients, and their families. The Survey Research Group utilizes standardized and semi-structured telephone interviews as well as self-administered questionnaires. While many of their research studies are part of the RCI BMT portfolio, the SRG has also partnered with the BMT CTN, Bioinformatics Research, and Health Services Research Program to assist these groups with their research portfolio.

The Survey Research Group consists of a supervisor, research assistant, and five research interviewers. This team conducts surveys regarding medical health, quality of life, and healthcare utilization, and it provides support in the collection of study materials, such as consent forms and buccal swab kits by following up with subjects via telephone when needed. The Survey Research Group plays a key role in the overall success and productivity of the RCI BMT team by providing a unique resource and HCT researchers. The group’s accomplishments over the past year include:

- Supported eight active studies;
- Participated in the development of one upcoming study.

3.4 Long Term Follow-Up of Patients in Clinical Trials

The CIBMTR continues to assist in long term follow-up of all patients involved in the Clinical Trials Support Program’s BMT CTN and RCI BMT clinical trials except those led by cooperative groups. After the primary and/or secondary study endpoints have been reached, the CIBMTR takes primary responsibility for follow-up. In 2014, the CIBMTR was involved in follow-up for 4,670 patients from 29 clinical trials (Table 3.1).
Table 3.1. CIBMTR Long Term Follow-Up of Patients Enrolled in BMT CTN Clinical Trials

<table>
<thead>
<tr>
<th>BMT CTN Protocol</th>
<th>Accrual Status</th>
<th>Date Opened to Accrual</th>
<th>Date Closed to Accrual</th>
<th>Number of Patients Enrolled</th>
<th>Number of Patients Followed in 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>0101</td>
<td>Closed</td>
<td>12/1/2003</td>
<td>9/21/2006</td>
<td>600</td>
<td>280</td>
</tr>
<tr>
<td>0102</td>
<td>Closed</td>
<td>11/15/2003</td>
<td>3/30/2007</td>
<td>709</td>
<td>374</td>
</tr>
<tr>
<td>0201</td>
<td>Closed</td>
<td>1/20/2004</td>
<td>10/16/2009</td>
<td>551</td>
<td>183</td>
</tr>
<tr>
<td>0301</td>
<td>Closed</td>
<td>1/24/2006</td>
<td>12/2/2013</td>
<td>97</td>
<td>76</td>
</tr>
<tr>
<td>0302</td>
<td>Closed</td>
<td>8/25/2005</td>
<td>3/24/2008</td>
<td>180</td>
<td>54</td>
</tr>
<tr>
<td>0303</td>
<td>Closed</td>
<td>6/30/2005</td>
<td>12/24/2006</td>
<td>47</td>
<td>25</td>
</tr>
</tbody>
</table>
### Table 3.1. CIBMTR Long Term Follow-Up of Patients Enrolled in BMT CTN Clinical Trials

<table>
<thead>
<tr>
<th>BMT CTN Protocol</th>
<th>Accrual Status</th>
<th>Date Opened to Accrual</th>
<th>Date Closed to Accrual</th>
<th>Number of Patients Enrolled</th>
<th>Number of Patients Followed in 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>0401 Phase III Rituxan / BEAM vs Bexxar / BEAM with autoHCT for persistent or relapsed chemotherapy-sensitive diffuse large B cell non-Hodgkin lymphoma</td>
<td>Closed</td>
<td>12/7/2005</td>
<td>7/17/2009</td>
<td>224</td>
<td>84</td>
</tr>
<tr>
<td>0402 Phase III randomized, multicenter trial comparing sirolimus / tacrolimus with tacrolimus / methotrexate as GVHD prophylaxis after HLA-matched, related PBSC transplantation</td>
<td>Closed</td>
<td>11/20/2006</td>
<td>10/28/2011</td>
<td>314</td>
<td>158</td>
</tr>
<tr>
<td>0403 Randomized double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor Enbrel (etanercept) for the treatment of acute noninfectious pulmonary dysfunction (idiopathic pneumonia syndrome) following alloHCT</td>
<td>Closed</td>
<td>8/27/2007</td>
<td>9/14/2011</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>0501 Multicenter, open label, randomized trial comparing single vs double umbilical cord blood HCT in pediatric patients with leukemia and MDS</td>
<td>Closed</td>
<td>10/16/2006</td>
<td>2/29/2012</td>
<td>224</td>
<td>136</td>
</tr>
<tr>
<td>0502 Phase II study of alloHCT for older patients with AML in first morphologic complete remission using a NMA preparative regimen</td>
<td>Closed</td>
<td>1/29/2007</td>
<td>12/29/2011</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>0601 Unrelated donor HCT for children with severe sickle cell disease using a RIC regimen</td>
<td>Closed</td>
<td>6/27/2008</td>
<td>4/24/2014</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>0603 Multicenter, Phase II trial of NMA conditioning and HCT of partially HLA-mismatched bone marrow for patients with hematologic malignancies</td>
<td>Closed</td>
<td>10/17/2008</td>
<td>5/17/2010</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>BMT CTN Protocol</td>
<td>Accrual Status</td>
<td>Date Opened to Accrual</td>
<td>Date Closed to Accrual</td>
<td>Number of Patients Enrolled in 2014</td>
<td></td>
</tr>
<tr>
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<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>0604 Multicenter, Phase II trial of NMA conditioning and HCT of umbilical cord blood from unrelated donors in patients with hematologic malignancies</td>
<td>Closed</td>
<td>12/23/2008</td>
<td>3/31/2010</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>0701 AlloHCT using RIC for relapsed follicular cell non-Hodgkin lymphoma using related or unrelated donors</td>
<td>Closed</td>
<td>4/27/2009</td>
<td>10/22/2012</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>0702 Trial of single autologous transplant with or without consolidation therapy vs tandem autoHCT with lenalidomide maintenance</td>
<td>Closed</td>
<td>6/1/2010</td>
<td>11/15/2013</td>
<td>758</td>
<td></td>
</tr>
<tr>
<td>0801 Phase II/III randomized, multicenter trial comparing sirolimus plus prednisone and sirolimus / calcineurin inhibitor plus prednisone for the treatment of chronic GVHD</td>
<td>Closed</td>
<td>4/15/2010</td>
<td>3/26/2013 (Ph II) 12/9/2013 (Ph III)</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>0802 Multicenter randomized, double blind, Phase III trial evaluating corticosteroids with mycophenolate mofetil vs corticosteroids with placebo as initial systemic treatment of acute GVHD</td>
<td>Closed</td>
<td>2/1/2010</td>
<td>11/14/2011</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td>0803 High-dose chemotherapy with autologous stem cell rescue for aggressive B cell lymphoma and Hodgkin lymphoma in HIV-infected patients</td>
<td>Closed</td>
<td>7/12/2010</td>
<td>5/15/2013</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>0901 Randomized, multicenter Phase III study of alloHCT comparing regimen intensity in patients with MDS or AML</td>
<td>Closed</td>
<td>6/2/2011</td>
<td>4/18/2014</td>
<td>272</td>
<td></td>
</tr>
</tbody>
</table>
### Table 3.1. CIBMTR Long Term Follow-Up of Patients Enrolled in BMT CTN Clinical Trials

<table>
<thead>
<tr>
<th>BMT CTN Protocol</th>
<th>Accrual Status</th>
<th>Date Opened to Accrual</th>
<th>Date Closed to Accrual</th>
<th>Number of Patients Enrolled</th>
<th>Number of Patients Followed in 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>0902 Phase III randomized, multicenter trial testing whether exercise or stress management improves functional status and symptoms of autoHCT and alloHCT recipients</td>
<td>Closed</td>
<td>1/3/2011</td>
<td>6/1/2012</td>
<td>711</td>
<td>494</td>
</tr>
<tr>
<td>0903 AlloHCT for hematological cancers and MDS in HIV-infected individuals</td>
<td>Open</td>
<td>5/11/2012</td>
<td>N/A</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>1101 Multi-center Phase III randomized trial of RIC and HCT of double unrelated umbilical cord blood vs HLA-haploidentical related bone marrow for patients with hematologic malignancies</td>
<td>Open</td>
<td>6/19/2012</td>
<td>N/A</td>
<td>134</td>
<td>123</td>
</tr>
<tr>
<td>1102 Multi-center biologic assignment trial comparing RIC alloHCT to hypomethylating therapy or best supportive care in patients aged 50-75 with intermediate-2 and high risk MDS</td>
<td>Open</td>
<td>12/16/2013</td>
<td>N/A</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td>1202 Prospective multi-center cohort for the evaluation of biomarkers predicting risk of complications and mortality following alloHCT</td>
<td>Open</td>
<td>6/11/2013</td>
<td>N/A</td>
<td>1,271</td>
<td>1,256</td>
</tr>
<tr>
<td>1203 Multi-center Phase II trial randomizing novel approaches for GVHD prevention compared to contemporary controls</td>
<td>Open</td>
<td>9/17/2014</td>
<td>N/A</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>1204 RIC for children and adults with hemophagocytic syndromes or selected primary immune deficiencies</td>
<td>Open</td>
<td>11/14/2013</td>
<td>N/A</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>1205 Easy-to-read informed consent (ETRIC) for HCT clinical trials</td>
<td>Open</td>
<td>11/26/2013</td>
<td>N/A</td>
<td>39</td>
<td>39</td>
</tr>
</tbody>
</table>
The CIBMTR is also involved in a large prospective outcomes study evaluating patients who do versus those who do not receive keratinocyte growth factor (KGF) to prevent mucositis. This FDA-required study is sponsored by Sobi, which manufactures KGF. Study accrual was completed in May 2014 with 2,250 matched pairs. While the primary purpose of this study is to follow a large number of patients to support the long term safety of this therapy, because of the study size and duration, we expect this cohort to be a valuable resource for other CIBMTR studies of late effects after HCT.

3.5 USE OF IMMUNOLOGIC DATA FROM THE RESEARCH SAMPLE REPOSITORY

Within the Immunobiology Research Program, the CIBMTR leverages the NMDP / Be The Match’s investment in its unrelated donor-recipient specimen Research Sample Repository with the NIH’s investment in the CIBMTR Research Database. Linking outcomes data to immunologic data available in the Research Sample Repository supports studies that include genetic and immunobiologic data and clinical phenotype data.

The Related Donor Research Sample Repository is a unique opportunity to enhance immunobiologic research. Related donor and recipient samples are better matched than unrelated recipients for HLA, a measure of immunological compatibility, thus reducing the confounding effects of HLA disparity in clinical research. The Related Donor Research Repository facilitates an organized approach to studying transplant biology across the full spectrum of allogeneic HCT.

As of December 2014, the number of centers submitting related recipient-donor sample pairs for the Related Donor Research Sample Repository increased to 63 centers (up from 52 in 2013). The related pair samples are an important addition to the existing sample repository. There was an approximately 40% increase in the related donor transplant sample inventory in the last year.

As of December 2014, the Research Repository included:

- 1,815,832 aliquots;
- 18,901 cell lines;
- 54,556 samples from unrelated donors and 3,870 from related donors;
- 52,626 samples from unrelated recipients and 4,113 from related recipients;
- 9,643 samples from unrelated cord blood units;
- 31,464 samples from complete unrelated adult donor-recipient pairs, 3,483 from complete related donor-recipient pairs, and 3,322 from unrelated cord-recipient pairs.

The Immunobiology Research group continues to manage the Research Repository inventory and immunogenetic testing programs that add critical HLA and killer-cell immunoglobulin-like receptors data for use in CIBMTR clinical outcomes studies. In 2014, the group enhanced the testing programs by incorporating additional typing. The Immunobiology Research group completed high resolution HLA typing on 1,145 related and 2,500 unrelated HCT donor / cord and recipient pairs, bringing the total to more than 17,500 unrelated donor / cord and recipient pairs that have been retrospectively high resolution typed for HLA-A, -B, -C, -DRB1 and -DQB1; more than 70% include -DPB1. These HLA data have facilitated seminal publications on the impact of high resolution HLA matching in unrelated donor (Lee et. al. Blood 2007) and umbilical cord blood (Eapen et al. Blood 2013) transplantation.

In 2014, the Immunobiology Research group implemented a new inventory management system, LabVantage, for clinical trial specimens collected for the BMT CTN and RCI BMT. The sample
inventory details were also integrated into the CIBMTR Data Warehouse to support inventory query report automation. Additionally, the group distributed 8,313 research samples in support of Working Committee studies.

### 3.6 OBSERVATIONAL STUDIES

The Clinical Outcomes Research Program currently supports 209 Scientific Working Committee studies in progress. Total numbers of new, ongoing, and completed studies by year are displayed in **Table 3.2**. We continue to encourage new investigators to participate in and lead studies. In 2014, as in the past two years, more than half of the proposals submitted for consideration at the 2015 BMT Tandem Meetings were developed by principal investigators who had not previously submitted a proposal to use our data.

<table>
<thead>
<tr>
<th>Year</th>
<th>Completed</th>
<th>New</th>
<th>Continuing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>22</td>
<td>39</td>
<td>113</td>
<td>135</td>
</tr>
<tr>
<td>2006</td>
<td>34</td>
<td>49</td>
<td>135</td>
<td>169</td>
</tr>
<tr>
<td>2007</td>
<td>41</td>
<td>33</td>
<td>162</td>
<td>203</td>
</tr>
<tr>
<td>2008</td>
<td>38</td>
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</tr>
<tr>
<td>2009</td>
<td>76</td>
<td>58</td>
<td>209</td>
<td>285</td>
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<tr>
<td>2010</td>
<td>74</td>
<td>50</td>
<td>217</td>
<td>291</td>
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<tr>
<td>2011</td>
<td>55</td>
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<tr>
<td>2012</td>
<td>65</td>
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<td>256</td>
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<tr>
<td>2013</td>
<td>51</td>
<td>46</td>
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<td>228</td>
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<tr>
<td>2014</td>
<td>46</td>
<td>43</td>
<td>163</td>
<td>209</td>
</tr>
<tr>
<td><strong>TOTALS</strong></td>
<td><strong>502</strong></td>
<td><strong>431</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Outcomes Research Program studies conducted by the Scientific Working Committees resulted in 48 publications in 2014. **Table 3.3** lists the number of papers published by each Scientific Working Committee. **Appendix H** lists the publications.
Within the study portfolio, the CIBMTR aspires to provide novel observational studies in malignant and non-malignant blood and other disorders, including use of genetically engineered cellular products.

3.6.1 Non-Transplant Therapy Research Initiatives

With the consensus and support of its Advisory Committee, the CIBMTR is committed to collecting data on non-transplanted patient populations. The CIBMTR is working collaboratively with the Primary Immune Deficiency Disease Consortium to add transplant outcomes data to data on non-transplant therapy collected by the Consortium. Additionally, the CIBMTR is amending its registration of cases to more easily accommodate data collection for cellular and other therapies that do not involve transplantation.

Myelodysplastic syndrome (MDS) is more common in the elderly, many of whom were denied access to HCT therapy in the US due to lack of Medicare insurance coverage by the Centers for Medicare and Medicaid Services (CMS). To help secure Medicare coverage for these patients, the CIBMTR, NMDP / Be The Match, American Society for Blood and Marrow Transplantation (ASBMT), and other organizations partnered with CMS to launch a Coverage with Evidence Development (CED) study, using data in the CIBMTR Research Database that are collected to fulfill SCTOD requirements. The CED approach allows CMS to provide coverage for procedures and to advocate for clinical studies that inform policy decisions. In 2010, the CIBMTR launched the CMS-approved study, “Assessment of Stem Cell Transplantation in Medicare Beneficiaries with Myelodysplastic Syndrome and Related Disorders.” As of December 2014, 121 centers are participating, and 913 patients ≥65 years old, 685 patients 55-64 years old, and 189 patients <54 years old are enrolled.

### Table 3.3. 2014 Publications by Scientific Working Committees

<table>
<thead>
<tr>
<th>Scientific Working Committee</th>
<th>Number of Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Leukemia</td>
<td>3</td>
</tr>
<tr>
<td>Chronic Leukemia</td>
<td>4</td>
</tr>
<tr>
<td>Donor Health and Safety</td>
<td>2</td>
</tr>
<tr>
<td>Graft Sources and Manipulation</td>
<td>5</td>
</tr>
<tr>
<td>Graft-vs-Host Disease</td>
<td>3</td>
</tr>
<tr>
<td>Health Services and International Issues</td>
<td>3</td>
</tr>
<tr>
<td>Immunobiology</td>
<td>10</td>
</tr>
<tr>
<td>Late Effects and Quality of Life</td>
<td>5</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Pediatric Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Plasma Cell Disorders and Adult Solid Tumors</td>
<td>3</td>
</tr>
<tr>
<td>Primary Immune Deficiencies, Inborn Errors of Metabolism, and Non-Malignant Marrow Disorders</td>
<td>2</td>
</tr>
<tr>
<td>Regimen-Related Toxicity and Supportive Care</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>48</strong></td>
</tr>
</tbody>
</table>
3.0 SCIENTIFIC RESOURCE UTILIZATION PLAN ACCOMPLISHMENTS

A follow-up study to the ongoing Centers for Medicare and Medicaid Services study of HCT outcomes is now collecting comparison data for a cohort of patients receiving non-HCT therapy for MDS. The CIBMTR is combining its resources with those of the BMT CTN to do this in a cost-effective manner. Through November 2014, 28 centers have been activated and 42 patients enrolled.

3.7 BIOSTATISTICAL APPROACHES

Optimization of the CIBMTR data analysis process is, in part, accomplished through enhanced biostatistical approaches. Through the Statistical Methodology Research Program, the CIBMTR has enjoyed a positive, collaborative association with the Division of Biostatistics in the MCW Institute for Health and Society since 1985, an association that is a distinctive asset and crucial to the success of CIBMTR research. This long-standing relationship has many benefits, including:

- Ensuring the statistical integrity of CIBMTR scientific activities;
- Contributing to results in articles on HCT-related statistical issues for clinical audiences;
- Supporting Working Committee members and investigators in developing scientific study protocols using CIBMTR data.

HCT is a complex process with multiple competing risks and dramatic changes in the risks of specific events over time. The CIBMTR has developed and evaluated the statistical models used in HCT research while also acknowledging that it is important to guide the research community in appropriate application and interpretation of these sophisticated models. Therefore, the CIBMTR’s statistical research development goals are two-fold: development of the new models and new statistical methods themselves and comparison of these models and methods with existing solutions using the Research Database.

The Division of Biostatistics faculty has substantial collective experience in assessing the unique problems associated with HCT research, and the statistical techniques and methodology they develop enable rigorous analysis of these data. In their statistical oversight of CIBMTR studies, this group directly and indirectly trains and mentors the Master’s-level statisticians, positively influencing the overall integrity of CIBMTR data used in its published works. The combined expertise of these statistical partners is a unique asset that continually contributes to the strength of the CIBMTR research portfolio.

In 2014, biostatistical faculty published four statistical methodology papers. These publications are listed in Appendix H and incorporate the following topics:

- Comparison of cumulative incidence functions with early or late weightings and with an R-CIFsmry package;
- Comparison of statistics in association tests of genetic markers for survival outcomes;
- Use of a revised Fisher model on the analysis of quantitative trait loci with multiple alleles;
- Verification of a subdistribution hazards model with cumulative sums of residuals.
3.8 HEALTH SERVICES RESEARCH IN HCT

The CIBMTR conducts research through the Health Services Research Program in collaboration with NMDP / Be The Match Patient and Health Professional Services and the Health Services and International Issues Working Committee. The Health Services Research Program agenda includes six focus areas: research, system capacity, health policy, program evaluation, clinical trial support, and training / education; additional detail for each focus area is provided below. To meet its scientific goals, the Health Services Research Program continues to collaborate with other investigators and explore opportunities for additional funding. The program’s 2014 publications are listed in Appendix H.

Research

- **Transplant provider and center factors and outcomes of alloHCT.** A national survey of US transplant centers was conducted to obtain information about transplant center personnel, infrastructure, and care delivery models as well as their influence on overall survival after allogeneic HCT. Two manuscripts are under preparation; one will describe the results of the survey, and the second will describe the association of center factors with survival.

- **Individualized care plans for HCT survivors.** In 2013, the Health Services Research Program was awarded $1.2 million by the Patient Centered Outcomes Research Institute to conduct this two-phase study. The first phase of the study has been completed. It involved focus groups of patients / caregivers and transplant center and community clinical providers to optimize survivorship care plan content, format, and delivery for HCT survivors; data analysis in progress. The second phase includes a randomized, controlled study managed by the RCI BMT and will evaluate the effectiveness of the optimized survivorship care plan; the protocol has been released to participating centers, and we expect the study to open for enrollment in the first quarter of 2015.

- **Secondary claims data analysis.** The Health Services Research Program continues to gain experience in using secondary claims data for investigation of the costs of HCT. One study is evaluating the feasibility of using a commercial claims database (Truven Health Analytics MarketScan®) for investigating costs of HCT vs no HCT for older patients with acute myeloid leukemia.

System Capacity

- **HCT in 2020: A health care resource and infrastructure assessment.** The NMDP / Be The Match, in collaboration with other key organizations, experts, and stakeholders, is in the fifth year of an initiative to address system capacity challenges to the growth of HCT. The Health Services Research Program provides expertise and support to the working groups in areas such as survey research, data analysis, literature review, and dissemination.

- **Identifying HCT patient housing and caregiver challenges and potential interventions.** This study included focus groups and a national survey of HCT social workers to identify challenges to patient housing and caregiver availability as well as to learn what solutions centers have in place to help patients with these challenges. Manuscript preparation in ongoing.

- **HCT multidisciplinary care teams: Burnout, moral distress, and career satisfaction.** This study will survey physicians, mid-level providers, pharmacists, and nurses who work with BMT patients to understand issues around burnout, moral distress, compassion fatigue, and
career satisfaction. The protocol is under IRB review, and we anticipate the survey will be implemented in January 2015.

Evaluation

- **Post-transplant care guides.** Patient-focused post-transplant care guides were developed to facilitate follow-up care for HCT recipients. To evaluate the effectiveness of the guides overall, a longitudinal, repeat-measures survey is administered at 6, 12, and 24 months post-transplant to alloHCT recipients. Results of this evaluation will be used to improve the care guides and educational interventions on patient-provider communication.

Policy

- **Comparing Medicaid coverage of HCT across the US.** This observational study analyzed Medicaid coverage of HCT by state to describe differences in HCT benefit sets; a manuscript has been published in the Journal of Oncology Practice.
- **Payer-partnered approach to community based referral for HCT.** The Health Services Research Program successfully obtained funding from the National Comprehensive Cancer Network / Pfizer to conduct this study to understand referral barriers to transplantation. The first phase of this study will conduct a survey of referring hematologists-oncologists to understand knowledge gaps and barriers to referral. Educational materials developed through this survey will be evaluated in a subsequent project that will focus on hematologist-oncologists affiliated with a specific payer group.

Clinical Trial Support

- **Easy-to-read informed consent forms for HCT clinical trials** (Health Services Research Program / BMT CTN collaboration). This NHLBI-funded study evaluates the effectiveness of a novel consent form for the BMT CTN and will describe barriers to implementation of more patient-friendly consent documents. The Health Services Research Program conducted interviews of investigators, research coordinators, and IRB personnel at 10 transplant centers to address this issue. Analyses of the interview transcripts are presently being conducted.
4.0 DISSEMINATION OF RESULTS

4.1 BMT TANDEM MEETINGS

The BMT Tandem Meetings are co-sponsored with the ASBMT and are held annually in February. They include five days of plenary sessions, concurrent scientific sessions, and other meetings. Reports on recent progress and updates in basic science, translational research, and clinical studies are targeted to worldwide physicians and scientists with an interest in HCT. The meetings include sessions geared toward investigators, but ancillary meetings include sessions specific to pediatricians, mid-level practitioners and transplant nurses, BMT center administrators, BMT CTN coordinators and investigators, and other allied professionals. Attendance at the BMT Tandem Meetings increases annually; its current levels are just under 3,000 registrants.

4.2 PRESENTATIONS

In 2014, 46 CIBMTR study investigators presented results at national and international conferences. Numbers of presentations at the BMT Tandem Meetings and American Society of Hematology (ASH) annual meeting are displayed in Table 4.1. At the 2014 American Society of Clinical Oncology annual meeting, three investigators presented posters. At the European Group for Blood and Marrow Transplantation (EBMT) annual meeting, two investigators presented, one an oral presentation and the other a poster. At the Interscience Conference on Antimicrobial Agents and Chemotherapy, one investigator conducted an oral presentation, and at the Society for Clinical Trials Annual Meeting, another investigator conducted an oral presentation. A complete list of presentations is provided in Appendix I.

<table>
<thead>
<tr>
<th>Year</th>
<th>Oral</th>
<th>Poster</th>
<th>Total</th>
<th>Oral</th>
<th>Poster</th>
<th>Total</th>
</tr>
</thead>
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<td>5</td>
<td>11</td>
<td>14</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>2010</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>16</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>2011</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>13</td>
<td>5</td>
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<tr>
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<td>6</td>
<td>12</td>
<td>18</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>2013</td>
<td>8</td>
<td>1</td>
<td>9</td>
<td>17</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>2014</td>
<td>13</td>
<td>3</td>
<td>16</td>
<td>15</td>
<td>8</td>
<td>23</td>
</tr>
</tbody>
</table>

4.3 STANDARD REPORTS

Reports and other informational documents are distributed at national and international conferences, via mailings, and at small and large group meetings. They are also posted publicly on various websites, including the CIBMTR and C.W. Bill Young Program websites. Newsletters are distributed electronically.

4.3.1 Report of Survival Statistics for BMT

The CIBMTR publishes a detailed report on survival statistics describing the use and outcome of autoHCT and alloHCT in the approximately 350 transplant centers that participate and provide data to the CIBMTR.
4.3.2 Transplant Data by US Center Report

Annually, as part of the HRSA contract, the CIBMTR reports HCT volumes and demographic data to transplant centers. The information is made available to patients and the public via the C.W. Bill Young Cell Transplantation Program website (bloodcell.transplant.hrsa.gov).

4.3.3 Annual Report on Transplant Center Survival Rates

A center-specific survival analysis comparing the one-year survival rates among US centers, this report contains outcomes for transplants using both related and unrelated donors. The purpose of the report is to provide potential HCT recipients, their families and the general public a comparison of survival rates among the centers in the C.W. Bill Young Cell Transplantation Program network. Transplant centers may use these reports for quality improvement initiatives. Results are published on the Program website (bloodcell.transplant.hrsa.gov).

4.3.4 Summary Slides

Using information from the Research Database, the CIBMTR annually prepares and distributes charts and figures summarizing current uses and outcomes of alloHCT and autoHCT. These slides are developed in conjunction with the BMT Tandem Meetings, and they are available on the CIBMTR website as well as through the Information Request Service.

4.3.5 Summary of Accomplishments

Produced annually, this trifold document provides a high level summary of CIBMTR fiscal year accomplishments and high impact publications. In addition to being posted on the CIBMTR website, this document is distributed via social media, mailings to supporters, at national and international conferences, and in a variety of meetings.

4.3.6 Study Summaries for Patients

The CIBMTR publishes summaries of research articles for patients and their caregivers on the CIBMTR website. Research articles are selected by the members of the Consumer Advocacy Committee and are developed as a collaborative effort among the CIBMTR Medical Writer, first author of the publication, Consumer Advocacy Committee members, and NMDP / Be The Match Patient and Health Professional Services. The summaries are written in plain language at a high school reading level. They incorporate an outcomes-focused title and important points in addition to the full summary. This allows readers to learn from the study even if they do not read the entire summary. Three summaries were published this year:

- Allo Transplant Helps Some Children with Neuroblastoma
- Allo Transplant Helps Some Older Patients with AML
- Very Few Donors have Severe Side Effects from Donation: Blood Stem Cell Donors have Fewer than Bone Marrow Donors

During their September 2014 meeting, the Consumer Advocacy Committee discussed opportunities for further dissemination of the patient summaries. The CIBMTR will continue to explore opportunities for dissemination of these summaries during the next reporting period.
4.3.7 Newsletters

The CIBMTR publishes two newsletters:

- **CIBMTR Newsletter.** This newsletter is published at least twice per year. In addition to being posted on the CIBMTR website, it is distributed to the CIBMTR network of approximately 5,000 physicians, data managers, pharmacists, IT professionals, and other personnel. Previously, printed editions of the newsletter were distributed by mail and at various meetings and conferences. This year the CIBMTR implemented an electronic distribution system through Campaign Monitor. Newsletter articles feature updates on Working Committees, the SCTOD, data management and collection, and noteworthy events in the HCT community.

- **Data Matters Training Newsletter.** The Data Matters Training Newsletter is published monthly via email and contains updates on projects, announces training opportunities and manual updates, and provides answers to frequently asked questions. Newsletter content is developed as a collaborative effort among several internal departments.
5.0 RESOURCE SHARING

5.1 PUBLICATIONS

The CIBMTR generated 81 publications in 2014:

- 48 Clinical Outcomes Research Program Scientific Working Committee publications
- 12 Clinical Trials Support Program publications
  - 10 BMT CTN publications
  - 2 RCI BMT publications
- 2 Health Services Research Program publications
- 4 Statistical Methodology Research Program publications
- 2 Bioinformatics publications
- 13 Coordinating Center publications

A complete list of publications is provided in Appendix H.

![Figure 5.1. CIBMTR Publications by Year](image)

5.2 WEBSITES

5.2.1 CIBMTR Public Internet Presence

The CIBMTR’s websites include training and support; a shared communications and networking environment; and web access to CIBMTR data for the Working Committees, transplant centers, scientific investigators, and CIBMTR staff members. The CIBMTR’s Public Internet Presence comprises three distinct websites, each with its own purpose and security model.

5.2.1.1 Public Site

The CIBMTR website (cibmtr.org) is unrestricted and provides information about the CIBMTR and its research. It supports the Working Committees and BMT CTN through information about how to submit a proposal, access to a listing and summaries of all studies in process, and access to a summary of all CIBMTR publications. The website facilitates data and information requests, and it provides access to all current and past data collections forms, training manuals, and videos as well as...
other materials for both investigators and data professionals. The website information is, in part, supported by DISCO, which maintains data on more than 670 studies, more than 900 publications (since 1972), and 1,545 authors and their institutions at time of publication. In 2014, the CIBMTR public website had approximately 368,000 unique page views.

### 5.2.1.2 Collaborative Site
The Collaborative site (collaborate.cibmtr.org) uses the SharePoint Enterprise Collaboration platform to promote cooperative work among CIBMTR staff members and provides a communication platform for specific studies and initiatives. This site is secured by username and password, and user-specific security credentials are assigned.

The CIBMTR uses the site for storing and sharing protocol and consent documents, donor / recipient tracking tools, confidential committee information, data, manuscript drafts, and other relevant information. While only two Working Committees currently use the Collaborate site on a regular basis, it is available to all for sharing information.

### 5.2.1.3 Portal Site
The portal site (portal.cibmtr.org) delivers custom applications to CIBMTR staff and partners, including investigators, transplant centers, and clinical research coordinators. Three applications are currently hosted on this site: DBtc (Section 2.2.2.2), Center Volumes Portal (Section 2.2.2.3), and Patient One-Year Survival Calculator – Allogeneic Transplants (Section 2.2.2.4).

### 5.2.2 NMDP / Be The Match Internet Presence
The NMDP / Be The Match Internet Presence consists of two websites, one designed for the public and the other for professionals. CIBMTR data and research findings are presented on both websites.

#### 5.2.2.1 BeTheMatch.org
BeTheMatch.org is designed for patients and families, donors, and supporters. It incorporates personal stories of donors and recipients, opportunities for support, and detailed information about transplantation written for the public. The website provides scientific information in lay terms related to specific diseases, various treatment options, the process of transplantation, and life after transplant. It also addresses concerns related to specific populations, including children and caregivers.

#### 5.2.2.2 BeTheMatchClinical.org
BeTheMatchClinical.org is designed for clinicians, network participants, payors, and bioinformatics professionals. For clinicians, the website provides access to evidence-based tools, clinical guidelines, presentation slides, outcomes data, and education courses on HCT. The website also provides information specific to types of network participants: transplant centers, donor centers, apheresis and collection centers, and cord blood banks. For payors, BeTheMatchClinical.org offers information to help individuals understand BMT, determine coverage, and answer employer and patient questions. For individuals interested in bioinformatics, the website provides resources and access to expertise for immunogenetic-focused research and operational bioinformatics as well as frequently used HLA tools.
5.2.3 HRSA Blood Cell Transplant Website

HRSA’s Blood Cell Transplant website (bloodcell.transplant.hrsa.gov) provides information for the public, physicians, and other constituents. It incorporates transplant resources, donor information, and cord blood information as well as research, data, and outcomes. CIBMTR data and research findings are incorporated in numerous ways, including through CIBMTR-created reports:

- US Survival Report;
- Transplant Data by US Center Report;
- Transplant Data by Disease Report.

5.3 DATA RESOURCES

5.3.1 Research Database

The CIBMTR collects data for approximately 20,500 new transplant recipients annually as well as a continually increasing volume of follow-up data on previously reported recipients and donors. These data are maintained in the Research Database, which now contains information on more than 390,000 transplant recipients going back to transplants performed in 1968. Data and information from the Research Database are shared in a variety of ways (Tables 5.1 and 5.2), and the Coordinating Center takes care to ensure shared data are appropriately utilized and interpreted (Section 3).

<table>
<thead>
<tr>
<th>Table 5.1. Utilization of CIBMTR Research Database-Related Resources Accessible through the CIBMTR Website, January 1 - December 1, 2014</th>
<th>Total N*</th>
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</thead>
<tbody>
<tr>
<td>Information Request Service</td>
<td>462</td>
</tr>
<tr>
<td>CIBMTR Webpages</td>
<td></td>
</tr>
<tr>
<td>Data Management Manual</td>
<td>45,464</td>
</tr>
<tr>
<td>Data Collection Forms</td>
<td>38,036</td>
</tr>
<tr>
<td>Web-based US Transplant Reports</td>
<td>21,477</td>
</tr>
<tr>
<td>Data Management Training and Reference</td>
<td>14,125</td>
</tr>
<tr>
<td>Summary Slides</td>
<td>8,618</td>
</tr>
<tr>
<td>Publication List</td>
<td>2,877</td>
</tr>
<tr>
<td>Annual BMT Tandem Meetings Working Committee and Data Management Meetings Materials</td>
<td>1,313</td>
</tr>
<tr>
<td>Working Committee Studies Lists</td>
<td>1,269</td>
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<tr>
<td>Statistical Resources</td>
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</tr>
<tr>
<td>Patient Resources</td>
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<tr>
<td>Procedures and Progress Reports</td>
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<tr>
<td>Newsletter</td>
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</tr>
<tr>
<td>Data Back to Centers Application</td>
<td>469</td>
</tr>
<tr>
<td><strong>CIBMTR Webpages TOTAL</strong></td>
<td><strong>136,861</strong></td>
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</table>
Table 5.2. Utilization of CIBMTR Research Database-Related Resources Accessible through the CIBMTR Website, January 1 - December 1, 2014

<table>
<thead>
<tr>
<th>Other CIBMTR Research Database-Related Resources</th>
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</thead>
<tbody>
<tr>
<td>External Webpages</td>
</tr>
<tr>
<td>HRSA US Survival Report</td>
</tr>
<tr>
<td>HRSA Transplant Data by US Center Report</td>
</tr>
<tr>
<td>HRSA Transplant Data by Disease Report</td>
</tr>
<tr>
<td>Be The Match US Center Listing Report</td>
</tr>
<tr>
<td>Resources Available to CIBMTR Transplant-Center Members</td>
</tr>
<tr>
<td>Annual Report on Transplant Survival Rates</td>
</tr>
<tr>
<td>Survival Outcomes Calculator (available to physicians only)</td>
</tr>
<tr>
<td>FormsNet Data-Back-to Centers Application</td>
</tr>
<tr>
<td>Resources Available upon Request</td>
</tr>
<tr>
<td>Report of Survival Statistics for BMT</td>
</tr>
<tr>
<td>US Center Volumes Dataset</td>
</tr>
</tbody>
</table>

5.3.1.1 Information Request Service

The CIBMTR aims to provide maximum access to the data it collects and generally responds to information requests within two days. Information requests can be submitted at www.cibmtr.org and bloodcell.transplant.hrsa.gov as well as by mail, fax, and phone. These requests often come from physicians and patients seeking information about transplant outcomes. For the conduct of clinical trials, researchers request data for multiple purposes, including evaluation of potentially eligible patients or centers, review of current transplant practices and therapies for protocol development, and assessment of accrual patterns and barriers during the conduct of the trial. Table 5.3 summarizes the information requests submitted to the CIBMTR in 2014.

Table 5.3. Data Requests Addressed by the CIBMTR January 1 – December 1, 2014

<table>
<thead>
<tr>
<th>Type of organization</th>
<th>Number of Requests</th>
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</thead>
<tbody>
<tr>
<td>Physician/Researcher</td>
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<tr>
<td>Pharmaceutical/Biotech Company</td>
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</tr>
<tr>
<td>Patient or Relative</td>
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</tr>
<tr>
<td>Patient Advocacy Group</td>
<td>46</td>
</tr>
<tr>
<td>Market Research Firm</td>
<td>18</td>
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<tr>
<td>Federal Government Agency</td>
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</tr>
<tr>
<td>Student</td>
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</tr>
<tr>
<td>News Media</td>
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</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>462</strong></td>
</tr>
</tbody>
</table>
5.3.1.2 CIBMTR Research Database-Related Webpages within the CIBMTR Website

The CIBMTR provides data and information from the Research Database on the CIBMTR website in a variety of formats.

- **Data Management Manual** (45,464 unique page views). A comprehensive reference document for completing the TED forms and CRFs. The manual also details SCTOD reporting requirements, describes protocols and the consent process, and includes downloadable versions of essential forms.
- **Data Collection Forms** (38,036 unique page views). Provides access to current and retired versions of the forms used by the CIBMTR to collect standard data elements for all transplant recipients.
- **Web-based US Transplant Reports** (21,477 unique page views). Directs users to the Be The Match US Center Listing Report and the following customizable reports of patient survival and transplant available through the HRSA Website:
  - Disease-specific survival estimates at 100-days, 1-year, and 3-year post-HCT (estimates are also available by patient age, patient gender, patient race, or cell source);
  - The number of bone marrow and cord blood transplants performed at a specific transplant center;
  - The number of bone marrow and cord blood transplants reported for a specific disease (also available by patient age, patient gender, patient race, cell source, and the year when the transplant was performed).
- **Data Management Training and Reference** (14,125 unique page views). Provides access to a wide variety of CIBMTR data management training and reference materials.
- **Summary Slides** (8,618 unique page views). Includes charts and figures summarizing current uses and outcomes of alloHCT and autoHCT.
- **Publication List** (2,877 unique page views). Searchable descriptive list of more than 900 publications resulting from the use of CIBMTR data and statistical resources.
- **Annual BMT Tandem Meetings Working Committee and Data Management Meetings Materials** (1,313 unique page views). Provides access to agendas, handouts, and educational materials from specific meetings at the BMT Tandem Meetings:
  - Working Committee Meetings;
  - Clinical Research Professionals / Data Management Conferences.
- **Working Committee Studies Lists** (1,269 unique page views). A summary of the planned, in-progress, and recently published CIBMTR clinical outcomes studies for each Working Committee.
- **Statistical Resources** (1,258 unique page views). Provides access to resources offered through the unique partnership between the CIBMTR and MCW Division of Biostatistics, including biostatistical publications and a series of statistical lectures targeted at basic and clinical investigators.
- **Patient Resources** (758 unique page views). Includes:
  - Post-transplant care recommendations for adult and pediatric autoHCT and alloHCT recipients available to help patients and clinicians understand and plan for the specialized care of transplant recipients;
  - Patient-level summaries of CIBMTR research articles.
5.0 RESOURCE SHARING

- **Newsletter** (483 unique page views). Published at least twice per year. Articles feature updates on Working Committees, the SCTOD, data management and collection, and noteworthy events in the HCT community.
- **Data Back to Centers Application** (469 unique page views). Links to the FormsNet DBtC application that provides CIBMTR member centers the ability to retrieve all the TED-level (and TED-level equivalent) data their center has reported to the CIBMTR.

5.3.1.3 External Webpages Presenting Data Summaries Prepared using the CIBMTR Research Database

- **HRSA US Survival Report.** Disease-specific post-HCT survival estimates by the length of time after transplant: 100 days, 1 year, and 3 years. Survival estimates are also available by patient age, patient gender, patient race, or cell source.
- **HRSA Transplant Data by US Center Report.** The number of bone marrow and cord blood transplants performed at a specific transplant center.
- **HRSA Transplant Data by Disease Report.** The number of bone marrow and cord blood transplants reported for a specific disease. Totals are also available by patient age, patient gender, patient race, cell source, and the year when the transplant was performed.
- **Be The Match US Center Listing Report.** Transplant center specific information about facilities, personnel, diseases treated, cost, and transplant experience, including the number of transplants performed and survival rates by age, disease type, and disease stage.

5.3.1.4 Data Resources Available to CIBMTR Transplant Center Members

- **Annual Report on Transplant Survival Rates.** A comprehensive summary of the web-based US transplants reports available through the HRSA website distributed annually to each US CIBMTR-reporting center.
- **Survival Outcomes Calculator (available to physicians only).** Computes one-year survival rate estimates based on user-selected critical patient-, disease-, and transplant-related factors known to affect transplant outcomes.
- **FormsNet Data-Back-to Centers Application.** A web-based application that provides centers the ability to retrieve all the TED-level (and TED-level equivalent) data their center has reported to the CIBMTR.

5.3.1.5 Other CIBMTR Data Resources Available to Physicians and Researchers upon Request (and to Corporations through the CIBMTR Corporate Membership Program)

- **Report of Survival Statistics for BMT.** A highly detailed report on survival statistics that describes use and outcome of autoHCT and alloHCT in the more than 500 centers who have participated in the CIBMTR.
- **US Center Volumes Dataset.** Center-specific pre-transplant patient-, disease-, and transplant-related characteristics data for nearly all allogeneic and a majority of autologous hematopoietic stem cell transplants performed in the US between 2008 and 2012.
5.3.2 Research Repository

The CIBMTR provides access to more than 1.8 million sample aliquots available through the Research Repository, including pre-transplant related and unrelated donor / recipient (or cord blood) pairs as well as recipient blood samples for investigative use. The Research Repository also provides a unique resource to investigators for retrospective analysis of immune response determinants and transplant outcomes.

The Research Repository currently houses more than 31,000 cases for which samples from both the transplant donor and recipient are available and complete clinical data have been collected and verified. The majority of the samples have complete high resolution data available for HLA-A, B, C, DRB1/3/4/5, DQ, and DP loci. In addition, the Research Repository contains research samples from approximately 3,500 related transplant pairs.

In 2014, the CIBMTR distributed 8,313 research samples in support of various studies, and 20 manuscripts utilizing research samples and immunobiology clinical outcomes data were published, which is almost twice as many manuscripts as published last year (Figure 5.2).

![Figure 5.2. CIBMTR Publications Utilizing Immunobiology Research Samples and Clinical Outcomes Data](image-url)
6.0 FUTURE PLANS

During the next reporting period, there will be a strong focus on the Data Sharing Initiative and the IT Roadmap constructed in 2014. The CIBMTR will continue to work toward an IT Data Warehouse system built on the foundation of quality data, flexibility of data use, and ease of data access. Details of the IT Roadmap include:

- **Complete legacy data consolidation into a single research source.** Work is ongoing to consolidate into a single source legacy data that were captured separately by the IBMTR and NDMP before our formal affiliation in 2004. The planned completion of this initiative in 2015 is expected to create a more robust consolidated resource with the ability to more efficiently provide data without the need to conduct manual data merges. Further, this will serve as a platform of longitudinal consolidated data to seed the Data Warehouse.

- **Implement key data validations in FormsNet, close to the point of data capture.** Key data fields, which currently are validated at entry into the Research Database, up to a month after they are captured, will be checked near the point of data submission, either within FormsNet or as part of the Data Warehouse.

- **Centralize management of metadata throughout the organization into a single Metadata Mart.** Traceability of metadata along the CIBMTR Research Data Life Cycle is critical to preserving scientific logical and conceptual meaning of data as changes are made to reflect the evolution and dynamism of the science. Centralized management of data fields increases efficiencies and minimizes the potential for error. The CIBMTR plans to expand the existing Metadata Mart to include metadata used in the existing Research Database to link common data elements on data collection forms and the data fields used in research retrievals.

- **Define use cases for data sharing.** The CIBMTR will begin to inventory, analyze, and document uses of data by external and internal stakeholders. These use cases will be prioritized for design and implementation in the new Data Warehouse and help determine prioritization of data sharing projects.

In 2014, the Donor and Recipient data were added to the Data Warehouse for use in on demand and ad hoc internal testing, analysis, and reporting. Having these data in the warehouse will save time for internal staff when querying data, when cleaning up data, and for quality control. Also in 2014, the CIBMTR integrated into the Data Warehouse, the inventory data from the Research Repository and developed reporting tools to support BMT CTN sample submission compliance monitoring and monthly HRSA reporting on related sample collection. Both initiatives are foundational to the Data Sharing Initiative. Additional projects to build the warehouse and its capabilities will continue.

The introduction of a more flexible CIBMTR Recipient ID (CRID) Assignment Form is planned in 2015. The new form is designed to establish a patient ID independent of treatment, allowing the CIBMTR to expand data collection to patients who receive cellular therapy and other non-HCT treatments.

Risk management and IT security will be ensured through oversight of all hardware and software, effective management of user accounts and information sharing as well as event management.
The goals under the Scientific Resource Utilization Plan will continue to focus on the review and refinement of current organizational practices, including:

- Review Working Committee metrics for overall productivity, study completion, and study impact.
- Limit the number of studies to those with highest impact; support studies with important clinical and policy implications.
- Support Working Committee Chairs to be active leaders in the committee.
- Regularly share metrics as a committee management resource.
- Provide effective tracking and management tools for all studies.
- Process reviews to streamline data merging both internally with the Research Repository and clinical trial data and externally with transplant centers and corporate partners.
- Optimize and enhance the quality and scope of the Research Database.
- Conduct operational process reviews and updates to better capture high quality, research data.
- Expand ongoing staff developmental and organizational training initiatives.
- Review for scientific content the data collection follow-up forms.
- Update consequences of centers with poor audit performance.
- Create a working group to assess opportunities for use of the new flexible CRID form to capture data of non-HCT patients.
- Outreach to transplant centers through the site visit program.
- Expand CIBMTR data sharing products and systems.
- Collaborate with transplant center network partners, other registries, and corporate partners.
- Encourage and support of new investigators.
- Expand use of outcomes data to assist in the design, implementation, and long term follow-up of clinical trials.
- Present results at critical conferences and meetings.
- Publish easy to read summaries of key publications in HCT.
- Support and expand data sharing with international registries.
- Develop new statistical methodologies.
- Expand Health Services Research initiatives.
7.0 IMPACT OF THE CIBMTR

The CIBMTR has collected HCT outcomes data worldwide for more than 40 years, resulting in a Research Database with information from more than 390,000 transplant recipients. These data are available to investigators and others interested in HCT and treatments for cancer and other life-threatening diseases. More than 900 publications have resulted from analyses of these data. CIBMTR studies have changed clinical practice and helped to improve survival and quality of life for patients undergoing or being considered for this complex procedure. The organization has become a respected leader in HCT research by providing a unique resource of information and expertise to medical and scientific communities.

The CIBMTR leverages its U24 funding to support a broad array of research programs in a cost-effective manner through its expert staff of physicians, statisticians, immunologists, and clinical research and IT professionals.

To ensure broad input into the research process and efficient use of resources, the CIBMTR facilitates 15 Working Committees focused on specific research areas, such as Leukemia and Lymphoma, Donor Health and Safety, Immunobiology, GVHD, Late Effects, and Health Services. One of the goals of the CIBMTR is to promote and develop young investigators in BMT research. A strategy the CIBMTR uses to accomplish this is to link senior investigators and junior investigators on our Working Committees. Success in attracting young investigators is evaluated annually.

Since 1993, the CIBMTR has held an annual meeting, the BMT Tandem Meetings, and has co-sponsored the meeting with the ASBMT since 1995. The Meetings are the largest North American gathering of worldwide experts in BMT patient care, clinical investigation, and laboratory research. These meetings provide a forum for HCT physicians, scientists, allied health professionals, BMT center administrators, pharmacists, mid-level providers, and transplant nurses as well as BMT CTN coordinators and investigators. The CIBMTR’s Working Committees and Advisory Committee meet in person at these meetings, and data manager training for CRCs draws participants from transplant centers worldwide.

The CIBMTR’s statistical resources and Research Database facilitate new research initiatives and provide a foundation of data, which support high impact studies that otherwise could not be accomplished. CIBMTR outcomes data is routinely utilized by insurers, has been used to support FDA applications for new devices, and supports the design and planning of clinical trials. The CIBMTR collaborates with the ASBMT and provides data that support policy development. It also is in discussions with the Foundation for the Accreditation of Cellular Therapy (FACT) to align the CIBMTR data audit program with the FACT accreditation process.

With the consensus and support of its Advisory Committee, the CIBMTR is committed to the collection of data on a non-transplanted patient population. A follow-up study to the ongoing CMS study of HCT outcomes is now collecting comparison data for a cohort of patients receiving non-HCT therapy for MDS. The CIBMTR is combining its resources with those of the BMT CTN to do this in a cost-effective manner. Similarly, the CIBMTR is working collaboratively with the Primary Immune Deficiency Disease Consortium to add transplant outcomes data to data on non-transplant therapy collected by the Consortium. Additionally, the CIBMTR is amending its registration of cases to more easily accommodate data collection for cellular and other therapies that do not involve transplantation.
CIBMTR publications cover a wide range of issues, some with important implications for clinical practice and transplantation biology, such as:

- Comparison of umbilical cord blood with adult donor transplants;
- Evaluation of the association between cord-recipient HLA-matching and outcomes of umbilical cord donor transplants;
- Late effects of transplantation;
- Comparisons with non-transplant therapy;
- Outcomes of transplantation for rare non-malignant diseases;
- Immunogenetic influences on transplantation outcomes.

Since 2006, the CIBMTR has administered the SCTOD for the HRSA-sponsored C.W. Bill Young Cell Transplantation Program, which was established by the Stem Cell Therapeutic and Research Act of 2005. The CIBMTR’s infrastructure and expertise in data collection, management, and analysis provide efficient management of the SCTOD for both the government and participating HCT programs. The CIBMTR expanded the denominator of patients in its Research Database and the scope of its research through its SCTOD activities, with benefit to new and traditional projects such as:

- Health Services Research focusing on improved access to HCT;
- Piloting a mechanism to collect patient-reported outcomes;
- Providing better access to data and educational materials through the CIBMTR Public Internet Presence;
- Facilitating better communication among participating centers and research collaborators using web-based tools;
- Collaborating with domestic and international organizations in data exchange to increase the data available worldwide to study HCT;
- Continuing to develop new biostatistical methodology for analyzing HCT.

Lastly, some of the most important studies being conducted through the CIBMTR’s Working Committees include:

- Determination of transplant outcomes in rare diseases, in common diseases for which transplants are rarely performed, and in new indications, such as autoimmune diseases;
- Identification of patient-related factors like age and performance score, disease-related factors like stage and duration, and treatment-related factors like optimal pre-transplant therapy and conditioning regimens, which affect transplant outcomes;
- Description of donor safety and outcomes after bone marrow or peripheral blood donation;
- Determination of long-term effects of HCT on patient quality of life and late complications like second cancers;
- Evaluation of the impact of HLA and other immunogenetic locus donor / recipient matching on alloHCT outcomes;
- Relative efficacy of HLA-identical sibling, alternative allogeneic donor, and autoHCT for specific diseases;
- Determination of optimal statistical models to study survival after transplantation;
- Relative efficacy of transplant and non-transplant treatments.

Thousands of hours of voluntary efforts from physicians and scientists spent using these data to address important issues in HCT and other cancer treatments validate the need for this unique resource. The inclusive nature of the CIBMTR Working Committees and data access policies make
these research data available to many. The Coordinating Center, through its integration of scientific, statistical, data management, and analytical expertise, helps advance research and clinical practice for the benefit of thousands of patients.
8.0 WORKING COMMITTEE STUDIES

The CIBMTR is founded on the premise of effective collaboration of researchers and clinicians, working together to pursue relevant issues in HCT. To accomplish this goal, the CIBMTR’s 15 Working Committees shape the Clinical Outcomes Research Program that leads to publications. Volunteer members can propose, design, and implement studies. This section summarizes the status of each Working Committee study.

8.1 ACUTE LEUKEMIA WORKING COMMITTEE

Co-Chair: Steven Devine, MD, Ohio State Medical Center, James Cancer Center
Email: steven.devine@osumc.edu

Co-Chair: Marcos de Lima, MD, University Hospitals Case Medical Center
Email: marcos.delima@uhhospitals.org

Co-Chair: Brenda Sandmaier, MD, Fred Hutchinson Cancer Research Center
Email: bsandmai@fredhutch.org

Scientific Director: Daniel Weisdorf, MD, CIBMTR Minneapolis
Email: weisd001@umn.edu

Asst Scientific Dir: Wael Saber, MD, MS, CIBMTR Milwaukee
Email: wsaber@mcw.edu

PhD Statistician: Mei-Jie Zhang, PhD, CIBMTR Milwaukee
Email: meijie@mcw.edu

MS Statistician: Hailin Wang, MPH, CIBMTR Milwaukee
Email: hwang@mcw.edu

RECENTLY COMPLETED STUDIES

Study # LK04-01


Abstract: Purpose: To identify favored choice of transplantation in patients with acute promyelocytic leukemia (APL) in second complete remission. Patients: We studied 294 APL patients receiving allogeneic (n=232) or autologous (62) HCT in CR2 reported to the CIBMTR from 1995 to 2006 including pre-HCT PML/RARµ status in 155 (49% of allogeneic and 66% of autologous). Methods: Patient characteristics and transplant characteristics, including TRM, OS, and DFS were collected and analyzed for both univariate and multivariate outcomes. Results: With median follow-up of 115 (allogeneic) and 72 months (autologous), 5-year DFS favored autologous 63% (49-75%) compared to allogeneic 50% (44-57%)
Multivariate analysis showed significantly worse DFS after allogeneic HCT (HR 1.88, 95% CI 1.16-3.06, p=0.011) and age >40 years (HR 2.30, 95% CI 1.44-3.67, p=0.0005). OS was significantly worse after allogeneic HCT (HR 2.66, 95% CI 1.52-4.65, p=0.0006), age >40 (HR 3.29, 95% CI 1.95-5.54, p<0.001), and CR1<12 months (HR 1.56, 95% CI 1.07-2.26, p=0.021). Positive pre-HCT PML-RARµ status in 17/114 allogeneic and 6/41 autologous transplants did not influence relapse, treatment failure, or survival in either group. The survival advantage for autografting was attributable to increased 3-year TRM, allogeneic 30% vs autologous 2%, and GVHD.

Conclusion: We conclude that autologous HCT yields superior OS for APL in CR2. Long term DFS in autologous recipients, even with MRD+ grafts remains an important subject for further study.

**Study # LK07-03b**


**Abstract:** Tyrosine kinase inhibitors (TKIs) and RIC/NMA conditioning HCTs have changed the therapeutic strategy for CML patients. We analyzed post-HCT outcomes of 306 CML patients reported to the CIBMTR aged 40 years and older undergoing RIC/NMA HCT from 2001 to 2007: 117 (38%) aged 40 to 49 years, 119 (39%) 50 to 59 years, and 70 (23%) 60 years or older. The majority (74%) had treatment with imatinib before HCT. At HCT, most patients aged 40 to 49 years were in CP1 (74%), compared with 31% aged 60 years or older. Siblings were donors for 56% aged 40 to 49 years; older cohorts had more unrelated donors. The majority received peripheral blood grafts and RIC across all age groups. 3-year OS (54%, 52%, and 41%), day +100 grade II-IV acute GVHD (26%, 32%, and 32%), chronic GVHD (58%, 51%, and 43%), and 1-year TRM (18%, 20%, and 13%) were similar across ages. The 3-year relapse incidence (36%, 43%, and 66%) and DFS (35%, 32%, and 16%) were inferior in the oldest cohort. Importantly, for CP1 patients, relapse and DFS were similar across age cohorts. Allogeneic RIC HCT for older patients with CML can control relapse with acceptable toxicity and survival in TKI-exposed CML, especially if still in CP1.

**Study # LK07-03c**


Abstract:
NHL disproportionately affects older patients who uncommonly receive allogeneic HCT. We analyzed CIBMTR data on 1,248 patients ≥40 years receiving RIC or NMA HCT for aggressive (n=668) and indolent (n=580) NHL. Aggressive lymphoma was more frequent in the oldest cohort [(age 40-54) 49% vs (55-64) 57% vs (≥65) 67%, p=0.0008]; fewer patients ≥65 had prior autografting (26% vs. 24% vs. 9%; p=0.002). Rates of relapse, acute and chronic GVHD, and NRM at one year were similar [22%, 95% CI 19-26%; 27%, 95% CI 23-31%; 34%, 95% CI 24-44%]. PFS and OS survival at 3 years was slightly lower in older cohorts [OS: 54%, 95% CI 50-58%; 40%, 95% CI 36-44%; 39%, 95% CI 28-50%; p<0.0001]. Multivariate analysis revealed no significant effect of age on acute or chronic GVHD or relapse. Age ≥55 years, KPS<80, and HLA-mismatch adversely impacted NRM, PFS, and OS. Disease status at HCT, but not histologic subtype, worsened NRM, relapse, PFS, and OS. Even for patients ≥55 years, OS still approached 40% at 3 years, suggesting HCT affects long-term remissions and remains underutilized in qualified older patients with NHL.

PRELIMINARY RESULTS

Study # LK11-01
Title: Impact of extramedullary disease on the outcome of allogeneic hematopoietic cell transplantation in acute myeloid leukemia
Study Chairs: Sagun Goyal (Saint Louis University)
Geoffrey Uy (Washington University School of Medicine)
MS Statistician: Hai-Lin Wang (hwang@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Submitted
Abstract: The impact of extramedullary disease (EMD) in AML on the outcomes of alloHCT is unknown. Using data from the CIBMTR, we compared the outcomes of patients who had EMD of AML at any time prior to transplant to a cohort of AML patients without EMD. We reviewed data from 9,797 AML patients, including 814 with EMD from 310 reporting centers and 44 different countries who underwent alloHCT between and 1995-2010. The primary outcome was OS after alloHCT. Secondary outcomes included LFS, relapse rate, and TRM. In a multivariate analysis, the presence of EMD did not affect either OS (HR 1.00, 95% CI 0.91-1.09), LFS (0.98, 95% CI 0.89-1.09), TRM (RR 0.92, 95% CI 0.80-1.16, p=0.23) or relapse (RR 1.03, 95% CI 0.92-1.16, p=0.62). Furthermore, the outcome of patients with EMD was not influenced by the location, timing of EMD, or intensity of conditioning regimen. The presence of EMD in AML does not affect...
transplant outcomes and should not be viewed as an independent adverse prognostic feature.

Study # LK12-01

Title: Chemotherapy versus allogeneic hematopoietic cell transplantation in Philadelphia chromosome negative adult acute lymphoblastic leukemia

Study Chairs: Matthew Seftel (Princess Margaret Cancer Centre) Donna Neuberg (Dana-Farber Cancer Institute)

MS Statistician: Hai-Lin Wang (hwang@mcw.edu)

PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)

Study Status: Manuscript preparation

Abstract: Introduction: In adults with Ph- ALL, the optimal post-remission therapy remains uncertain. Although allogeneic HCT in CR1 has become a widely adopted curative strategy, the need for HCT may be supplanted by intensive, pediatric-style chemotherapy regimens. These two approaches have not previously been compared. Methods: We evaluated the outcomes of 422 related or unrelated donor HCT recipients aged 18-50 years with Ph-ALL in CR1 between 06/2002 and 12/2011 as reported to the CIBMTR. This was compared to a concurrent cohort of 108 Ph- ALL CR1 pts (18-50 years) who received a Dana Farber Cancer Institute (DFCI) ALL Consortium pediatric regimen consisting of intensive, non-HCT therapy. Primary outcome was DFS. Patients in the DFCI chemotherapy cohort who received HCT in CR1 were censored at the day of HCT. Left-truncated analysis methods were used to adjust time from CR1 to transplant. Results: The HCT cohort was older (median age 34 vs 30 years, p=0.001) and had higher diagnostic WBC counts (median 12x10⁹/L [range <1-515] vs 8x10⁹/L [1-1424], p=0.001, respectively). The proportion of patients with T-ALL was lower in the HCT cohort (14% vs. 22%, p=0.03), while the incidence of t(4;11)/MLL was similar in both groups (8% vs 10%, respectively). Of the HCT cohort, 396 (94%) underwent MA conditioning. Donor source was matched related donor in 176 (42%), 8/8 unrelated donors in 168 (40%), and 75 (18%) from 7/8 unrelated donors. In univariate analyses, cumulative incidence of relapse at 4 years was similar in both groups [HCT 25% (19-28) vs chemo 23% (15-32), p=0.97]. Two-year TRM was higher in the HCT cohort [HCT 33% (28-39) vs chemo 4% (1-8), p<0.0001]. At 4 years, DFS was superior in the chemo cohort [HCT 40% (35-45) vs chemo 71% (60-79), p<0.0001]. Four-year OS also favored chemo [HCT 45% (40-50) vs chemo 73% (63-81), p<0.0001]. In multivariable analysis, independent factors predictive of treatment failure (relapse or death) were HCT [HR 3.11 (2.08-4.66), p<0.001] and the presence of central nervous system disease at diagnosis [HR 1.56 (1.03-2.38), p=0.04]. The sole factor associated with poorer OS was the administration of HCT [HR 2.86 (1.88-4.34), p<0.0001]. The favorable OS with chemo was maintained when restricting the HCT cohort to those recipients with related donors or fully matched (8/8) unrelated donors and those whose time from diagnosis to CR1 was <8 weeks [HR 2.14 (1.36-3.35), p=0.001]. Similar outcomes were seen when restricting the HCT cohort to those who achieved CR1 <8 weeks from diagnosis and received MA
conditioning. Conclusion: In this comparison of two cohorts of younger Ph-
adults in CR1, post-remission therapy with an intensive, pediatric-inspired,
chemotherapy-based regimen conferred a survival advantage when compared to
allogeneic HCT. The high TRM associated with HCT is a major factor in
determining outcomes after HCT. In an era of increasing adoption of pediatric
regimens for adults with Ph- ALL, allogeneic HCT may no longer be required for
the majority of patients who achieve CR1. These data support the need for
randomized controlled studies in Ph- ALL comparing pediatric-inspired non-
HCT regimens to allogeneic HCT-based therapy.

Study # LK12-02
Title: Allogeneic hematopoietic stem cell transplantation for FLT3/ITD positive acute
myeloid leukemia in first complete remission
Study Chairs: Abhinav Deol (Karmanos Cancer Institute - Wayne State University)
Salyka Sengsayadeth (Vanderbilt University Medical Center)
Madan Jagasia (Vanderbilt University Medical Center)
MS Statistician: Hai-Lin Wang (hwang@mcw.edu)
PhD Statistician: Kwang Woo Ahn (kwooahn@mcw.edu)
Study Status: Manuscript preparation
Abstract: Relapse after allogeneic HCT remains a major cause of transplant failure. Patients
with FLT3 mutated AML tend to have poor prognosis and are often referred for
early HCT. We studied 511 patients to determine if FLT3 mutations impact
transplant outcomes. Adults with a diagnosis of de-novo AML, with available
FLT3 mutation status in CR1 or CR2 who underwent an HLA-matched sibling or
unrelated donor (8/8 or 7/8) HCT after MAC, NMA, or RIC reported to the
CIBMTR from 2008-2011 were included. Clinical outcomes following HCT for
FLT3 positive and FLT3 negative AML patients were compared adjusting for
significant patient-, disease-, and HCT-related variables. 511 patients met the
inclusion criteria: 158 (31%) with FLT3 mutations. Median follow-up of survivors
was 37 months (range, 12-65). The FLT3 mutated group had significantly higher
WBC count at diagnosis, more patients with normal cytogenetics, and more
cycles of pre-HCT consolidation. Univariate analysis showed increased
probability of relapse after HCT (log-rank p=0.01) in the FLT3 positive group but
no significant differences in OS (log-rank p=0.13). There were no statistical
differences in NRM, RFS, or the cumulative incidence of acute and chronic
GVHD. In multivariate analysis performed excluding the confounder “WBC
count at diagnosis”, FLT3 mutation status had a statistically significant negative
effect on risk of relapse (p=0.05), but no effect on overall mortality. We could not
address the differential impact of varying FLT3 mutations or interaction of other
molecular aberrations with FLT3. In addition, we did not have information about
post relapse interventions. Encouragingly, nearly 50% of patients with FLT3
positive AML who underwent allogeneic HCT in CR were long-term survivors
after allogeneic HCT. Though associated with augmented risks of relapse, FLT3
mutation status does not adversely impact long-term survival. Pre-emptive
strategies using FLT3 inhibitors after HCT may reduce relapse risk and should be studied prospectively in order to improve outcomes of these high-risk patients.

**Study # LK12-03**

**Title:** Survival after relapse following allogeneic hematopoietic cell transplantation for acute myeloid leukemia

**Study Chairs:**
- Nelli Bejanyan (University of Minnesota Medical Center)
- Mei-Jie Zhang (Medical College of Wisconsin)
- Daniel Weisdorf (University of Minnesota Medical Center)

**MS Statistician:** Hai-Lin Wang (hwang@mcw.edu)

**PhD Statistician:** Mei-Jie Zhang (meijie@mcw.edu)

**Study Status:** Submitted

**Abstract:** Despite the curative potential of alloHCT, a large number of patients with AML experience leukemia relapse after HCT. Although subsequent remissions can be achieved with salvage therapy, they are usually short lived. We evaluated survival of AML patients relapsing after alloHCT to identify prognostic factors for survival after post-transplant relapse. 1,788 pediatric and adult AML CR1 and CR2 patients relapsed post-transplant (1990-2010). The median age at HCT was 30 years (range <1-76). De novo leukemia occurred in 81% and intermediate risk cytogenetics in 45%. 1,374 patients (77%) underwent MA and 936 patients (52%) related donor HCT. Active GVHD prior to relapse occurred in 727 subjects (41%). Median time from transplant to relapse was 7 months (range 1-177). At relapse, 357 patients (20%) received supportive care, whereas 1,231 patients (69%) received intensive therapy, including CT alone (n=660), DLI±CT (n=202; DLI+CT=51) and 2nd alloHCT±CT and/or DLI (n=369; 49% 2nd alloHCT were MA). Among evaluable patients (n=846) who received intensive therapy, CR rate was 29% (n=246) [15.6% for CT alone (n=443), 37.4% for DLI±CT (n=139), and 47.3% for 2nd alloHCT±CT±DLI (n=264)]. After a median follow up of 39 months (range <1-193) after relapse, 229 patients (13%) survived with 5-year OS of 3% (95% CI 2-5%) for patients relapsing within 6 months, 11% (95% CI 8-14%; p<0.0001 comparing to <6 mo) for 6 months – 2 years, 21% (95% CI 14-28%; p<0.0001 comparing to <6 months) for 2-3 year and 31% (95% CI 23-39%; p<0.0001 comparing to <6 mo) for ≥3 year groups. Persisting AML (n=1,271, 71%) was the most common cause of death. In multivariable analysis, longer time from alloHCT to relapse (RR 0.55 6 month – 2 years, 0.39 2-3 years, and 0.28 ≥3 years; p<0.0001) and RIC (RR 0.77, 95% CI 0.66-0.88, p=0.0002) were associated with significantly lower mortality. In contrast, age over 40 years (RR 1.42, 95% CI 1.24-1.64, p<0.0001), active GVHD at relapse (RR 1.25, 95% CI 1.13-1.39, p<0.0001), adverse cytogenetics (RR 1.37, 95% CI 1.09-1.71, p=0.0062), mismatched URD (RR 1.61, 95% CI 1.22-2.13, p=0.0008), or cord blood (RR 1.23, 95% CI 1.06-1.42, p=0.0078) HCT had inferior survival. We confirm poor survival of AML patients relapsing after alloHCT. However, patients with relapse beyond six months have better survival and may benefit from intensive therapy, DLI, or 2nd alloHCT.
Acute biphenotypic leukemias (bearing markers of myeloid and lymphoid origin, ABiL) are rare (2-5% of all acute leukemias) and are considered puzzling both with regard to their cell of origin as well as to the optimal treatment approach. The diagnostic criteria for ABiL were revised by the WHO in 2008. In the pediatric age group, the prognosis of ABiL is reported to be intermediate between acute lymphoblastic and acute myeloid leukemia. In the adult age group, ABiL generally has an unfavorable prognosis. As far as allogeneic transplant for ABiL is concerned, only small series of cases have been published to date. In the current study, the CIBMTR database was queried for patients with ABiL who received an allogeneic transplant between 1996 and 2013 being younger than 70 years of age (n=468). Patients with primary induction failure (n=19) and transplanted in relapse (n=27) were excluded. After detailed review of pathology, cytogenetic, and flow cytometry reports of 241 cases submitted as ABiL, those without complete data to confirm WHO criteria (n=157) were excluded. Of 84 cases with complete immunophenotyping data for review, 48 co-expressed Myeloid and B-lymphoid markers (M+B) and 28 Myeloid and T-lymphoid markers (M+T). The median age of the patients was 19 years; 56% were male; the median WBC at diagnosis was 17,000; and 36% received a bone marrow transplant, 33% a peripheral blood graft, and 31% cord blood stem cells. The conditioning regimen was myeloablative in 87% and RIC/NMA in 10% of cases. The 3-year overall survival was 61% (95% CI 46-74%) in My+B group and 73% (95% CI 54-88%) in My+T group. At 3 years post transplant, 75%, 48%, and 60% survival rates were observed in younger than 20, 20-40, and older than 40 years age groups, respectively. No notable differences in 3-year overall survival among those transplanted in CR1 and CR2 (64% and 69%, respectively). Patients with normal / intermediate cytogenetics (n=44) and those with bcr/abl+/poor cytogenetics (n=27) had similar 3-year survival rates: 62% and 70%, respectively. In conclusion, allogeneic transplant is a valid treatment option for patients with ABiL and should be explored in patients without significant comorbidities. A study in a larger context is planned.
STUDIES IN PROGRESS

Study # LK09-02
Title: Impact of monosomal karyotype on the outcomes of hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndrome
Study Chairs: Minoo Battiwalla (National Heart Lung and Blood Institute - NIH)
              Marcelo Pasquini (Froedtert & Medical College of Wisconsin)
MS Statistician: Kenny Hu (zhu@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Analysis in progress

Study # LK13-01
Title: Evaluating outcomes of reduced-intensity conditioning allogeneic hematopoietic cell transplantation in older adult lymphoblastic leukemia patients reported to the CIBMTR and EBMT: impact of age on transplant outcomes
Study Chairs: Ashley Rosko (University Hospitals Case Medical Center)
              Marcos de Lima (University Hospitals Case Medical Center)
              Mohamad Mohty (Hotel Dieu)
              Veronika Bachanova (University of Minnesota Medical Center)
MS Statistician: Hai-Lin Wang (hwang@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Analysis in progress

Study # LK13-02
Title: Prognostic significance of cytogenetic abnormalities in patients with Philadelphia-negative acute lymphoblastic leukemia undergoing allogeneic hematopoietic cell transplantation in complete remission
Study Chairs: Veronika Bachanova (University of Minnesota Medical Center)
              Aleksandr Lazaryan (University of Minnesota Medical Center)
MS Statistician: Hai-Lin Wang (hwang@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Data file preparation

Study # LK14-01
Title: Effect of post-remission consolidation chemotherapy prior to allogeneic transplantation for acute lymphocytic leukemia in first complete remission: A Center for International Blood and Marrow Transplant Research Study
Study Chairs: Nelli Bejanyan (University of Minnesota Medical Center)
              Aleksandr Lazaryan (University of Minnesota Medical Center)
              Daniel Weisdorf (University of Minnesota Medical Center)
MS Statistician: Hai-Lin Wang (hwang@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Protocol development
### Study # LK14-02

**Title:** Prognostic factors in patients ≥60 years undergoing allogeneic hematopoietic cell transplantation for acute myeloid leukemia in first and second complete remission  
**Study Chairs:** Vikas Gupta (Princess Margaret Cancer Centre)  
Fotios Michelis (Princess Margaret Cancer Centre)  
**MS Statistician:** Hai-Lin Wang (hwang@mcw.edu)  
**PhD Statistician:** Mei-Jie Zhang (meijie@mcw.edu)  
**Study Status:** Protocol development

### Study # SC14-02

**Title:** An analysis of myeloablative clofarabine and busulfan conditioning (CloBu4) versus other myeloablative conditioning regimens for relapsed / refractory acute myeloid leukemia (AML) not in remission at time of allogeneic  
**Study Chairs:** Parameswaran Hari (Froedtert & Medical College of Wisconsin)  
Shin Mineishi (University of Alabama at Birmingham)  
Thomas Braun (University of Michigan School of Public Health)  
**MS Statistician:** Hai-Lin Wang (hwang@mcw.edu)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development

### Study # LK14-03

**Title:** Autologous transplant vs arsenic trioxide for acute promyelocytic leukemia in second complete remission  
**Study Chairs:** Martin Tallman (Memorial Sloan Kettering Cancer Center)  
Chezi Ganzel (Sharre Zedek Medical Center)  
Sean Devlin (Memorial Sloan Kettering Cancer Center)  
**MS Statistician:** Hai-Lin Wang (hwang@mcw.edu)  
**PhD Statistician:** Sean Devlin (devlins@mskcc.org)  
**Study Status:** Analysis in progress
8.2 AUTOIMMUNE DISEASES AND CELLULAR THERAPIES WORKING COMMITTEE

Co-Chair: Steven Pavletic, MD, NIH NCI Experimental Transplantation and Immunology Branch  
Email: pavletis@mail.nih.gov  
Co-Chair: Mitchell Cairo, MD, New York Medical College  
Email: mitchell_cairo@nymc.edu  
Co-Chair: Ian Lewis, MBBS, PhD, Royal Adelaide Hospital  
Email: ian.lewis@health.sa.gov.au  
Co-Chair: David McKenna, MD, University of Minnesota Medical Center, Fairview  
Email: mcken020@umn.edu  
Co-Chair: Stefanie Sarantopoulos, MD, PhD, Duke University Medical Center  
Email: stefanie.sarantopoulos@duke.edu  
Scientific Director: Marcelo Pasquini, MD, MS, CIBMTR Milwaukee  
Email: mpasquini@mcw.edu  
PhD Statistician: Ruta Brazauskas, PhD, CIBMTR Milwaukee  
Email: ruta@mcw.edu  
MS Statistician: Jiaxing Huang, MS, CIBMTR Milwaukee  
Email: jiaxhuang@mcw.edu

PRELIMINARY RESULTS

Study # AD09-01

Title: Long-term outcomes after autologous hematopoietic cell transplantation for severe multiple sclerosis

Study Chair: Paolo Muraro (Imperial College)  
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)  
PhD Statistician: Maria Pia Sormani (EBMT)  
Study Status: Manuscript preparation  
Abstract: Background: AutoHCT is being investigated as a treatment for poor prognosis MS, aiming to achieve clinical stabilization and protracted remission from disease activity. Long-term outcomes, however, have only been reported from small case series. The objective of our study was evaluating long-term outcomes after HCT for treatment of MS in a large, international retrospective cohort study.

Methods: Eligible cases had received autoHCT for the treatment of MS between 01/1995 and 12/2006 and had a minimum set of data including Expanded Disability Status Score (EDSS) at baseline, subtype of MS at baseline, information on the treatment protocol, and at least one follow-up visit / report after HCT. The primary outcomes were MS PFS from time prior to stem cell mobilization and OS. The probabilities of PFS and OS were calculated using Kaplan-Meier survival curves, and Cox regression multivariate analysis models was run using a Cox model.

Findings: Data were collected from 23 centers in 13 countries, for 281 evaluable patients with median follow up of 6.6 years (range 0.2-16 years). The population
included 164 women (58%) and an overall median age at HCT of 37 years (range 14-65); 46 patients had relapsing remitting MS (16%), 186 had secondary progressive MS (66%), 32 had primary progressive MS (11%), and 17 had progressive relapsing MS (6%). The median EDSS score prior to mobilization was 6.5 (range 1.5-9.0). Five-year probabilities of PFS and OS were 49% (95% CI 43-55 %) and 9% (95% CI 91-95 %), respectively. Factors affecting MS progression were age older than 37 years (HR 1.40, p=0.04), progressive vs relapsing forms of MS (HR 1.6, p=0.02) and >2 previous line of MS therapy (HR 1.6, p=0.005). There were no differences in outcomes related to the source of data (CIBMTR or EBMT). Confirmed neurological improvement was documented in >20% of patients with relapsing MS for up to year 4 post-transplant, in significantly greater proportions than in patients with progressive forms.

Interpretation: We report the largest study to date describing long-term outcomes in HCT for MS. Although the majority of patients had progressive forms of MS and failed to respond to prior treatment, the results demonstrate that nearly half of the patients survived free from neurological progression for five years after HCT. Younger age, relapse remitting MS, and fewer lines of prior therapy were associated with better outcomes. Earlier transplantation in patients with active inflammatory disease may improve the outcomes.

STUDIES IN PROGRESS

Study # CT10-01
Title: Donor leukocyte infusion versus second allogeneic hematopoietic cell transplantation for disease relapse after first allogeneic hematopoietic cell transplantation
Study Chairs: Noelle Frey (Abramson Cancer Center University of Pennsylvania Medical Center) Alison Loren (Perelman School of Medicine at the University of Pennsylvania) David Porter (Abramson Cancer Center University of Pennsylvania Medical Center)
MS Statistician: Zhenhuan Hu (zhu@mcw.edu)
PhD Statistician: Jennifer Le-Rademacher (jlerade@mcw.edu)
Study Status: Analysis in progress

Study # AD12-01
Title: The effect of allogeneic hematopoietic cell transplantation on the activity and progression of multiple sclerosis
Study Chair: George Georges (Fred Hutchinson Cancer Research Center)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Data collection / data file preparation
8.2 AUTOIMMUNE DISEASES AND

CELLULAR THERAPIES WORKING COMMITTEE

Study # AD13-01
Title: Hematopoietic cell transplantation for systemic lupus erythematosus
Study Chairs: Sarfaraz Hasni (NIH - National Institute of Arthritis and Musculoskeletal and
Skin Diseases)
Steven Pavletic (NIH - NCI Experimental Transplantation and
Immunology Branch)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Data collection / data file preparation

Study # CT13-01
Title: Utility of donor leukocyte infusion for the treatment of drug-resistant viral or
fungal infections in allogeneic hematopoietic cell transplantation recipients: a
CIBMTR analysis
Study Chair: Görgün Akpek (Banner MD Anderson Cancer Center)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Data collection / data file preparation

PLANNED STUDY

Study # AC14-01
Title: Long term outcomes after autoHCT for rapidly progressive systemic
scleroderma
Study Chairs: Dominique Farge (Hôpital Saint-Louis)
Marcelo Pasquini (Froedtert & Medical College of Wisconsin)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol pending
8.3 CHRONIC LEUKEMIA WORKING COMMITTEE

Co-Chair: Matt Kalaycio, MD, Cleveland Clinic Foundation
Email: kalaycm@ccf.org

Co-Chair: Edwin Alyea, MD, Dana Farber Cancer Institute
Email: edwin_alyea@dfci.harvard.edu

Co-Chair: Uday Popat, MD, MD Anderson Cancer Center
Email: upopat@mdanderson.org

Scientific Director: Wael Saber, MD, MS, CIBMTR Milwaukee
Email: wsaber@mcw.edu

PhD Statistician: Kwang Woo Ahn, PhD, CIBMTR Milwaukee
Email: kwooahn@mcw.edu

MS Statistician: Zhenhuan Hu, MS, CIBMTR Milwaukee
Email: zhu@mcw.edu

RECENTLY COMPLETED STUDIES

Study # CK02-01b


Abstract: Cy in combination with Bu or TBI are the most commonly used MA conditioning regimens in patients with CML. We used data from the CIBMTR to compare outcomes in adults who underwent HCT for CML in first chronic phase following MA conditioning with Cy in combination with TBI, Bu, or IV Bu. Four hundred thirty-eight adults received HLA-matched sibling grafts, and 235 received well-matched grafts from unrelated donors from 2000 through 2006. Important differences existed between the groups in distribution of donor relation, exposure to tyrosine kinase inhibitors, and year of transplantation. In multivariate analysis, relapse occurred less frequently among patients receiving IV Bu compared to TBI (RR 0.36, P=0.022) or oral Bu (RR 0.39, P=0.028), but non-relapse mortality and survival were similar. A significant interaction was detected between donor relation and the main effect in LFS. Among recipients of HLA-identical sibling grafts, but not URD grafts, LFS was better in patients receiving IV (RR 0.53, P=0.025) or oral Bu (RR 0.64, P=0.017) compared to TBI. In CML in first chronic phase, Cy in combination with IV Bu was associated with...
less relapse than TBI or oral Bu. LFS was better following IV or oral Bu compared to TBI.

**Study # CK06-03 / CK07-01b**


**Abstract:** Purpose: Allogeneic HCT can cure some CLL subjects. This study compared outcomes of MA and RIC transplants from HLA-MSD for CLL. Patients and Methods: From 1995-2007, there were 297 CLL subjects reported to the CIBMTR who received MA (N=163) and RIC (N=134) MSD HCT. The MA subjects were less often transplanted after 2000 and less commonly received anti-thymocyte globulin (4% vs. 13%, p=0.004) or prior antibody therapy (14% vs. 53%, p<0.001). Results: RIC was associated with a greater likelihood of platelet recovery and less grade 2-4 acute GVHD compared to MA conditioning. One- and five-year TRM were 24% (95% CI 16-33%) vs. 37% (95% CI 30-45%, p=0.023) and 40% (95% CI 29-51%) vs. 54% (95% CI 46-62%; p=0.036), and the relapse / progression rates were 21% (95% CI 14-29%) vs. 10% (95% CI 6-15%, p=0.020) and 35% (95% CI 26-46%) vs. 17% (95% CI 12-24%, p=0.003). MA conditioning was associated with better PFS (RR 0.60, 95% CI 0.37-0.97, p=0.038) and three-year survival in transplants before 2001, but for subsequent years, RIC was associated with better PFS and survival (RR 1.49, 95% CI 0.92-2.42, p=0.10; and RR 1.86, 95% CI 1.11-3.13, p=0.019). Pre-transplant disease status was the most important predictor of relapse (p=0.003) and PFS (p=0.0007) for both forms of transplant conditioning. Conclusion: MA and RIC MSD transplants are effective for CLL. Future strategies to decrease TRM and reduce relapses are warranted.

**Study # SC11-06**


**Abstract:** MDS are myeloid clonal hematologic disorders that are most commonly diagnosed in the seventh decade of life. Several treatment options are currently available. However, alloHCT remains the only curative therapy. Unfortunately, despite the higher incidence of MDS in the older population, less than 10% of patients undergoing alloHCT for MDS are >65 years old. In this paper, we discuss the various treatment options in older patients with high-risk MDS with particular emphasis on the role of alloHCT in older MDS patients.

**Abstract:** Because the outcome of allogeneic HCT is predominantly influenced by disease type and status, it is essential to be able to stratify patients undergoing HCT by disease risk. The DRI was developed for this purpose. In the present study, we analyzed 13,131 patients reported to the CIBMTR who underwent HCT between 2008 and 2010. The DRI was refined using hazard ratios for mortality in multivariable regression models. The original DRI stratified patients into 4 groups with 2-year OS ranging from 64% to 24% (p<0.0001 for all pair-wise comparisons between groups) and was the strongest prognostic factor regardless of age, conditioning intensity, graft source, or donor type. We further refined the DRI into an index that could function as either a 4-group or 7-group breakdown, with improved prediction ability compared with the original DRI or other existing schemes. The validated and refined DRI can be used as a flexible and robust tool for prognostication; to facilitate the conduct and interpretation of single-center, multi-center, or registry retrospective studies; to adjust center outcome data; and to stratify patients entering clinical trials that enroll patients across disease categories.

**PRELIMINARY RESULTS**

**Study # CK13-01**

**Title:** Outcomes of allogeneic hematopoietic cell transplantation in children and young adults with chronic myeloid leukemia: a CIBMTR cohort analysis

**Study Chairs:** Sonali Chaudhury (Ann & Robert H. Lurie Children’s Hospital of Chicago)
Nobuko Hijiya (Ann & Robert H. Lurie Children’s Hospital of Chicago)

**MS Statistician:** Zhen-Huan Hu (zhu@mcw.edu)
**PhD Statistician:** Rodney Sparapani (rsparapa@mcw.edu)

**Study Status:** Manuscript preparation

**Abstract:** CML in pediatrics (<18 years) is relatively rare and constitutes 2–3% of leukemias. Data on allogeneic HCT in this population is scarce. Since the introduction of TKI, the number of HCT in patients with CML, especially early disease, has diminished. However, as pediatric patients and young adults have long life expectancy and lower morbidity with HCT in general, and are likely to be exposed to prolonged TKI therapy with increased risk for complications, HCT for early disease may still benefit this population.

We retrospectively evaluated outcomes in patients receiving MA HCT reported to the CIBMTR, comparing pediatric patients (n=212) to young adults (n=200). In the <18 years group, 5 year OS and LFS was 71% (95% CI 65-77) and 51% (95% CI 43-58) respectively. In adjusted analysis, there was a statistically insignificant
effect of prior TKI therapy on LFS (P=0.07), OS (0.06), TRM (P=0.47), or relapse (P=0.88). Favorable factors for OS were early disease, use of MSD, use of BM or UCB grafts. LFS was superior with the use of TBI, non alemtuzumab based regimens, and recent (>2006) HCTs. Five year OS and LFS for the 18-25 year group was 71% (95% CI 65-77) and 24% (18-31), respectively. In adjusted analysis, there was no statistical difference in OS (P=0.66) or LFS (P=0.4) for the 18-25 year group compared to the pediatric group. Favorable factors for OS/DFS remained early disease, MSD, and use of BM grafts.

In conclusion, allogeneic HCT outcomes were comparable in children and young adults and HCT should remain an option for young patients with CML, especially with a MSD using TBI containing regimens and BM as the stem cell source. We could not demonstrate an advantage for TKI use prior to HCT. Long term toxicities of TKI as well as allogeneic HCT need to be further evaluated in this group.

Study # CK13-02

Title: Allogeneic hematopoietic cell transplantation for adult chronic myelomonocytic leukemia

Study Chairs: Hien Duong (Cleveland Clinic)
Mojtaba Akhtari (The Nebraska Medical Center)

MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: Kwang Woo Ahn (kwooahn@mcw.edu)

Study Status: Manuscript preparation

Abstract: Allogeneic HCT is the only potentially curative treatment for patients with chronic myelomonocytic leukemia (CMML); however, there are little data regarding prognostic factors and transplant outcomes. Recently a CMML-specific prognostic scoring system (CPSS) was validated in the non-transplant setting. We sought to validate this scoring system in the HCT setting. We identified 209 adult patients undergoing HCT for CMML reported to the CIBMTR from 2001 through 2012. The median age at transplant was 57 years (range 23-74), with a majority being male (70%). Most had KPS of 90-100% (61%). Eighty eight (42%) patients had low / intermediate-1 while 79 (38%) had intermediate-2 / high, and 42 (20%) had missing CPSS scores. Based on CPSS definition, 50% had favorable, 19% had intermediate, 17% had poor risk, and cytogenetic data were missing for 14%. Median time from diagnosis to transplant was 8 months (range 2-170). HCT were performed with HLA identical siblings (35%), matched unrelated donors (45%), partially-matched unrelated donors (15%), or mismatched / indeterminate matched unrelated donors (4%). Patients received bone marrow (16%) or peripheral blood (84%). Patients received myeloablative (51%), reduced-intensity (41%), non-myeloablative (<5%), or other (<4%) conditioning regimens. GVHD prophylaxis was cyclosporine-based (37%), FK-506-based (61%), methotrexate alone (<1%), or missing (<1%). Median follow up was 51 months (range of 3-122). On multivariate analyses, CPSS scores, KPS, and graft source were significant predictors of OS (p=0.004, p=0.01, p=0.01 respectively). Higher CPSS scores were not associated with DFS, relapse, or TRM (p=0.2, p=0.1, p=0.08, respectively). To
investigate why higher CPSS scores were associated with higher mortality, we performed analysis restricted to patients with relapse following HCT. Those with intermediate-2 / high risk had nearly two-fold increase in risk of death after relapse compared to those with low / intermediate-1 CPSS scores. Corresponding rates for low / intermediate-1 risk groups, OS at 1 year, 3 years, and 5 years were 61%, 48%, and 44%, respectively, and for intermediate-2 / high risk groups were 38%, 32%, and 19%, respectively. OS of patients who received pre-HCT treatment with hypomethylating agents, chemotherapy, or both was not different compared to those who received no therapy prior (p=0.96). In summary, CPSS scores, lower KPS scores, and bone marrow as graft source were associated with poorer outcomes following HCT.

STUDIES IN PROGRESS

Study # CK10-02
Title: The impact of treatment with second-generation tyrosine kinase inhibitors on the outcomes of hematopoietic cell transplantation for patients with chronic myeloid leukemia
Study Chairs: Richard Maziarz (Oregon Health and Science University) Jeffrey Szer (Royal Melbourne Hospital)
MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # CK11-02
Title: Development of a prognostic scoring system to predict relapse of myelodysplastic syndrome after allogeneic hematopoietic cell transplantation
Study Chair: Brian Shaffer (Memorial Sloan Kettering Cancer Center)
MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: Kwang Woo Ahn (kwooahn@mcw.edu)
Study Status: Analysis in progress

Study # CK12-01
Title: A decision analysis of the optimal timing of allogeneic hematopoietic cell transplantation in chronic myeloid leukemia in the era of tyrosine kinase inhibitors
Study Chairs: Hans Lee (The University of Texas MD Anderson Cancer Center) Jorge Cortes (The University of Texas MD Anderson Cancer Center) Marcos de Lima (University Hospitals Case Medical Center)
MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development
Study # CK12-02b
Title: A retrospective assessment of outcomes of patients who have undergone allogeneic hematopoietic cell transplant for chronic lymphocytic leukemia based on histocompatibility leukocyte antigen type
Study Chair: Brian Hill (Cleveland Clinic)
MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # CK13-03
Title: Hematopoietic stem cell transplantation vs. chemotherapy for low and intermediate IPSS risk MDS
Study Chair: Wael Saber (CIBMTR Milwaukee)
MS Statistician: Wael Saber (wsaber@mcw.edu)
Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # CK14-01
Title: Outcomes of umbilical cord transplantation for myelodysplastic syndrome
Study Chairs: Matt Kalaycio (Cleveland Clinic)
Aaron Gerds (Cleveland Clinic)
MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # CK14-02
Title: Validation of DFCI prognostic score for previously treated chronic lymphocytic leukemia patients who underwent reduced intensity conditioning allogeneic HCT
Study Chairs: Haesook Kim (Dana Farber Cancer Institute)
Jennifer Brown (Dana Farber Cancer Institute)
MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development
8.4 DONOR HEALTH AND SAFETY WORKING COMMITTEE

Co-Chair: Paul O’Donnell, MD, PhD, Fred Hutchinson Cancer Research Center  
Email: podonnel@fredhutch.org

Co-Chair: Michael Pulsipher, MD, Primary Children’s Hospital  
Email: michael.pulsipher@hsc.utah.edu

Scientific Director: Bronwen Shaw, MBChB, PhD, CIBMTR Milwaukee  
Email: beshaw@mcw.edu

PhD Statistician: Brent Logan, PhD, CIBMTR Milwaukee  
Email: blogan@mcw.edu

MS Statistician: Pintip Chitphakdithai, PhD, CIBMTR Minneapolis  
Email: pchitpha@nmdp.org

MS Statistician: Deidre Kiefer, MS, CIBMTR Minneapolis  
Email: dkiefer@nmdp.org

RECENTLY COMPLETED STUDIES

Study # DS09-05b


Abstract: We compared serious early and late events experienced by 2,726 BM and 6,768 PBSC donors who underwent collection of PBSC or BM between 2004 and 2009 as part of a prospective study through the NMDP. Standardized FDA definitions for SAEs were used, and all events were reviewed by an independent physician panel. BM donors had an increased risk for SAEs (2.38% for BM vs 0.56% for PBSC, OR 4.13, P<0.001), and women were twice as likely to experience an SAE (OR for men 0.50, P=0.005). Restricting the analysis to life-threatening, unexpected, or chronic / disabling events, BM donors maintained an increased risk for SAEs (0.99% for BM vs 0.31% for PBSC, OR 3.20, P<0.001). Notably, the incidence of cancer, autoimmune illness, and thrombosis after donation was similar in BM vs PBSC donors. In addition, cancer incidence in PBSC donors was less than that reported in the general population (SEER Program database). In conclusion, SAEs after donation are rare but more often occurred in BM donors and women. In addition, there was no evidence of increased risk for cancer, autoimmune illness, and stroke in donors receiving G-CSF during this period of observation.

Study # DS10-01


Abstract:
Little information exists on the effect of race and ethnicity on collection of PBSC for alloHCT. We studied 10,776 donors from the NMDP who underwent PBSC collection from 2006-2012. Self-reported donor race / ethnic information included Caucasian, Hispanic, Black / African American (AA), Asian/Pacific Islander, and Native American. All donors were mobilized with subcutaneous filgrastim (G-CSF) at an approximate dose of 10 µg/kg/d for 5 days. Overall, AA donors had the highest median yields of mononuclear cells (MNC)/L and CD34+ cells/L blood processed (3.1 x 10^9 and 44 x 10^6 respectively) while Caucasians had the lowest median yields at 2.8 x 10^9 and 33.7 x 10^6, respectively. Multivariate analysis of CD34+/L mobilization yields using Caucasians as the comparator and controlling for age, gender, body mass index, and year of apheresis revealed increased yields in overweight and obese AA and Asian / Pacific Islander donors. In Hispanic donors, only male obese donors had higher CD34+/L mobilization yields compared to Caucasian donors. No differences in CD34+/L yields were seen between Caucasian and Native American donors. Characterization of these differences may allow optimization of mobilization regimens to allow enhancement of mobilization yields without compromising donor safety.

PRELIMINARY RESULTS

Study # DS05-02b
Title: Quality of life for older (>60) related donors compared to younger (18-60) related adult donors
Study Chairs: Galen Switzer (University of Pittsburgh)
               Michael Pulsipher (University of Utah School of Medicine / Primary Children’s Hospital)
MS Statistician: Deidre Kiefer (dkiefer@nmdp.org)
PhD Statistician: N/A
Study Status: Manuscript preparation
Abstract: It is critical to understand health-related quality of life (HRQoL) among older related siblings who are increasingly asked to donate hematopoietic stem cells. Findings presented here are from a five year study of RD safety and HRQoL (RDSafe). The goal was to compare HRQoL in older vs. younger adult RD. Participants were older adult RD (ages >60 years, median=65 years, n=105) and younger adult RD (ages 18-60, median=42 years, n=59) who donated PBSC at domestic US centers between 3/2010 and 4/2013. Data were collected via structured telephone interviews at pre-donation, and 4 weeks and 1-year post-donation. Interviews focused on socio-demographics, physical and mental health, and donation-related perceptions using well-validated instruments including the
SF-12v2 to assess general physical / mental health. Odds-ratios for dichotomous variables t-tests for continuous variables and mixed linear models were used to examine age group differences.

Demographics: Older RD were less likely to be employed, and more likely be white, married, and to have children. Pre-donation: Pre-donation, older RD had poorer physical health (t=−3.28, p<0.01) but did not differ from younger RD on psychosocial variables, including general mental health, depression, and anxiety. There were no group differences in ambivalence, satisfaction, or medical concerns about donation although older RD were more likely to consult their physician about donation (OR 13.18, p<0.001). Older RD had fewer work / family concerns (t=−2.04, p<0.05). Post-donation: 4-weeks post-donation, there were no group differences in general physical health, mental health, or any of 12 donation-related symptoms. Older RD were less likely to report donation-related pain (t=−2.29, p<0.05) and continued to have fewer work / family concerns about the donation process (t=−3.39, p<0.01). At one-year post-donation, there were no differences in general physical and mental health or in the percent of RD reporting feeling completely back to normal. There was a nonsignificant trend for older RD to report a longer recovery period (t=1.78; p=0.08). Older RD reported fewer current problems sleeping (OR=0.39; p<0.05) but did not differ from younger RD on any other symptoms or in concern about longer-term donation effects. Mixed linear models indicated that older RD had poorer physical health (primarily pre-donation) but better mental health. There was no main effect difference by data collection time point and no age by time interaction for physical or mental health.

Despite having somewhat poorer overall general pre-donation health, older RD experience similar – and in some domains better – donation-related HRQoL compared to younger RD. This is a reassuring finding that supports the use of older family members as donors and will further inform the counseling and consent of older RD.

**Study # DS09-04**

**Title:** Race / socioeconomic status and donor center size on bone marrow and peripheral blood stem cells donor experience

**Study Chair:** Michael Pulsipher (University of Utah School of Medicine / Primary Children’s Hospital)

**MS Statistician:** Deidre Kiefer (dkiefer@nmdp.org)

**PhD Statistician:** Brent Logan (blogan@mcw.edu)

**Study Status:** Manuscript preparation

**Abstract:** Previous studies have identified risks of collection-related pain and symptoms associated with sex, BMI, and age in unrelated donors undergoing collection at NMDP centers. We hypothesized that other important factors (race, SES, and collection center experience as reflected by numbers of procedures performed) might affect rates of pain / symptoms in donors. We assessed outcomes by five race categories, four SES levels, and collection center volume. The study cohort included 2,726 BM and 6,768 PBSC donors collected between 2004 and 2009.
Skeletal pain and 10 symptoms were measured and scaled 1-4 as published previously (Pulsipher, Blood 2013). Pain / symptoms are reported as peak levels over mobilization and collection (PBSC) or within two days of collection (BM) and at one week after collection. Generalized linear mixed models were used to fit logistic regression models with random effects by center; the three main effects of race, SES, and center volume were forced into the model, while other donor characteristics were added in a stepwise manner. For PBSC donors, race was not associated with differences in pain / symptoms during collection or one-week post donation. PBSC donors in higher SES levels reported higher peak symptom levels one-week post donation (p=0.02). No pattern of increased pain / symptoms was associated with centers that performed smaller number of PBSC collections. For BM donors, Black males reported significantly higher levels of pain after the procedure. No differences were noted by SES groups after BM collection. Different levels of BM collection experience were tested to determine cutpoints; the optimal cutpoint was noted to be one or fewer collections every two months. BM donors from centers collecting less than this frequency were more likely to have persistent symptoms. Conclusions: In general, race and SES have a minimal effect on symptoms associated with donation. Of note, however, centers performing ≤1 BM collection every 2 months have more symptoms reported after BM collection, and approaches should be developed by low volume centers to address this issue.

STUDIES IN PROGRESS

Study # DS05-02a
Title: Older adult related donors compared to adult related donors
Study Chair: Michael Pulsipher (University of Utah School of Medicine / Primary Children’s Hospital)
MS Statistician: Pintip Chitphakdithai (pchitpha@nmdp.org)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Analysis in progress

Study # DS05-02c
Title: Acute toxicities of related adult donors compared to unrelated adult donors
Study Chair: Michael Pulsipher (University of Utah School of Medicine / Primary Children’s Hospital)
MS Statistician: Deidre Kiefer (dkiefer@nmdp.org)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Analysis in progress

Study # DS05-02d
Title: Quality of life for related adult donors compared to unrelated adult donors
Study Chairs: Galen Switzer (University of Pittsburgh)
Michael Pulsipher (University of Utah School of Medicine / Primary
Study # DS05-02e
Title: Acute toxicities for pediatric related donors compared to adult related donors
Study Chair: Michael Pulsipher (University of Utah School of Medicine / Primary Children’s Hospital)
MS Statistician: Deidre Kiefer (dkiefer@nmdp.org)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Data collection / data file preparation

Study # DS05-02f
Title: Quality of life for related pediatric donors compared to normative pediatric cohort
Study Chairs: Galen Switzer (University of Pittsburgh)
Michael Pulsipher (University of Utah School of Medicine / Primary Children’s Hospital)
MS Statistician: Deidre Kiefer (dkiefer@nmdp.org)
PhD Statistician: N/A
Study Status: Analysis in progress

Study # DS05-02g
Title: Late toxicities and severe adverse events for related donors
Study Chair: Michael Pulsipher (University of Utah School of Medicine / Primary Children’s Hospital)
MS Statistician: Deidre Kiefer (dkiefer@nmdp.org)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Analysis in progress

Study # DS09-03
Title: Effects of multiple donations on marrow / peripheral blood stem cell donors
Study Chair: David Stroncek (NIH - Department of Transfusion Medicine, Clinical Center)
MS Statistician: Deidre Kiefer (dkiefer@nmdp.org)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Protocol development

Study # DS13-01
Title: Retrospective examination of the role quantity of bone marrow harvests performed by a harvest center has on the overall quality of the harvested product: assessment of the potential impacts bone marrow product quality has on utilization of bone marrow as a cell source for transplant
Study Chair: Nicole Prokopishyn (University of Calgary)
### Study # DS13-02

**Title:** A retrospective analysis to understand the potential mechanisms underlying the clinical impact of ABO incompatibility on allogeneic hematopoietic cell transplantation outcomes  

**Study Chair:** Bronwen Shaw (Froedtert & Medical College of Wisconsin)  
**MS Statistician:** Bronwen Shaw (beshaw@mcw.edu)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development

### Study # DS14-01

**Title:** Survey of the care and management of adult related allogeneic stem cell donors in the United States  

**Study Chairs:** Chloe Anthias (Anthony Nolan Research Institute)  
Bronwen Shaw (Froedtert & Medical College of Wisconsin)  
Paul O’Donnell (Fred Hutchinson Cancer Research Center)  

**MS Statistician:** Deidre Kiefer (dkiefer@nmdp.org)  
**PhD Statistician:** N/A  
**Study Status:** Data collection / data file preparation
RECENTLY COMPLETED STUDIES

Study # GS05-01


Abstract: Variations in cord blood manufacturing and administration are common, and the optimal practice is unknown. We compared processing and banking practices at 16 public cord blood banks (CBB) in the US, and assessed transplant outcomes on 530 single UCB MA transplantations for hematologic malignancies, facilitated by these banks. UCB banking practices were separated into three mutually exclusive groups based on whether processing was automated or manual; units were plasma and red blood cell reduced or buffy coat production method or plasma reduced. Compared to the automated processing system for units, the day-28 neutrophil recovery was significantly lower after transplantation of units that were manually processed and plasma reduced (red cell replete) (OR 0.19, p=0.001) or plasma and red cell reduced (OR 0.54, p=0.05). Day-100 survival did not differ by CBB. However, day-100 survival was better with units that were thawed with the dextran-albumin wash method compared to the “no wash” or “dilution only” techniques (OR 1.82, p=0.04). In conclusion, CBB processing has no significant effect on early (day 100) survival despite differences in kinetics of
neutrophil recovery implying advances in supportive care have in part overcome early mortality associated with slower neutrophil recovery.

**Study # GS12-01**


**Abstract:**
RIC/NMA regimens are increasingly used in allogeneic HCT. Reports have shown CD34+ dose to be important for transplant-outcome using MAC. The role of CD34+ dose of PBPCs has not been previously analyzed in a large population undergoing RIC/NMA HCT. We studied 1,054 patients aged 45-75 years, with AML or MDS transplanted between 2002 and 2011. Results of multivariate analysis showed that PBPC from HLA-matched siblings containing <4x10^6 CD34+/kg were associated with higher NRM (HR 2.03, p=0.001), overall mortality (HR 1.48, p=0.008), and lower neutrophil (OR 0.76, p=0.03) and platelet (OR 0.76, p=0.03) recovery. PBPCs from unrelated donors with CD34+ dose <6x10^6 CD34+/kg were also associated with higher NRM (HR 1.38, p=0.02) and overall mortality (HR 1.20, p=0.05). In contrast to reports after myeloablative HCT, CD34+ dose did not affect relapse or GVHD with either donor type. An upper cell dose limit was not associated with adverse outcomes. These data suggest that PBPC CD34+ dose >4x10^6 CD34+/kg and >6x10^6 CD34+/kg are optimal for HLA-matched sibling and unrelated donor HCT, respectively.

**Study # GS12-03**


**Abstract:**
We studied AML patients over age 50 in CR1 after adult URD (n=441 8/8 and n=94 7/8 HLA-matched) or UCB (n=205) transplantations. UCB recipients less often achieved CR1 within 8 weeks and more often received RIC and cyclosporin-based GVHD prophylaxis. Neutrophil recovery was slower in UCB (69% by day 28) vs 8/8 URD (97%) and 7/8 (91%) (p<0.001). Three-year TRM was higher and LFS lower with UCB (35% and 28%, respectively) vs 8/8 URD (27% and 39%). TRM was higher in 7/8 URD (41%, p=0.01), but LFS similar (34%, p=0.39). Three-year chronic GVHD was least in UCB (28%) vs 53% and 59% in 8/8 and 7/8 URD recipients. Three-year survival was 8/8 URD 43% (95% CI 38-48), UCB 30% (95%
CI 23-37) (p=0.002) and 7/8 URD 37% (95% CI 27-46). AlloHCT for AML in CR1 with any of these grafts extends LFS for over a third of older patients. In the absence of an 8/8 HLA-matched URD or when transplantation is needed urgently, UCB can provide extended survival. Less frequent chronic GVHD with UCB transplantation may be of particular value for older patients.

**Study # SC11-02a**


**Abstract:** Background: There have been no randomized trials that have compared PB to BM grafts in the setting of RIC transplants for hematologic malignancy. As immune modulation plays a significant role in sustaining clinical remission after RIC, we hypothesize that higher GVHD associated with PB transplantation may offer a survival advantage. Methods: The primary outcome evaluated was OS. Cox regression models were built to study outcomes after transplantation of PB (N=887) relative to BM (N=219) for patients with AML, MDS, and NHL, the three most common indications for unrelated RIC transplantation. Transplants were performed in the US between 2000 and 2008. Conditioning regimens consisted of an alkylating agent and fludarabine and GVHD prophylaxis involved a CNI with either MTX or MMF. Results: After adjusting for age, performance score, donor-recipient HLA-match, disease and disease status at transplantation, factors associated with overall survival, there were no significant differences in 5-year rates of survival after transplantation of PB compared to BM: 34% vs 38% with CNI-MTX and 27% vs 20% with CNI-MMF GVHD prophylaxis. Conclusion: Survival after transplantation of PB and BM are comparable in the setting of non-irradiation RIC regimens for hematologic malignancy. The effect of GVHD prophylaxis on survival merits further evaluation.

**Study # SC11-02b**


**Abstract:** We sought to determine whether differences in chronic GVHD rates would lead to survival differences comparing 2,463 PB and 1,713 BM HCT recipients. Patients had acute leukemia, CML, or MDS; received MAC regimens and CNI GVHD prophylaxis. There were no significant differences in long-term survival after transplantation of PB and BM except first chronic phase CML. For these patients, 5-year rate of survival was lower after transplantation of PB compared to BM (35% vs 56%, p=0.001). Although mortality risks were higher in patients with
chronic GVHD after both PB (HR 1.58, p<0.001) and BM (HR 1.73, p<0.001) transplants, its effect on mortality did not differ by graft (p=0.42). BM is the preferred graft for first chronic phase CML whereas either graft is suitable for other leukemias.

PRELIMINARY RESULTS

Study # GS08-01

Title: Reassessment of impact of donor age on outcomes after unrelated / related donor hematopoietic cell transplantation

Study Chair: Craig Kollman (Jaeb Center for Health Research)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Submitted

Abstract: We analyzed 6,349 adult unrelated donor transplantations performed in 1988–2006 to reexamine the effect of donor age and other donor characteristics including donor-recipient HLA matching on transplant outcomes. Patients had a hematologic malignancy (ALL, AML, CML, MDS) and approximately 40% were in first complete remission or first chronic phase. 93% of transplantations used donors younger than 50 (median 35.8, range 18-61). The majority of patients received MA preparative regimens (88%) and BM grafts (62%). All patients received CNI-containing GVHD prophylaxis, and 20% received in vivo T cell depletion. We identified three donor characteristics associated with overall survival: donor age, high resolution donor-recipient HLA-match, and ABO blood group match. Risk adjusted 5-year survival rates were 37%, 33%, and 29% with donors aged 18-32, 33-50, and >50 years, respectively (p<0.0001). Corresponding hazard ratios were 1.13 (p=0.0004) for donors aged 33–50 years and 1.29 (p<0.001) for donors >50 years compared with donors aged 18-32 years. Mortality risks were higher with one (HR 1.24, p<0.0001) and two (HR 1.62, p<0.0001) HLA-mismatches compared with HLA-matched transplants and minor (HR 1.10, p=0.002) or major (HR 1.13, p=0.001) ABO blood group mismatch compared with ABO-matched transplants. A sub-analysis investigated the possibility that the association with donor age may be due to underlying genetic disparity between donor and recipient. That is, recipients with rare HLA genotypes tend to have fewer matched donors to choose from and thus more likely to receive a graft from an older donor. Recipient genotypes were assigned to quartiles using frequency data from 4 million NMDP donors as a reference. The lowest frequency quartile was associated with donors older than 50 (p<0.0001) and higher rates of HLA mismatching (p<0.001), but no association was found between genotype frequency and overall mortality. Acute GVHD risks were associated with donor age and HLA match and donor parity, the only donor characteristic associated with chronic GVHD. In summary, the data recommend the consideration of donor age and ABO blood group match to maximize
survival when selecting among comparably HLA-matched adult unrelated stem cell donors for treatment of a hematologic malignancy.

**Study # GS13-01**

**Title:** Comparable 3-year disease-free survival regardless of anti-thymocyte globulin inclusion in pediatric myeloablative cord blood transplantation for acute lymphoblastic leukemia

**Study Chairs:** Doris Ponce (Memorial Sloan Kettering Cancer Center)
Juliet Barker (Memorial Sloan Kettering Cancer Center)
Miguel-Angel Perales (Memorial Sloan Kettering Cancer Center)

**MS Statistician:** Junfang Chen (juchen@mcw.edu)

**PhD Statistician:** Rodney Sparapani (rsparapa@mcw.edu)

**Study Status:** Manuscript preparation

**Abstract:**

Background: CB is routinely used as an alternative stem cell source for the treatment of children with acute leukemia and has been associated with high rates of DFS. However, one controversial issue in pediatric CB transplantation is the role of ATG as immunoprophylaxis. While inclusion of ATG in the conditioning may decrease the risk of GVHD, it could potentially abrogate GVL effects and increase the risk of opportunistic infections. Thus, we compared outcomes in a uniform group of pediatric patients with ALL who underwent MA CB transplantation with or without ATG. Methods: Patients with ALL in morphologic remission (CR1 n=106, CR2 n=146, CR3 n=45) aged ≤ 20 years transplanted between 01/2007-12/2011 with high-dose TBI-based conditioning and single or double unit CB grafts were eligible for analysis. CB units were 4-6/6 HLA-A,-B at the antigen-level, -DRB1 allele matched to the recipient, and had CB unit with cryopreserved total nucleated cell dose of ≥2.5x10^7/kg/unit. Cox regression models were built to evaluate potential differences in outcome in ATG versus non-ATG CB transplant recipients. The primary endpoint was three-year DFS. Results: Of 297 patients, 92 received ATG and 205 did not. Age and disease status were similar in each group whereas ATG recipients were less likely to be CMV seropositive and more likely to receive single unit CB grafts. While neutrophil engraftment was similar in each group, the risk of day 100 grade II-IV acute GVHD [30% (95% CI 21-40) vs 54% (95% CI 47-61), p=0.0002] and 3-year chronic GVHD [22% (95% CI 14-31) vs 43% (95% CI 36-50), p=0.0008] were decreased in ATG recipients. However, day 100 grade III-IV acute GVHD was comparable: 11% (95% CI 5-18) in ATG vs 17% (95% CI 12-23) in non-ATG recipients, p=0.15. The 3-year TRM was similar in both groups: 16% (95% CI 10-25) in ATG vs 17% (95% CI 13-23) in non-ATG recipients (p=0.98). Relapse was also similar in ATG and non-ATG recipients: 17% (95% CI 10-23) vs 27% (95% CI 21-34, p=0.12), respectively. In multivariate analysis, negative CMV serostatus was associated with reduced TRM risk [HR 0.55 (95% CI 0.30-0.98), p=0.004] whereas remission status CR2 or CR3 significantly increased relapse risk [HR 2.18 (95% CI 1.22-3.89), p=0.008], but inclusion of ATG had no effect on either outcome. With a median follow-up of survivors of 36 months (range 5-72), the 3-year DFS was 66% (95% CI 56-76) and 55% (95% CI 48-62) in ATG and non-ATG...
recipients, respectively (p=0.23). The distribution of causes of death was similar in each group. In multivariate analysis, treatment failure risk was increased in patients transplanted in CR2 or CR3, but the inclusion of ATG had no effect (p=0.24). Conclusion: Inclusion of ATG in pediatric myeloablative CB transplant for ALL is associated with a decreased risk of grade II-IV acute GVHD and chronic GVHD but not severe grade III-IV acute GVHD. There was no difference in three-year DFS in each group, and multivariate analysis revealed ATG inclusion had no impact upon treatment failure risk. These results indicate that optimization of both ATG and non-ATG conditioning platforms are needed in order to further improve CB transplantation survival in children with ALL. Unanswered questions include the impact of the formulation, dose, and timing of ATG administration. These findings cannot be extrapolated for other diagnoses, reduced intensity conditioning, or adults.

**STUDIES IN PROGRESS**

**Study # GS13-02**

**Title:** Matching between umbilical cord blood units in double umbilical cord blood transplantation  
**Study Chair:** Claudio Brunstein (University of Minnesota Medical Center)  
**MS Statistician:** Junfang Chen (juchen@mcw.edu)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development

**Study # GS14-01**

**Title:** Outcomes after T-cell replete haploidentical and matched related and unrelated donor hematopoietic stem cell transplantation  
**Study Chairs:** Olle Ringdén (Karolinska University Hospital, Centre for Allogeneic Stem Cell Transplantation)  
Ephraim Fuchs (Johns Hopkins University Sidney Kimmel Cancer Center)  
Stefan Ciurea (The University of Texas MD Anderson Cancer Center)  
Sai Ravi Pingali (The University of Texas MD Anderson Cancer Center)  
Alberto Mussetti (Memorial Sloan Kettering Cancer Center)  
Miguel-Angel Perales (Memorial Sloan Kettering Cancer Center)  
**MS Statistician:** Junfang Chen (juchen@mcw.edu)  
**PhD Statistician:** Mei-Jie Zhang (meijie@mcw.edu)  
**Study Status:** Analysis in progress
<table>
<thead>
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<tr>
<td><strong>Title:</strong> Association between recipient and donor sex and clinical outcome after allogeneic hematopoietic stem cell transplantation</td>
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<tr>
<td><strong>Study Chairs:</strong> Philippe Armand (Dana Farber Cancer Institute) Haesook Kim (Dana Farber Cancer Institute)</td>
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<tr>
<td><strong>MS Statistician:</strong> Junfang Chen (<a href="mailto:juchen@mcw.edu">juchen@mcw.edu</a>)</td>
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<td><strong>PhD Statistician:</strong> TBD</td>
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8.6 GRAFT-VS-HOST DISEASE WORKING COMMITTEE

Co-Chair: Corey Cutler, MD, MPH, Dana Farber Cancer Institute
   Email: corey_cutler@dfci.harvard.edu
Co-Chair: Daniel Couriel, MD, University of Michigan
   Email: dcouriel@umich.edu
Co-Chair: Amin Alousi, MD, MD Anderson Cancer Center
   Email: aalousi@mdanderson.org
Scientific Director: Mukta Arora, MD, MS, CIBMTR Minneapolis
   Email: arora005@umn.edu
Scientific Director: Steve Spellman, MBS, CIBMTR Minneapolis
   Email: sspellma@nmdp.org
PhD Statistician: Tao Wang, PhD, CIBMTR Milwaukee
   Email: taowang@mcw.edu
MS Statistician: Michael Hemmer, MS, CIBMTR Milwaukee
   Email: mhemmer@mcw.edu

RECENTLY COMPLETED STUDIES

Study # GV04-02 / GV05-03c


Abstract: Purpose: Malignancy relapse remains a major obstacle for successful alloHCT. Chronic GVHD is associated with fewer relapses. However, when studying effects of chronic GVHD on relapse, it is difficult to separate from acute GVHD effects as most cases of chronic GVHD occur within the first year post-transplant at the time when acute GVHD is still active. Experimental design: The current study based on CIBMTR registry data investigated chronic GVHD and its association with the incidence of late relapse and survival in 7,489 patients with AML, ALL, CML, and MDS who were leukemia-free at 12 months after MAC alloHCT. Results: Forty-seven percent of the study population was diagnosed with chronic GVHD at 12 months after transplant. The protective effect of chronic GVHD on relapse was present only in patients with CML (RR 0.47, 95% CI 0.37-0.59, P<0.0001). Chronic GVHD was significantly associated with higher risk of TRM (RR 2.43, 95% CI 2.09-2.82, P<0.0001) and inferior OS (RR 1.56, 95% CI 1.41-1.73, P<0.0001) for all diseases. In patients with CML, all organ sites and presentation types of chronic GVHD were equally associated with lower risk of late relapse. Conclusions: These results indicate that clinically relevant anti-
leukemia effects of chronic GVHD on late relapses are present only in CML but not in AML, ALL, or MDS. Chronic GVHD in patients who are one-year survivors after MAC alloHCT is primarily associated with higher TRM and inferior survival.

**Study # GV06-04**


**Abstract:** Although transplant practices have changed over the last decades, there is no information on trends in incidence and outcome of chronic GVHD over time. This study utilized the central database of the CIBMTR to describe the time trends for chronic GVHD incidence, NRM, and the risk factors for chronic GVHD. The 12-year period was divided into three intervals: 1995-1999, 2000-2003, 2004-2007, and included 26,563 patients with acute leukemia, CML, and MDS. In the multivariate analysis, the incidence of chronic GVHD was shown to be increased in more recent years (OR 1.19, p<0.0001) and this trend was still seen when adjusting for donor type, graft type, or conditioning intensity. In patients with chronic GVHD, NRM has decreased over time, but at five-years post-transplant there were no significant differences among different time periods. Risk factors for chronic GVHD were in line with previous studies. This is the first comprehensive characterization of the trends in chronic GVHD incidence and underscores the mounting need for addressing this major late complication of transplantation in future research.

**Study # GV11-04**

Abstract: We previously reported a risk score that predicted mortality in patients with chronic GVHD after HCT between 1995-2004 and reported to the CIBMTR. We sought to validate this risk score in an independent CIBMTR cohort of 1,128 patients with chronic GVHD transplanted between 2005-2007 using the same inclusion criteria and risk-score calculations. According to the sum of the overall risk score (range 1 to 12), patients were assigned to 4 risk groups (RGs): RG1 (0-2), RG2 (3-6), RG3 (7-8), and RG4 (9-10). RG3 and 4 were combined as RG4 comprised only 1% of the total cohort. Cumulative incidences of NRM and probability of OS were significantly different between each RG (all p<0.01). NRM and OS at 5 years after chronic GVHD for each RG were 17% and 72% in RG1, 26% and 53% in RG2, and 44% and 25% in RG 3, respectively (all p<0.01). Our study validates the prognostic value of the CIBMTR chronic GVHD RGs for OS and NRM in a contemporary transplant population. The CIBMTR chronic GVHD RGs can be used to predict major outcomes, tailor treatment planning, and enrollment in clinical trials.

PRELIMINARY RESULTS

Study # GV11-03

Title: A retrospective comparison of tacrolimus versus cyclosporine with methotrexate for immunosuppression after allogeneic hematopoietic cell transplantation according to graft and donor type

Study Chairs: Yoshihiro Inamoto (National Cancer Center Hospital)
Paul Martin (Fred Hutchinson Cancer Research Center)
Alvaro Urbano-Ispizua (University of Barcelona, IDIBAPS, and Institute of Research Josep Carreras)
Mary Flowers (Fred Hutchinson Cancer Research Center)

MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Manuscript preparation

Abstract: Combinations of CSP with MTX have been widely used for immunosuppression after allogeneic transplantation for acquired aplastic anemia. We compared outcomes with TAC+MTX vs CSP+MTX after transplantation from HLA-identical siblings (SIB) or URD in a retrospective cohort of 949 patients with severe aplastic anemia. Study endpoints included hematopoietic recovery, graft failure, acute GVHD, chronic GVHD, and overall mortality. TAC+MTX was used more frequently in older patients and in recent years in both groups. In multivariate analysis, TAC+MTX was associated with a lower risk of overall mortality in URD recipients and with slightly earlier neutrophil recovery in SIB recipients. Other outcomes and causes of death did not differ statistically between the two regimens. Although no firm conclusions were reached regarding which GVHD prophylaxis is better, the use of TAC+MTX might decrease overall mortality in URD recipients with acquired aplastic anemia.
STUDIES IN PROGRESS

Study # SC10-02
Title: Chronic graft-versus-host disease and relapse in cord blood transplants in children with leukemia
Study Chair: Mary Eapen (Froedtert & Medical College of Wisconsin)
MS Statistician: Mary Eapen (meapen@mcw.edu)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Analysis in progress

Study # GV11-02
Title: Acute and chronic graft-versus-host disease after unrelated umbilical cord blood transplantation: analysis of risk factors and outcomes
Study Chairs: Yi-Bin Chen (Dana Farber Cancer Institute)
Corey Cutler (Dana Farber Cancer Institute)
MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Analysis in progress

Study # GV12-01
Title: Outcomes of grades 3-4 acute graft-versus-host disease post-allogeneic hematopoietic cell transplantation: how much progress was achieved?
Study Chair: H. Jean Khoury (Emory University Hospital)
MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # GV12-02
Title: Prognostic implications of acute upper gastrointestinal graft-versus-host disease in patients undergoing myeloablative hematopoietic cell transplantation
Study Chairs: Sarah Nikiforow (Dana Farber Cancer Institute)
Corey Cutler (Dana Farber Cancer Institute)
MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation
Study # GV13-01
Title: Impact of donor sex, parity, and sibling / unrelated status on outcomes of allogeneic hematopoietic cell transplantation
Study Chairs: Anita Kumar (Abramson Cancer Center University of Pennsylvania Medical Center)
Alison Loren (Perelman School of Medicine at the University of Pennsylvania)
MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # GV13-02
Title: The impact of the combination and sequence of immunosuppressive treatments on outcomes of acute graft-versus-host disease: a methodological exercise in modeling adaptive treatment strategies
Study Chairs: Elizabeth Krakow (Maisonneuve-Rosemont Hospital)
Erica Moodie (Gill University Health Centre - Royal Victoria Hospital)
MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statisticians: Tao Wang (taowang@mcw.edu)
Elizabeth Krakow (elizabeth.krakow@mail.mcgill.ca)
Study Status: Analysis in progress

Study # GV14-01
Title: Comparison of mycophenolate versus methotrexate in combination with a calcineurin inhibitor for graft-versus-host disease prophylaxis in allogeneic HCT
Study Chairs: Betty Hamilton (Cleveland Clinic)
Saurabh Chhabra (Medical University of South Carolina)
Navneet Majhail (Cleveland Clinic)
Luciano Costa (University of Alabama at Birmingham)
Robert Stuart (Medical University of South Carolina)
Dennis Kim (Princess Margaret Hospital)
Olle Ringdén (Karolinska University Hospital, Centre for Allogeneic Stem Cell Transplantation)
MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development
Study # GV14-02
Title: Influence of donor and recipient age on risk for acute and chronic graft versus host disease in children receiving bone marrow transplantation
Study Chairs: Muna Qayed (Emory University Hospital)
 John Horan (Columbia University Medical Center)
MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # SC14-03
Title: Comparison of survival and clinical endpoints for pediatric patients with acute graft versus host disease from the CIBMTR registry with those for patients from the OSIRIS Protocol 275 Study
Study Chair: Donna Skerrett (Mesoblast, Inc.)
MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: TBD
Study Status: Data collection / data file preparation
8.7 HEALTH SERVICES AND INTERNATIONAL ISSUES WORKING COMMITTEE

Co-Chair: Yoshiko Atsuta, MD, PhD, Nagoya University Graduate School of Medicine
Email: y-atsuta@med.nagoya-u.ac.jp

Co-Chair: Carmem Bonfim, MD, Hospital de Clinicas Curitiba
Email: carmembonfim@gmail.com

Co-Chair: Jignesh Dalal, MD, The Children’s Mercy Hospitals and Clinics
Email: jdalal2002@gmail.com

Co-Chair: Theresa Hahn, PhD, Roswell Park Cancer Institute
Email: theresa.hahn@roswellpark.org

Scientific Director: Wael Saber, MD, MS, CIBMTR Milwaukee
Email: wsaber@mcw.edu

PhD Statistician: Ruta Brazauskas, PhD, CIBMTR Milwaukee
Email: ruta@mcw.edu

MS Statistician: Naya He, MPH, CIBMTR Milwaukee
Email: nhe@mcw.edu

RECENTLY COMPLETED STUDIES

Study # HS10-01


Abstract: Adolescents and young adults (AYAs, ages 15 to 40 years) with cancer have not experienced survival improvements to the same extent as younger and older patients. We compared changes in survival after MA alloHCT for ALL among children (n=981), AYAs (n=1,218), and older adults (n=469) who underwent transplantation over 3 time periods: 1990 to 1995, 1996 to 2001, and 2002 to 2007. Five-year survival varied inversely with age group. Survival improved over time in AYAs and paralleled that seen in children; however, overall survival did not change over time for older adults. Survival improvements were primarily related to lower rates of early TRM in the most recent era. For all cohorts, relapse rates did not change over time. A subset of 222 AYAs between the ages of 15 and 25 at 46 pediatric or 49 adult centers were also analyzed to describe differences by center type. In this subgroup, there were differences in transplantation practices among pediatric and adult centers, although HCT outcomes did not differ by center type. Survival for AYAs undergoing MA alloHCT for ALL improved at a similar rate as survival for children.
Study # HS11-02


Abstract: Several studies have shown comparable survival outcomes with different graft sources, but the relative resource needs of HCT by graft source have not been well studied. We compared total hospital length of stay in the first 100 days after HCT in 1,577 patients with acute leukemia in remission who underwent HCT with a UCB, MUD, or MMUD graft between 2008 and 2011. To ensure a relatively homogenous study population, the analysis was limited to patients with AML and ALL in CR1 or CR2 who underwent HCT in the US. To account for early deaths, we compared the number of days alive and out of the hospital in the first 100 days post-transplantation. For children who received MAC, the median time alive and out of the hospital in the first 100 days was 50 days for single UCB recipients, 54 days for double UCB recipients, and 60 days for MUD BM recipients. In multivariate analysis, use of UCB was significantly associated with fewer days alive and out of the hospital compared with MUD BM. For adults who received MAC, the median time alive and out of the hospital in the first 100 days was 52 days for single UCB recipients, 55 days for double UCB recipients, 69 days for MUD BM recipients, 75 days for MUD PBSC recipients, 63 days for MMUD BM recipients, and 67 days for MMUD PBSC recipients. In multivariate analysis, UCB and MMUD BM recipients had fewer days alive and out of the hospital compared with recipients of other graft sources. For adults who received a RIC regimen, the median time alive and out of the hospital during the first 100 days was 65 days for single UCB recipients, 63 days for double UCB recipients, 79 days for MUD PBSC recipients, and 79 days for MMUD PBSC recipients. Similar to the other two groups, receipt of UCB was associated with a fewer days alive and out of the hospital. In conclusion, length of stay in the first 100 days post-transplantation varies by graft source and is longer for UCB HCT recipients. These data provide insight into the resource needs of patients who undergo HCT with these various graft sources.

Study # IS12-02

Abstract: An earlier report identified higher risks of acute and chronic GVHD in White children compared with the Japanese after HLA-matched sibling transplantations. The current analysis explored whether racial differences are associated with GVHD risks after unrelated UCB transplantation. Included are patients of Japanese descent (n=257) and Whites (n=260; 168 of 260 received ATG). Transplants were performed in the US or Japan between 2000 and 2009; patients were aged 16 years or younger, had acute leukemia, were in CR, and received a MAC regimen. The median ages of the Japanese and Whites who received ATG were younger at five years compared with eight years for Whites who did not receive ATG. In all groups, most transplants were mismatched at one or two HLA loci. Multivariate analysis found no differences in risks of acute GVHD between the Japanese and Whites. However, chronic GVHD was higher in Whites who did not receive ATG compared with the Japanese (HR 2.16; P<0.001), and TRM was higher in Whites who received ATG compared with the Japanese (RR 1.81, P=0.01). Nevertheless, there were no significant differences in overall survival between the three groups.

PRELIMINARY RESULTS

Study # HS07-02b

Title: Long-term financial impact of allogeneic hematopoietic cell transplantation on patient and family

Study Chairs: Kate Pederson (National Marrow Donor Program)
Navneet Majhail (Cleveland Clinic)

MS Statistician: Naya He (nhe@mcw.edu)
PhD Statistician: N/A

Study Status: Manuscript preparation

Abstract: Patients and caregivers are at risk for financial hardship around the time of transplantation and during recovery post-transplant. We conducted a pilot study to evaluate the feasibility of capturing patient / caregiver out-of-pocket costs in the first 100 days post-transplant and the long-term financial impact of transplant on patient’s household. Thirty patients were enrolled at three centers. The out-of-pocket phase of this study has been published in Bone Marrow Transplant in 2013. The long-term financial impact phase of the study has been completed, and a manuscript is under preparation. For this second phase, CIBMTR Survey Research Group coordinators contacted and interviewed patients about their household’s financial health at 6-, 12-, 18- and 24-months post-transplant. Our study demonstrated the feasibility of collecting these data and will assist in the design of a larger project focusing on this issue. It also identified preliminary data on financial issues faced by patients and their caregivers as they recover from their transplant.
Study # IS09-02
Title: Outcomes comparison of the effect of human leukocyte antigen-matched sibling donor transplantation for severe aplastic anemia across different regions
Study Chair: Rajat Kumar (CancerCare Manitoba / University of Manitoba)
MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: Kwang Woo Ahn (kwoohan@mcw.edu)
Study Status: Manuscript preparation
Abstract: BM is the preferred graft source for treatment of SAA with HCT due to the lower risk of chronic GVHD and better survival compared to mobilized PBSC. However, this may not apply to all economic regions, as graft failure rate is often higher in regions where patients frequently present later in their disease course and with heavier transfusion load. Patients with SAA who received HCT from an HLA-matched sibling donor from 1995 to 2009 and reported to the CIBMTR (N=1,885) or the Japan Society for Hematopoietic Cell Transplantation (JSHCT, N=560) were analyzed. The study population was categorized by gross national income per capita and region / countries into three groups: high income countries (HIC), US and Canada (US-C, N= 504), other HIC (OHIC, N=1,280) and other combined group that included upper middle (UM), low middle (LM) and low income countries (LIC) (UM-LM-LIC, N=661). PBSC was used as the graft source in 72% of HCT in LM-LIC, compared to 17% in HIC and 13% in UMIC. The following demographics differed significantly in the combined UM-LM-LIC group compared to the HIC group: women in 36% (HIC-44%), performance scores <90% in 45% (US-C 32%, OHIC 29%), CMV positive donors / recipients in 77% (US-C 63%, OHIC 54%), median time from diagnosis to HCT <3 months in 40% (US-C 61%, OHIC 44%), prior use of ATG in 6% (US-C 24%, OHIC-23%). Three-year probabilities of OS for PBSC and BM graft source were 62% (95% CI 51-72%) and 88% (95% CI 84-91%, p<0.01) in US-C, 78% (95% CI 72-83%) and 88% (95% CI 86-90%, p<0.01) in OHIC, and 64% (95% CI 55-72%) and 69% (95% CI 65-74%, p=0.2) in UM-LM-LIC, respectively. Rates of chronic GVHD were generally higher with PBSC irrespective of economic region. Multivariate analysis showed that overall mortality was higher in the following groups (a) UM-LM-LIC, (b) PBSC, (c) low KPS (<90%), and (d) time from diagnosis to transplant >6 months.

Study # IS10-02
Title: Total body irradiation prior to hematopoietic cell transplantation: a pattern of care study
Study Chair: Christopher Barker (Memorial Sloan Kettering Cancer Center)
MS Statistician: Sanghee Hong (sangheesanghee@gmail.com)
Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: Jennifer Le-Rademacher (jlerade@mcw.edu)
Study Status: Manuscript preparation
Abstract: Purpose: To summarize the patterns of TBI as part of HCT conditioning over time, and compare them with non-TBI based conditioning and to describe characteristics of TBI techniques used and whether they changed in the last 15
years. Patients / Methods: Data of 215,341 first HCTs from 596 centers in 52 countries between 1995 and 2010 were analyzed. Associations of country, patient, disease, transplant center, and transplant regimen with use of TBI were made, and subset analyses were performed to assess trends over time. Further subset analyses of patients undergoing allogeneic HCT were performed to characterize radiation therapy techniques such as dosage, fractionation, shielding, and additional involved field radiation. Results: Radiation therapy was given as TBI, TLI, or both in 42.7%, 2.7%, and 0.5% of patients undergoing first allogeneic HCT. TBI is most commonly given to a dose of 12 Gy in six fractions over three days, with lung shielding. Non-myeloablative doses have been used more frequently in recent years. Non-TBI radiation therapy was used in 11% of patients prior to TBI, and 4% of patients prior to TLI. A decline in the use of radiation therapy as part of HCT was noted over the years for patients of all ages and diseases, except for patients with acute lymphoblastic leukemia undergoing allogeneic HCTs. TBI was performed as part of 8.2% of autologous HCTs and has been used less frequently in recent years. Radiation therapy was used more often prior to HCT for advanced or high risk malignancies or those with central nervous system involvement. Radiation therapy was used with a wide range of frequency in different regions of the world (11-41%), with no clear association with human development index. Conclusions: Use of radiation therapy as part of HCT is changing over time, with TBI being used with lower doses and less frequently in all diseases except ALL in allogeneic HCT.

Study # HS11-01
Title: Generalizability of Blood and Marrow Transplant Clinical Trials Network 0201 results: prognostic and outcome differences between participants and nonparticipants

Study Chairs: Nandita Khera (Mayo Clinic Arizona)
Stephanie J. Lee (Fred Hutchinson Cancer Research Center)

MS Statistician: Naya He (nhe@mcw.edu)
PhD Statistician: Ruta Brazauskas (ruta@mcw.edu)
Study Status: Manuscript preparation

Abstract: Background: Controversy surrounds the question of whether clinical trial participants have better outcomes than comparable patients who are not treated within the context of a clinical trial. This question has not yet been explored in the field of BMT. A large randomized, multi-center study comparing PB with BM transplantation from URD, conducted by the BMT CTN found no significant survival differences between the two groups, though there was an increased risk of chronic GVHD with PBSC grafts.

Patients and Methods: We compared characteristics and outcomes of study participants (n=494) and nonparticipants (n=1,384) who appeared eligible and received similar treatment without enrolling on the BMT CTN trial at participating centers during the study time-period. Data were derived from the CIBMTR. Outcomes were compared between trial participants and non-participants using Cox proportional hazards regression models.
Results: No significant differences in age and sex distribution, race/ethnicity, disease distribution, HLA matching, comorbidities, and interval from diagnosis to HCT were seen between the participants and non-participants. Non-participants were more likely to have lower performance status, lower-risk disease, have older donors, and to receive myeloablative conditioning and ATG. Non-participants were more likely than participants to receive PBSC grafts (66% vs 50%, p<0.001). OS, TRM, and incidence of acute or chronic GVHD were comparable between the study participants and non-participants though increased relapse was seen in non-participants.

Conclusions: Despite differences in certain baseline characteristics, survival was comparable between study participants and non-participants. The results of the BMT CTN trial may be considered generalizable to the population of trial-eligible patients.

Study # IS13-01

Title: Impact of ethnicity on graft-versus-host disease rates after human leukocyte antigen-matched related bone marrow or peripheral blood stem cell transplantation for leukemia

Study Chairs: Junya Kanda (Saitama Medical School)
Yachiyo Kuwatsuka (Nagoya University Hospital)
Koji Nagafuji (Kurume University School of Medicine)

MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
PhD Statistician: Ruta Brazauskas (ruta@mcw.edu)

Study Status: Manuscript preparation

Abstract: Background: The risk of acute GVHD after HLA-matched sibling BM transplantation is lower in the Japanese than the North American Caucasians (Blood 2005, 105:1408). However, the impact of race on acute GVHD might differ according to graft source (BM vs PBSC) in HLA-matched sibling transplantations. To test the hypothesis, we analyzed data from the CIBMTR and the Japan Society for Hematopoietic Cell Transplantation.

Methods: North American Caucasian and Japanese patients who received their first allogeneic BM or PBSC transplantations from HLA-matched sibling for leukemia in complete remission for acute leukemia and in chronic or accelerated phase for chronic leukemia between 2000 and 2011 were eligible. Patients were 18-59 years, received MAC regimen, and used cyclosporine or tacrolimus-based GVHD prophylaxis. Patients who used in vivo or ex vivo T cell depletion methods were excluded. Effect of race (Caucasian vs Japanese), graft source (BM vs PBSC), and their interaction on transplant outcomes was evaluated in the Cox proportional hazards model adjusting for other significant variables.

Results: Median ages of the Caucasians and Japanese were 45 and 38 years, respectively. BM was used in 13% of the Caucasians, whereas that was used in 53% of the Japanese. Tacrolimus-based GVHD prophylaxis was used in 68% of the Caucasians and 7% of the Japanese. The cumulative incidence of grade 3-4 acute GVHD at 100 days post-transplant was 14% and 8% in the Caucasians and Japanese, respectively. In multivariate analysis, the interaction term between race
and graft source was not significant in any of the models, indicating that the impact of race on outcomes does not differ according to graft source. Therefore, we compared the impact of race and graft source independently. In that model, the risk of grade 3-4 acute GVHD was significantly lower in the Japanese than in the Caucasians (HR 0.74, 95% CI 0.57-0.96), which resulted in the lower risk of NRM in the Japanese (HR 0.69, 95% CI 0.54-0.89). The risk of relapse was also lower in the Japanese than in the Caucasians (HR 0.75, 95% CI 0.59-0.83). Low risk of NRM and relapse resulted in lower overall mortality rates in the Japanese (HR 0.70, 95% CI 0.54-0.90). The risk of grade 3-4 acute GVHD was significantly higher in the PBSC recipients than in the BM recipients (HR 1.63, 95% CI 1.20-2.20), which resulted in higher NRM (HR 1.31, 95% CI 1.04-1.65) in the PBSC recipients.

Conclusions: Irrespective of the type of graft sources, the risk of severe acute GVHD was lower in the Japanese, which resulted in the lower risk of NRM. The risk of severe acute GVHD was higher in the PBSC recipients, which resulted in the higher risk of NRM.

STUDIES IN PROGRESS

Study # HS08-01
Title: Accreditation deficiencies and survival outcomes post hematopoietic cell transplantation
Study Chair: Navneet Majhail (Cleveland Clinic)
MS Statistician: Naya He (nhe@mcw.edu)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Analysis in progress

Study # IS10-01
Title: Outcomes of hematopoietic cell transplantation for acute lymphoblastic leukemia: an international comparative analysis
Study Chairs: William Wood (University of North Carolina)
Navneet Majhail (Cleveland Clinic)
MS Statistician: Zhen-Huan Hu (zhu@mcw.edu)
Philip Zhang (pzhang@mcw.edu)
PhD Statistician: Ruta Brazauskas (ruta@mcw.edu)
Study Status: Data file preparation

Study # HS12-02
Title: Rates of transplantation in urban versus rural patients: are rural patients less likely to receive an allogeneic transplant?
Study Chairs: Kristjan Paulson (CancerCare Manitoba / University of Manitoba)
Matthew Seftel (Princess Margaret Cancer Centre)
David Szwajcer (CancerCare Manitoba / University of Manitoba)
MS Statistician: Kristjan Paulson (kpmulson@cancercare.mb.ca)
PhD Statistician: TBD
Study Status: Analysis in progress

Study # HS13-01
Title: The effect of pre-transplant depression on outcomes of hematopoietic cell transplantation for hematologic malignancies
Study Chairs: Areej El-Jawahri (Massachusetts General Hospital)
Yi-Bin Chen (Massachusetts General Hospital)
MS Statistician: Naya He (nhe@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # HS13-02
Title: Investigating inpatient health care utilization of matched sibling donor hematopoietic cell transplantation for children with sickle cell disease
Study Chairs: Staci Arnold (Columbia University Medical Center)
Prakash Satwani (Columbia University Medical Center)
MS Statistician: Naya He (nhe@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # HS13-03
Title: The impact of socioeconomic status on gene expression in leukocytes of hematopoietic stem cell transplant recipients
Study Chair: Jennifer M. Knight (Medical College of Wisconsin)
MS Statistician: Jennifer M. Knight (jmknight@mcw.edu)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Analysis in progress

Study # HI14-01
Title: Investigating clinical outcomes and inpatient health care resource utilization of hematopoietic cell transplantation for children with acute leukemia
Study Chairs: Staci Arnold (Columbia University Medical Center)
Richard Aplenc (Children's Hospital of Philadelphia)
Michael Pulsipher (Primary Children's Hospital)
Prakash Satwani (Columbia University Medical Center)
MS Statistician: Naya He (nhe@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation
8.8 IMMUNOBIOLOGY WORKING COMMITTEE

Co-Chair: Carlheinz Müller, MD, PhD, Zentrales Knochenmarkspender Register für die Bundesrepublik, Germany
Email: carlheinz.mueller@zkrd.de

Co-Chair: Michael Verneris, MD, University of Minnesota Medical Center, Fairview
Email: verneris@umn.edu

Co-Chair: Katharina Fleischhauer, MD, Universitätsklinikum Essen KMT
Email: katharina.fleischhauer@uk-essen.de

Scientific Director: Stephanie Lee, MD, MPH, CIBMTR, Fred Hutchinson Cancer Research Center
Email: sjlee@fredhutch.org

Scientific Director: Steve Spellman, MBS, CIBMTR Minneapolis
Email: sspellma@nmdp.org

PhD Statistician: Tao Wang, PhD, CIBMTR Milwaukee
Email: taowang@mcw.edu

MS Statistician: Mike Haagenson, BS, MS, CIBMTR Minneapolis
Email: mhaagens@nmdp.org

RECENTLY COMPLETED STUDIES

Study # R02-40 / R03-63d


Abstract: KIRs interact with HLA class I ligands to regulate NK cell development and function. These interactions affect the outcome of URD HCT. We have shown previously that donors with KIR B vs KIR A haplotypes improve the clinical outcome for patients with AML by reducing the incidence of leukemic relapse and improving LFS. Both centromeric and telomeric KIR B genes contribute to the effect, but the centromeric genes are dominant. They include the genes encoding inhibitory KIR that are specific for the C1 and C2 epitopes of HLA-C. We used an expanded cohort of 1,532 T cell replete transplants to examine the interaction between donor KIR B genes and recipient Class I HLA KIR ligands. The relapse protection associated with donor KIR B is enhanced in recipients who have one or two C1-bearing HLA-C allotypes, compared to C2 homozygous recipients, with no effect based on donor HLA. The protective interaction between donors with ≥2 vs 0-1 KIR B-motifs and recipient C1 was specific to transplants with class I mismatch at HLA-C [RR of LFS 0.57 (0.40-0.79); P=0.001] irrespective of the KIR ligand mismatch status of the transplant. The survival advantage and relapse protection in C1/x recipients compared to C2/C2 recipients was similar irrespective of the particular donor KIR B genes. Understanding the
interactions between donor KIR and recipient HLA class I can be used to inform donor selection to improve outcome of URD HCT for AML.

Study # R04-74d


Study # IB05-03b


Abstract: We investigated the influence of IL-7 receptor α-chain (IL-7Rα) gene haplotypes in donors on the outcome of HCT. Unlike the association between single donor SNPs and HCT outcome found previously, only trends towards association were found here, due to ‘dilution’ of SNPs into haplotypes.

Study # IB06-05


Abstract: Life-threatening GVHD limits the use of HLA-C-MMUD in transplantation. Clinicians lack criteria for donor selection when HLA-C-MMUD are a patient’s only option for cure. We examined the role for HLA-C expression levels to identify permissible HLA-C mismatches. The median fluorescence intensity, a proxy of HLA-C expression, was assigned to each HLA-C allotype in 1,975 patients and their HLA-C-MMUD. The association of outcome with the level of expression of patients’ and donors’ HLA-C allotypes was evaluated in multivariable models. Increasing expression level of the patient’s mismatched HLA-C allotype was associated with increased risks of grades III to IV acute GVHD, NRM, and mortality. Increasing expression level among HLA-C mismatches with residue 116 or residue 77/80 mismatching was associated with increased NRM. The immunogenicity of HLA-C mismatches in unrelated donor
transplantation is influenced by the expression level of the patient's mismatched HLA-C allotype. HLA-C expression levels provide new information on mismatches that should be avoided and extend understanding of HLA-C-mediated immune responses in human disease.

**Study # IB09-02**


**Abstract:** HLA-DP antigens are beta-alpha heterodimers encoded by polymorphic HLA-DPB1 and -DPA1 alleles, respectively, in strong linkage disequilibrium with each other. Non-permissive URD-recipient HLA-DPB1 mismatches across three different TCE groups are associated with increased mortality after HCT, but the role of HLA-DPA1 is unclear. We studied 1,281 onco-hematologic patients after 10/10 HLA-matched URD-HCT facilitated by the NMDP. Non-permissive mismatches defined solely by HLA-DPB1 TCE groups were associated with significantly higher risks of TRM compared to permissive mismatches (HR 1.30, CI 1.06-1.53, p=0.009) or allele matches. Moreover, non-permissive HLA-DPB1 TCE group mismatches in the GVH direction significantly decreased the risk of relapse compared to permissive mismatches (HR 0.55, CI 0.37-0.80, p=0.002) or allele matches. Splitting each group into HLA-DPA1*02:01 positive or negative, in frequent linkage disequilibrium with HLA-DPB1 alleles from two of the three TCE groups, or into HLA-DPA1 matched or mismatched, did not significantly alter the observed risk associations. Our findings suggest that the effects of clinically non-permissive HLA-DPB1 TCE group mismatches are independent of HLA-DPA1 and that selection of donors with non-permissive DPB1 TCE mismatches in GVH direction might provide some protection from disease recurrence.

**Study # IB10-03**


**Abstract:** To assess the impact of the genetic variation in toll-like receptors (TLR) on outcome after MAC alloHCT, we have investigated 29 SNPs across 10 TLRs in 816 patients and donors. Only donor genotype of TLR8 rs3764879, which is located on the X chromosome, was significantly associated with outcome at the Bonferroni corrected level P≤0.001. Male hemizygosity and female homozygosity
for the minor allele were significantly associated with DFS [HR 1.47 (95% CI 1.16-1.85), P=0.001]. Further analysis stratified by donor sex due to confounding by sex, was suggestive for associations with OS [male donor: HR 1.41 (95% CI 1.09-1.83), P=0.010; female donor: HR 2.78 (95% CI 1.43-5.41), P=0.003], DFS [male donor: HR 1.45 (95% CI 1.12-1.87), P=0.005; female donor: HR 2.34 (95% CI 1.18-4.65), P=0.015] and TRM [male donor: HR 1.49 (95% CI 1.09-2.04), P=0.012; female donor: HR 3.12 (95% CI 1.44-6.74), P=0.004]. In conclusion, our findings suggest that the minor allele of TLR8 rs3764879 of the donor is associated with outcome after MAC alloHCT.

Study # IB11-02


Abstract: Cytotoxic T-lymphocyte antigen-4 (CTLA-4) plays an essential role in T cell homeostasis and immune responses. AG and GG genotypes of donor SNP rs4553808 in patients after URD HCT have been shown to be an independent predictor of inferior RFS and OS compared to the AA genotype. Adults with AML and advanced MDS undergoing a first 8/8 or 7/8 HLA matched URD HCT were included. Primary outcomes were impact of SNP rs4553808 on RFS, OS, NRM, and the cumulative incidence of acute GVHD and chronic GVHD. Multivariable analysis after adjusting for significant donor and recipient characteristics showed no significant association between SNP rs4553808 and OS (p=0.07); RFS (p=0.41); NRM (p=0.25); and incidence of acute GVHDII (p=0.21), acute GVHDIII (p=0.007), and chronic GVHD (p=0.13). Our results indicate that CTLA-4 SNPs do not have significant impact on HCT outcomes.

Study # IB11-05


Abstract: MDS are stem cell disorders that can progress to AML. While HCT can be curative, additional therapies are needed for a disease that disproportionally affects the elderly. We tested the ability of a CD16xCD33 BiKE to induce NK cell function from 67 MDS patients. Compared to age-matched normal controls, CD7+ lymphocytes, NK cells, and CD16 expression were markedly decreased in MDS patients. Despite this, reverse-antibody dependent cell-mediated
cytotoxicity assays showed potent degranulation and cytokine production when resting MDS-NK cells were triggered with an agonistic CD16 mAb. Blood and marrow MDS-NK cells treated with BiKE significantly enhanced degranulation, TNF-α and IFN-γ production against HL-60 and endogenous CD33+ MDS targets. MDS patients had a significantly increased proportion of immunosuppressive CD33+ myeloid derived suppressor cells (MDSC) that negatively correlated with MDS lymphocyte populations and CD16 loss on NK cells. Treatment with the CD16xCD33 BiKE successfully reversed MDSC immunosuppression of NK cells and induced MDSC target cell lysis. Lastly, the BiKE induced optimal MDS-NK cell function irrespective of disease stage. Our data suggest that the CD16xCD33 BiKE functions against both CD33+ MDS and MDSC targets and may be therapeutically beneficial for MDS patients.

Study # IB11-06


Abstract: No allogeneic CTL responses are detected in vitro for the isolated mismatch in the HLA alleles C*03:03 and C*03:04. HCT with URD showed no association between the HLA-C allele mismatches (CAMM) with adverse outcomes; whereas antigen mismatches at this and other HLA loci have deleterious effects. It was hypothesized that the absence of effect of the CAMM resulted from the predominance of the mismatch C*03:03/C*03:04. Cohorts of 4,779 and 1,854 patients with hematologic malignancies receiving URD HCT matched in 8/8 and 7/8 HLA alleles were examined. Transplants mismatched in HLA-C antigens or mismatched in HLA-A, B, or DRB1 presented significant differences (p<0.0001) in mortality (HR 1.37, 1.30), DFS (HR 1.33, 1.27), TRM (HR 1.54, 1.54), and grade III-IV acute GVHD (HR 1.49, 1.77) compared to the 8/8 group; transplants mismatched in other CAMM had similar outcomes with HR ranging 1.34-172 for these endpoints. In contrast, the C*03:03/C*03:04 mismatched and the 8/8 matched groups had virtually identical outcomes with HR ranging 0.96-1.05. The previous finding that CAMM do not associate with adverse outcomes is explained by the predominance (69%) of the permissible mismatch C*03:03/C*03:04 in this group; this mismatch is better tolerated than other HLA mismatches.

Study # IB12-02


Abstract:
We examined current outcomes of URD alloHCT to determine the clinical implications of donor-recipient HLA matching. Adult and pediatric patients who had undergone first MAC URD bone marrow or peripheral blood HCT for AML, ALL, CML, or MDS between 1999 and 2011 were included. All had high resolution typing for HLA-A, -B, -C, -DRB1. Of the total (n=8,003), cases were 8/8 (n=5,449), 7/8 (n=2,071), or 6/8 (n=483) matched. HLA mismatch (6-7/8) conferred significantly increased risk for grade II-IV and III-IV acute GVHD, chronic GVHD, TRM, and overall mortality compared to HLA matched cases (8/8). Type (allele / antigen) and locus (HLA-A, -B, -C, -DRB1) of mismatch were not associated with overall mortality. Among 8/8 matched cases, -DPB1 and -DQB1 mismatch resulted in increased acute GVHD, and -DPB1 mismatch had decreased relapse. Non-permissive -DPB1 allele mismatch was associated with higher TRM compared to permissive -DPB1 mismatch or -DPB1 match, and increased overall mortality compared to permissive -DPB1 mismatch in 8/8 (and 10/10) matched cases. Full matching at HLA-A, -B, -C, -DRB1 is required for optimal URD HCT survival and avoidance of non-permissive -DPB1 mismatches in otherwise HLA-matched pairs is indicated.

PRELIMINARY RESULTS

Study # IB07-03

Title: Analysis of killer immunoglobulin-like receptor ligands in reduced-intensity conditioning allogeneic hematopoietic cell transplantation

Study Chair: Ronald Sobecks (Cleveland Clinic)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Submitted

Abstract: NK cells are regulated by KIR interactions with HLA class I ligands. Several models of NK reactivity have been associated with improved outcomes following MAC alloHCT. We hypothesized that donor-recipient KIR-HLA interactions may impact RIC URD HCT outcomes. In 909 patients undergoing RIC-URD HCT for AML (n=612) and MDS (n=297), patients lacking HLA-Bw4 ligand for donor KIR3DL1 experienced lower relapse at 1 year [28% (95% CI 22-33%) vs 37% (95% CI 33-41%), p=0.005] and 5 years [32% (95% CI 27-38%) vs 42% (95% CI 39-46%), p=0.003] compared to Bw4+ patients. Patients lacking >1 KIR ligands experienced higher grade 3-4 acute GVHD (HR 1.5, 95% CI 1.11-1.91, p=0.007) compared to those with all ligands present. Absence of HLA-C2 for donor KIR2DL1 was associated with higher grade II-IV (HR 1.3, p=0.005) and III-IV acute GVHD (HR 1.5, p=0.002) compared to HLA-C2+ patients. AML patients with KIR2DS1+ HLA-C2 homozygous donors had greater TRM compared to others (HR 2.4, 95% CI
1.4-4.2, p=0.002). KIR-HLA combinations in RIC-URD HCT recapitulate some KIR-HLA effects observed in myeloablative HCT and may have implications for donor selection in RIC-URD HCT for AML/MDS.

Study # IB08-06

Title: Analysis of killer immunoglobulin-like receptor ligands in umbilical cord blood transplantation

Study Chairs: Vanderson Rocha (Churchill Hospital)
Ronald Sobecks (Cleveland Clinic)
Mary Eapen (Froedtert & Medical College of Wisconsin)

MS Statistician: Vincent He (vhe@mcw.edu)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Manuscript preparation

Abstract: The effect of KIR ligand incompatibility on outcomes after unrelated cord blood transplantation (UCBT) has been controversial. Eurocord found that KIR ligand mismatching was associated with decreased relapse incidence (RI) and improved OS and LFS for patients with ALL and for those with AML. Recently, the Japanese registry found no association between KIR ligand matching and LFS or OS in 643 UCBT recipients with acute leukemia. However, both studies have analysed the KIR ligand matching effect using low resolution typing of HLA-A,-B,-C and HLA-DRB1 high resolution. With the aim to clarify the KIR effect on outcomes (mainly RI and OS) in a larger series of single-UCBT recipients in the era of HLA-allele typing, we have analysed 1,098 patients with AML and ALL reported to Eurocord and CIBMTR. All patients received single UCBT and myeloablative conditioning regimen. HLA matching was defined using high resolution typing or imputation for HLA-A,-B,-C and DRB1. Patients and donors were categorized by their KIR-ligand expression for HLA C group 1 or 2 and Bw4 as KIR ligand matched or mismatched. Patients included in the earlier Eurocord analysis were excluded. Univariate and multivariate models were built to analyse the effect of KIR ligand matching on outcomes. Results: None of the 8/8 HLA-matched transplants were KIR ligand mismatched; therefore, they were excluded. Since HLA-match and KIR ligand mismatch were confounded, we conducted 2 separate analyses: a) 6-7/8 HLA-matched (n=501) and b) 3-5/8 HLA-matched transplants (n=586). In the group of 6-7/8 HLA matched, 291 recipients (58%) were KIR ligand-matched and 210 (42%) were mismatched. There were no statistically significant differences between these two groups for gender, age, CMV serostatus, type and remission disease status, cell dose, conditioning regimen, in vivo T cell depletion, transplant period, and follow-up (around 40 months). In the group of 3-5/8 HLA matched, 176 recipients (30%) were KIR ligand-matched and 410 (70%) were mismatched. In this HLA group (i.e 3-5/8), KIR ligand-matched patients were younger (<16 years, p=0.02) compared to the KIR ligand-mismatched patients. Other characteristics were similar between the KIR ligand matched and mismatched groups. In multivariate models for outcomes in both HLA groups (6-7/8 HLA and 3-5/8 HLA), KIR-match status was not associated with NRM, RI, LFS and OS. However, KIR ligand-mismatch was
associated with lower risks of grade 2-4 acute GVHD for transplants that were 3-5/8, HLA-matched (HR 0.63, p=0.001) but not for transplants that were 6-7/8 HLA-matched. KIR ligand-matching was not associated with chronic GVHD. The effect of KIR ligand-mismatching in the GVH direction, HVG direction, and bi-directional were also examined, and findings were consistent with the main analysis. Lower acute GVHD rates in the worst HLA-match group (3-5/8) with KIR ligand mismatch did not translate into a survival advantage when compared to similarly HLA-matched KIR ligand matched group. Disease-specific analysis were undertaken to further explore the effects of KIR ligand matching for ALL and AML separately. For patients with ALL, KIR match status was not associated with NRM, RI, LFS or OS in either HLA group. For patients with AML, KIR ligand status was not associated with any transplantation outcome after 6-7/8 HLA-matched transplants. However, KIR ligand mismatching was associated with higher NRM (HR 1.94, p=0.02) and lower OS (HR 1.51, p=0.03) after 3-5/8 HLA-matched transplants. In conclusion, in the setting of 6-7/8 HLA-matched transplants KIR ligand match status was not associated with leukemia recurrence or survival. Disease-specific analysis were undertaken to further explore the effects of KIR ligand matching for ALL and AML separately. For patients with ALL, KIR match status was not associated with NRM, RI, LFS or OS in either HLA group. For patients with AML, KIR ligand status was not associated with any transplantation outcome after 6-7/8 HLA-matched transplants. However, KIR ligand mismatching was associated with higher NRM (HR 1.94, p=0.02) and lower OS (HR 1.51, p=0.03) after 3-5/8 HLA-matched transplants. In conclusion, in the setting of 6-7/8 HLA-matched transplants KIR ligand match status was not associated with leukemia recurrence or survival. Our observation for AML, in the 3-5/8 HLA-matched group with KIR ligand mismatching is contradictory to the earlier Eurocord report. We hypothesize the observed differences may be attributable to better HLA-matching in the current analysis. Taken together, the data does not support selecting units based on KIR ligand match status as categorized in this analysis, when donor-recipient HLA-match considers allele-level HLA typing. It remains to be seen whether assignment of KIR ligand match status by genotyping will offer additional information.

**Study # IB10-01**

**Title:** Donor and recipient telomere length as predictors of outcomes after hematopoietic cell transplantation in patients with acquired severe aplastic anemia

**Study Chairs:** Shahinaz Gadalla (NIH - NCI Clinical Genetics Branch)
Sharon Savage (NIH - NCI Clinical Genetics Branch)

**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)

**PhD Statistician:** Tao Wang (taowang@mcw.edu)

**Study Status:** Submitted

**Abstract:**

Background: Telomeres protect chromosome ends and are markers of cellular aging and replicative capacity. The high cellular replicative need after HCT suggests a role for telomere length in transplant outcome. Methods: Pre-transplant relative leukocyte telomere length (LTL) was measured in 330 SAA patients (235 acquired, 85 Fanconi anemia, and 10 Diamond Blackfan anemia) and their unrelated donors. Patient data were collected by the CIBMTR. The log-rank test and Cox proportional hazard models were used to determine if recipient or donor telomere length was associated with HCT outcomes. Results: Patients were transplanted between 1989 and 2007 with a median follow-up of 6 years (range 5 months - 21 years). Longer donor LTL was associated with improved survival in SAA patients (5-year OS 56% vs 40%, in the long vs short,
respectively; \( p=0.0009 \). The association remained statistically significant after adjusting for donor age and factors influencing survival in SAA (HR 0.61, 95% CI 0.44-0.85, \( p=0.006 \)). Similar results were noted in analyses stratified on SAA subtype, recipient age, and conditioning regimen. There was no association between donor LTL and engraftment or GVHD. Pre-transplant LTL in the recipients was not associated with post-transplant outcomes. Conclusions: Our study provides evidence of a survival benefit associated with longer donor LTL in patients transplanted for SAA, independent of donor age. Including donor LTL in donor selection may improve recipient outcomes in HCT.

**Study # IB11-07**

**Title:** Effect of rituximab and ABO mismatch

**Study Chairs:**
- David Miklos (Stanford Hospital & Clinics)
- Aaron Logan (University of California, San Francisco)

**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)

**PhD Statistician:** Brent Logan (blogan@mcw.edu)

**Study Status:** Submitted

**Abstract:** We evaluated ABO associated outcomes in 1,737 patients who underwent alloHCT at Stanford University between January 1986 and July 2011. Grafts were 61% ABO matched, 18% major mismatched (MM), 17% minor MM, and 4% bidirectional MM. Median follow-up was six years. In multivariate analysis, OS was inferior in minor MM HCT (median 2.1 vs 6.3 years, HR 1.56, 95% CI 1.19-2.05, \( p=0.001 \)) in comparison with ABO matched grafts. ABO minor MM was associated with an increase in early NRM (18% vs 13%, HR 1.48, 95% CI 1.06-2.06, \( p=0.02 \)). In an independent CIBMTR analysis of 435 lymphoma patients receiving mobilized peripheral blood grafts, impairment of OS (HR 1.55, 95% CI 1.07-2.25, \( p=0.021 \)) and increased NRM (HR 1.72, 95% CI 1.11-2.68, \( P=0.03 \)) was observed in recipients of ABO minor MM grafts. A second independent analysis of a CIBMTR dataset including 5,179 patients with AML and MDS identified a non-significant trend toward decreased OS in recipients of ABO minor MM grafts and also found ABO major MM to be significantly associated with decreased OS (HR 1.19, 95% CI 1.08-1.31, \( P<0.001 \)) and increased NRM (HR 1.23, 95% CI 1.08-1.4, \( P=0.002 \)). ABO minor and major MM are risk factors for worse transplant outcomes, although the associated hazards may not be uniform across different transplant populations. Further study is warranted to determine which patient populations are at greatest risk, and whether this risk can be modified by graft manipulation or other peri-transplant treatments.

**Study # IB12-01**

**Title:** Human leukocyte antigen in reduced-intensity conditioning allogeneic hematopoietic cell transplantation outcomes

**Study Chair:** John Koreth (Dana Farber Cancer Institute)

**MS Statistician:** Hailin Wang (hwang@mcw.edu)

**PhD Statistician:** Kwang Woo Ahn (kwoooahn@mcw.edu)

**Study Status:** Manuscript preparation
Abstract: In MAC URD alloHCT, a 1-locus HLA-mismatch (-A, -B, -C, -DRB1) is associated with lower survival compared to fully matched pairs. However, data in RIC and NMA conditioning HCT are limited. We analyzed adult AML / ALL / CML / MDS recipients of first 8/8 HLA-matched or 1-locus mismatched unrelated donor (MUD, MMUD) RIC / NMA HCT performed in the period 1999-2011 and registered in the CIBMTR. HLA-A, -B, -C and -DRB1 loci were typed in all pairs at high resolution; -DQB1 and -DPB1 loci could not be evaluated in all pairs. Transplants involving ex-vivo T cell depletion, CD34+ selection, or post-transplant cyclophosphamide were excluded. OS was the primary outcome. Secondary outcomes included NRM, relapse, DFS, and acute and chronic GVHD. Individual locus mismatch was also assessed. Apart from HLA matching, variables related to patient (age, race, sex, KPS, diagnosis, disease-risk), donor (age, parity), both (sex match / ABO match / CMV match) treatment [conditioning intensity, TBI use, in-vivo T cell depletion (ATG), graft source (PB, BM) and GVHD prophylaxis (CyA-, Tac-based)] were considered. 2,588 RIC / NMA HCT (8/8 MUD: 2025; 7/8 MMUD: 563) from 144 centers and 12 countries were analyzed. Median follow up in 8/8 MUD and 7/8 MMUD was 38 and 48 months respectively. Diagnoses were AML (65%), ALL (8%), CML (7%), MDS (20%). Conditioning intensity was RIC (79%), NMA (21%). 58% received in-vivo T cell depletion. Graft source was PBSC (85%), BM (15%). GVHD prophylaxis was Tac-based (70%), CyA-based (27%). Mismatches involved HLA-A (188), -B (81), -C (219), and -DRB1 (75); with -DPB1 and -DQB1 typing available in 1,382 and 2,502 cases, respectively. Compared to 8/8 MUD, 7/8 MMUD recipients were more likely to be younger and ethnic minorities and to have older and parous donors. In univariate analyses, DQB1- and -DPB1 mismatch was not associated with worse OS, DFS, or NRM and was not further evaluated. There was a trend toward more grade II-IV acute GVHD in -DPB1 double (p=0.02) but not single mismatches. In multivariate models, 7/8 MMUD RIC HCT had worse grade II-IV and III-IV acute GVHD, NRM, DFS, and OS but not relapse or chronic GVHD. No significant interactions were identified between degree of HLA matching and other clinical variables. Adjusted 1- and 3-year NRM for 8/8 MUD vs 7/8 MMUD was 20.4% vs 28.9% (p<0.0001) and 29.2% vs 38.1% (p<0.0007), respectively. Adjusted 1- and 3-year OS was 54.7% vs 48.8% (p=0.01) and 37.4% vs 30.9% (p=0.005), respectively. There was no difference between allele and antigen mismatches. HLA-A, -B, -C, and -DRB1 locus mismatches were each associated with one or more impaired outcomes (acute GVHD, NRM, DFS, and/or OS). Compared to 8/8 MUD, both 7/8 allele and antigen MMUD RIC HCT have greater treatment toxicity and worse survival, of a magnitude similar to that seen in myeloablative transplantation. An isolated mismatch at HLA-A, -B, -C, or -DRB1 was associated with one or more adverse outcomes. In unrelated donor RIC / NMA HCT, matching for all alleles of HLA-A, -B, -C and -DRB1 loci results in superior outcomes.
Study # IB12-04b

Title: Effect of HLA-C allele matching in the context of recipient HLA-C encoded KIR ligand group (C1 or C2) on outcomes of unrelated hematopoietic stem cell transplantation

Study Chairs: Johannes Fischer (Universitätsklinikum Duesseldorf Klinik für Kinder)
Markus Uhrberg (Universitätsklinikum Duesseldorf Klinik für Kinder)

MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Tao Wang (taowang@mcw.edu)

Study Status: Manuscript preparation

Abstract:
Introduction: HLA-C-encoded KIR ligands (C1/C2) have been identified as important factors for the outcome of unrelated alloHCT. In a previous retrospective study, CML recipients bearing at least one C2 ligand showed worse survival when compared to C1C1 recipients (HR 5.9, p<0.01), especially when PBPC were used or in advanced disease stages. These initial findings were confirmed in a second cohort in advanced AML / CML, (but not in MDS or ALL / NHL) receiving PBPC. Notably, HLA-C allele matching contributed differentially to the transplantation outcome: it was beneficial in C1 patients but was detrimental in C2 recipients (increased TRM, HR 3.5, p<0.012; increased relapse, HR 2.7, p=0.06). We hypothesized that C1 patients have a high frequency of immuno-competent NK cells (icNK) enabling eradication of residual disease due to the genetically hard-wired sequential acquisition of KIR receptors during early reconstitution phase post HCT, with C1-specific NK cells emerging first. Alloreactive T cells - resulting from HLA-C mismatch - might thus not have an additional beneficial effect in C1 patients and might even be detrimental (e.g. increased GVHD), but may serve an important function in relapse control in C2 patients. The lack of disease control in HLA-C-matched C2 patients would thus be explained by a combination of insufficient numbers of icNK cells in the early phase and the lack of alloreactive T cells later post HCT. Consequently, this group exhibited poorest clinical outcome of all four groups defined by recipients KIR ligands and HLA-C allele matching in the investigated cohorts.

Patients and Methods: The aim of the present retrospective study was to determine the influence of HLA-C allele matching on the background of HLA-C encoded KIR ligand status in a large patient cohort (n=7,327, provided by the CIBMTR). Statistical analysis was performed by the CIBMTR. Patients received unrelated allografts between 1988 and 2009, with the majority of patients after 2000 (70%). 30% of the recipients were younger than 30 years, 67% younger than 40 years. 70% of patients had early, 5% intermediate, and 25% advanced disease (AML 40%, ALL 21%, CML 22%, MDS 17%). 56% received bone marrow, 44% PBPC. 80% received MAC. Endpoints were OS, acute GVHD II-IV and III-IV, extensive chronic GVHD, relapse, DFS, and NRM. Due to multiple comparisons and multiple endpoints, p<0.01 was considered as significant. All models were adjusted for significant clinical covariates. Stratification was used in cases of non-proportional hazards. Patient-donor pairs were classified according to the recipient HLA-C KIR ligand expression [C1C1, or C2 (C1C2 or C2C2)] and the degree of the HLA-C allele match.
Results: No difference in clinical outcome was found between C1C1 vs C2 patients receiving 7/8-loci matched donors, whether HLA-C was matched (all \( p>0.33 \)) or mismatched (all \( p>0.36 \)). There were too few events in a subset limited to AML and CML with advanced disease receiving PBSC to perform a subset analysis that recapitulated the original cohort. Conclusion: Our results did not confirm the previous observation that recipient C2 KIR ligand status is detrimental when HLA-C is matched.

Study # IB12-05
Title: Plasma YKL-40 and CHI3L1 genotype to predict mortality after allogeneic hematopoietic cell transplantation
Study Chairs: Brian Kornblit (University Hospital, Rigshospitalet)
            Peter Garred (University Hospital, Rigshospitalet)
            Lars Vindelov (University Hospital, Rigshospitalet)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Manuscript preparation
Abstract: Although alloHCT is a treatment option for a variety of malignant hematologic diseases, complications such as GVHD, infections, and relapse are still major causes of morbidity and mortality. Prognostic scores, such as the DRI and the HCT-CI, have proven useful in predicting relapse and TRM. However, to appropriately balance the likelihood of disease control against the risk of debilitating complications, still more accurate pretransplant markers are necessary to predict outcome. YKL-40 (chitinase-3-like-1 (CHI3L1)) is mainly secreted by cancer cells, macrophage, and neutrophils. YKL-40 regulates vascular endothelial growth factor and has a role in angiogenesis and inflammation, cell proliferation and differentiation, and remodeling of the extracellular matrix. High plasma YKL-40 levels have been associated with poor prognosis in patients with different types of cancers and inflammatory diseases. A previous study in HCT found that YKL-40 >95% age-adjusted level in recipients was associated with relapse and lower DFS and OS. High YKL-40 levels in donors were associated with more grade II-IV acute GVHD. We investigated the prognostic value of pre-transplant plasma YKL-40 in a validation cohort of 784 recipients and donors undergoing alloHCT for AML (n=626) or MDS (n=158) with 8/8 matched URD after MAC (n=566) or RIC (n=218). Transplantations were facilitated through the NMDP, and data collection and analysis were performed under the auspices of the CIBMTR. Samples were provided by the NMDP / CIBMTR and obtained pre-transplant from recipients and prior to mobilization from donors. \( P<0.05 \) was considered significant for validation of previous observations. Mean recipient pre-transplant YKL-40 plasma concentrations were elevated in patients with HCT-CI scores \( \geq 5 \) [HCT-CI 0: \( n=266, 106 \) (range 20-1,446) ng/ml; HCT-CI 1-2: \( n=244, 105 \) (range 20-1,176) ng/ml; HCT-CI 3-4: \( n=206, 106 \) (range 20-636) ng/ml; HCT-CI \( \geq 5 \): \( n=68, 171 \) (range 20-4,644) ng/ml; \( p<0.04 \)]. There was no difference (\( p=0.91 \)) in YKL-40 concentrations between recipients with AML [111 (range 20-4644) ng/ml] and MDS [113 (range 20-714) ng/ml]. There was
No association between recipient YKL-40 concentrations and cytogenetics or AML disease status (CR1 vs beyond first remission). In addition, MDS YKL-40 concentrations did not significantly increase with successively worse cytogenetics (p=0.67), IPSS (p=0.72), or KPS (p=0.86). Recipient YKL-40 levels above the age-adjusted 95% percentile were not associated with any outcomes (p=0.198). Donor YKL-40 levels >95% was associated with acute GVHD II-IV (HR 1.39, 95% CI 1.00-1.92, p=0.0466) as observed in the previous study. There was no association between donor YKL-40 and other outcomes. When age-adjusted YKL-40 percentile was used as a continuous variable, recipient and donor pre-transplant elevated YKL-40 were not associated with any outcomes (p>0.088). Analyses were also conducted to investigate the impact of extremely low and high YKL-40 level expression, and no associations were observed. In contrast to the prior study, no association between recipient pre-transplant YKL-40 concentrations and clinical outcome were observed. However, in agreement with the previous study, donor YKL-40 concentrations were associated with increased acute GVHD, suggesting that donors with a higher degree of inflammation prior to mobilization could increase risk of post transplant complications. However, this did not translate into increased risk of TRM. Although it is not known whether the associations between YKL-40 and outcome are causal or just bystander effects, our observations suggest that an inflammatory biomarker, such as YKL-40, that potentially defines a higher-risk donor population could be a valuable tool complementing clinical risk scores in HCT. In conclusion, age adjusted YKL-40 levels in the donor, but not recipient, were a prognostic indicator for acute GVHD risk in this population.

**Study # IB13-03**

**Title:** Significance of human leukocyte antigen class I and II allelic mismatching within and outside of human leukocyte antigen supertypes among recipients of single-allele mismatched unrelated allogeneic hematopoietic cell transplants: a Center for Internationala

**Study Chairs:** Aleksandr Lazaryan (University of Minnesota Medical Center)  
Daniel Weisdorf (University of Minnesota Medical Center)  
Mukta Arora (University of Minnesota Medical Center)

**MS Statistician:** Hailin Wang (hwang@mcw.edu)  
**PhD Statistician:** Tao Wang (taowang@mcw.edu)

**Study Status:** Manuscript preparation

**Abstract:** The diversity of the HLA class I and II alleles can be simplified by consolidating them into fewer supertype clusters based on functional or predicted structural similarities in epitope binding grooves of HLA molecules. HLA class I and II supertypes have been increasingly studied in association with immune susceptibility to infection and cancer with potential implications for vaccine development. However, the significance of individual allele mismatching within and outside of HLA class I or II supertypes remains unknown in the context of HCT. We, therefore, studied the impact of HLA supertype disparities on clinical outcomes of 1,934 patients with AML (45%), ALL (31%), CML (14%), or MDS
Who underwent 7/8 URD MAC HCT from 1999 to 2011 and were registered with CIBMTR. Median age at transplant was 35 years (range 1-70); 53% were males; 81% Caucasian; 56% received peripheral blood grafts; 50% were ABO-mismatched; 36% had in-vivo T-cell depletion; 62% received tacrolimus- and 36% cyclosporine A-based GVHD prophylaxis; 72% male or non-parous female donors; median follow up of survivors was 54 months (3-149). Supertype assignment methods of (1) revised main HLA anchor specificities (Sydney, 2008) and (2) bioinformatics (Doytchinova, 2004-05) were used to categorize single mismatched alleles into 6 HLA-A (A01, A01A03, A01A24, A02, A03, A24), 6 HLA-B (B07, B08, B27, B44, B58, B62), 2 HLA-C (C1, C2), and 5 DRB1 (DR1, DR3, DR4, DR5, DR9) supertypes. OS, DFS, relapse, TRM, acute GVHD, and chronic GVHD were compared across matched vs mismatched HLA-A (265 vs 429), -B (230 vs 92), -C (365 vs 349), and -DRB1 (153 vs 51) supertypes. We used predetermined a=0.01 for statistical significance as multiple exploratory analyses were conducted by Kaplan-Meier, Gray, and Cox proportional hazard methods. In the multivariable analysis, supertype B-mismatch was associated with increased risk of grade II-IV acute GVHD (HR 1.78, 95% CI 1.23-2.59, p=0.0025); however, no difference was found for grade III-IV acute GVHD or other clinical outcomes compared to supertype B-matches. Supertype DRB1-mismatch was associated with shorter neutrophil recovery (HR 0.51, 95% CI 0.36-0.71, p=0.0001), yet a trend toward inferior OS (HR 1.58, 95% CI 1.04-2.38, p=0.037) and higher TRM (HR 1.64, 95% CI 0.99-2.74, p=0.0565) compared to DRB1 matches within supertypes. There was no increased risk of GVHD with DRB1 supertype mismatch. No associations were observed between HLA-A and -C supertypes or aggregate supertype-matched vs -mismatched groups for any outcomes. Our analysis demonstrated differential influence of HLA supertype-based allele matching within -B and -DRB1 loci on clinical outcomes after myeloablative 7/8 URD HCT.

Study # IB13-05

Title: The impact of major histocompatibility complex class I chain-related gene A donor-recipient mismatches and MICA-129 polymorphism on unrelated donor hematopoietic cell transplantation for hematological malignancies

Study Chair: Medhat Askar (Cleveland Clinic)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Manuscript preparation
Abstract: Background: Previous reports from single centers suggested that MICA polymorphism and donor / recipient MICA mismatches are associated with chronic GVHD and acute GVHD (respectively) after URD HCT. MICA is both a transplantation antigen and a ligand recognized by the activating receptor NKG2D expressed by NK, NKT, CD8+ and TCRγδ+ T cells. Allelic variants of MICA due to a single amino acid substitution at position 129 result in significant differences in NKG2D binding. MICA alleles with a methionine (M) or valine (V)
have been classified as having strong or weak binding affinity for NKG2D, respectively.

Methods: We studied the association of MICA polymorphism (MICA-129) and MICA mismatches with URD HCT with 10/10 HLA match (n=552 pairs) or 9/10 (HLA-B mismatch only, n=161 pairs), reported to the CIBMTR between 2000 and 2011. Included were adult patients who had undergone a first URD BM or PBSC HCT for ALL, AML, or MDS. Pretransplant samples were obtained from the NMDP Research Repository. MICA typing was performed using rSSOP (One Lambda Thermo Fisher, Canoga Park, CA). Study outcomes included OS, DFS, TRM, relapse, acute GVHD, chronic GVHD, and engraftment. Variables considered in multivariate analyses included patient, disease, and transplant characteristics. A p value < 0.01 for the main effect was considered significant.

Results: Of the recipients, 101 were MICA-129 MM (14%), 363 MV (52%), and 239 VV (34%). Of the donors, 106 were MICA-129 MM (15%), 375 MV (53%), and 229 VV (32%). 27% of the pairs were MICA mismatched, 9 pairs had double (one 10/10 and eight 9/10), and 182 had single mismatches (83 10/10 and 99 9/10). At 0.01 significance level, there was no association between any outcome and MICA mismatch or MICA-129 polymorphism, with the exception of an unexpected finding of significantly higher relapse in association with MICA mismatches in 10/10 patients (HR 1.7, 95% CI 1.2-2.4, p=0.003) but not in 9/10 patients. There was a suggestion that MICA mismatches were associated with a higher risk of acute GVHD grades II-IV (HR 1.4, 95% CI 1.1-1.9, p=0.013) but not grades III-IV and with higher risk of chronic GVHD (HR 1.8, 95% CI 1.0-3.1, p=0.04). There were no significant interactions between MICA mismatches and HLA matching (9/10 vs 10/10). There was also a suggestion of an association between donor MICA-129 non-VV genotypes and slower platelet engraftment with HR 1.4 (95% CI 1.109-1.985, p=0.02).

Conclusions: In this cohort, neither MICA-129 polymorphism nor MICA mismatches were associated with HCT outcomes at a level that reached the predetermined level of statistical significance. This registry analysis in patients with ALL, AML, and MDS was discordant with prior reports of single center studies of patients with mixed diagnoses.

STUDIES IN PROGRESS

| Study # R04-75s | Immune response gene polymorphisms in unrelated donor hematopoietic cell transplantation. |
|-----------------|_________________________________________________________________________________|
| Study Chair:    | Effie Petersdorf (Fred Hutchinson Cancer Research Center)                           |
| MS Statistician:| Mike Haagenson (mhaagens@nmdp.org)                                                 |
| PhD Statistician:| Ted Gooley (tgooley@fredhutch.org)                                                 |
| Study Status:   | Ongoing                                                                              |
Study # R04-76c

Title: Identification of functional single nucleotide polymorphisms in unrelated hematopoietic cell transplantation (IHWG)

Study Chair: Effie Petersdorf (Fred Hutchinson Cancer Research Center)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Ted Gooley (tgooley@fredhutch.org)
Study Status: Ongoing

Study # IB07-04

Title: Employing advanced bioinformatics methods for predicting peptide specificities of human leukocyte antigen molecules in the characterization of permissible mismatches in hematopoietic cell transfer

Study Chair: Soren Buus (University of Copenhagen)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Ted Gooley (tgooley@fredhutch.org)
Study Status: Ongoing

Study # IB08-08

Title: Genome-wide association in unrelated donor transplant recipients and donors: a pilot study

Study Chair: Rakesh Goyal (Children’s Hospital of Pittsburgh of UPMC)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Analysis in progress

Study # IB09-01

Title: Clinical importance of minor histocompatibility complex haplotypes in umbilical cord blood transplantation

Study Chair: Effie Petersdorf (Fred Hutchinson Cancer Research Center)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Ted Gooley (tgooley@fredhutch.org)
Study Status: Ongoing

Study # IB09-03

Title: Clinical relevance of cytokine / immune response gene polymorphisms in umbilical cord blood transplantation

Study Chair: Effie Petersdorf (Fred Hutchinson Cancer Research Center)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: Ted Gooley (tgooley@fredhutch.org)
Study Status: Ongoing

Study # IB09-04

Title: D/R gene polymorphisms of drug metabolisms and innate immune response post allele matched unrelated donor hematopoietic cell transplantation
Study Chair: Vanderson Rocha (Churchill Hospital)  
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)  
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)  
Study Status: Analysis in progress

Study # IB09-05  
Title: Identification of functional single nucleotide polymorphisms in umbilical cord blood transplantation  
Study Chair: Effie Petersdorf (Fred Hutchinson Cancer Research Center)  
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)  
PhD Statistician: Ted Gooley (tgooley@fredhutch.org)  
Study Status: Ongoing

Study # IB09-07  
Title: Clinical significance of genome-wide variation in unrelated hematopoietic cell transplantation  
Study Chair: Effie Petersdorf (Fred Hutchinson Cancer Research Center)  
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)  
PhD Statistician: Ted Gooley (tgooley@fredhutch.org)  
Study Status: Ongoing

Study # IB10-04  
Title: A validation study of the role of base excision repair pathway as a predictor of outcomes after hematopoietic cell transplantation  
Study Chair: Mukta Arora (University of Minnesota Medical Center)  
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)  
PhD Statistician: Bharat Thyagarajan (tha0003@umn.edu)  
Study Status: Analysis in progress

Study # IB11-01  
Title: Analysis of the noninherited maternal antigen effect on the outcome of unrelated peripheral blood stem cell / bone marrow transplantation  
Study Chair: Gerhard Ehninger (Universitaetsklinikum Dresden)  
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)  
PhD Statistician: Tao Wang (taowang@mcw.edu)  
Study Status: Analysis in progress

Study # IB11-08  
Title: Synergism between minor and major histocompatibility antigens  
Study Chair: Eric Spierings (University Medical Center Utrecht)  
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)  
PhD Statistician: Ted Gooley (tgooley@fredhutch.org)  
Study Status: Ongoing
**Study # IB12-03**

**Title:** Effect of genetic ancestry matching on hematopoietic cell transplantation outcomes

**Study Chair:** Abeer Madbouly (National Marrow Donor Program)

**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)

**PhD Statistician:** TBD

**Study Status:** Sample typing

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**Study # IB12-04a**

**Title:** Determining the effects of human leukocyte antigen-C killer cell immunoglobulin-like receptors ligand expression on outcomes of unrelated hematopoietic cell transplantation

**Study Chair:** Jeffrey Venstrom (University of California San Francisco Medical Center)

**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)

**PhD Statistician:** Tao Wang (taowang@mcw.edu)

**Study Status:** Analysis in progress

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**Study # IB12-06**

**Title:** Natural killer cell genomics and outcomes after allogeneic hematopoietic cell transplantation for lymphoma

**Study Chair:** Veronika Bachanova (University of Minnesota Medical Center)

**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)

**PhD Statistician:** Tao Wang (taowang@mcw.edu)

**Study Status:** Analysis in progress

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**Study # IB13-01**

**Title:** Effect of allele-level human leukocyte antigen-matching after umbilical cord blood hematopoietic cell transplantation for non-malignant diseases in children

**Study Chairs:** Paul Veys (Great Ormond Street Hospital for Children)

Mary Eapen (Froedtert & Medical College of Wisconsin)

**MS Statistician:** Hailin Wang (hwang@mcw.edu)

**PhD Statistician:** TBD

**Study Status:** Protocol development

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**Study # IB13-02**

**Title:** Effects of human leukocyte antigen class I amino acid mismatches on hematopoietic cell transplantation outcomes

**Study Chair:** Susana Marino (University of Chicago Hospitals)

**MS Statistician:** Hailin Wang (hwang@mcw.edu)

**PhD Statistician:** Tao Wang (taowang@mcw.edu)

**Study Status:** Analysis in progress
Study # IB13-04
Title: Discrepancy analysis of microsatellite loci as a proxy measure for ancestral differentiation between donors and recipients: correlation between high scores and poorer overall survival in high resolution matched unrelated donor transplantation
Study Chairs: John Harvey (British Bone Marrow Registry)
Colin Steward (Bristol Children’s Hospital)
Vanderson Rocha (Churchill Hospital)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: TBD
Study Status: Sample typing

Study # IB13-08
Title: Interaction between single nucleotide polymorphisms and clinical data using predictive modeling on a Bayesian network framework: short and long term survival assessment of post hematopoietic cell transplantation
Study Chair: Reza Abdi (Dana Farber Cancer Institute)
MS Statistician: Hailin Wang (hwang@mcw.edu)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Analysis in progress

Study # IB13-09
Title: The development of machine learning based classifiers to define the alloreactivity of human leukocyte antigen mismatches in unrelated donor hematopoietic cell transplantation
Study Chair: Yoram Louzoun (Bar-Ilan University)
MS Statistician: Hailin Wang (hwang@mcw.edu)
PhD Statistician: Tao Wang (taowang@mcw.edu)
Study Status: Analysis in progress

Study # IB14-01
Title: Impact of human leukocyte antigen haplotypes on outcomes of allogeneic transplantation for B-cell non-Hodgkin lymphomas
Study Chairs: Brian Hill (Cleveland Clinic)
Marcelo Fernandez-Viña (Stanford Hospital & Clinics)
Marcos de Lima (University Hospitals Case Medical Center)
Basem William (University Hospitals Case Medical Center)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: TBD
Study Status: Protocol development
### Study # IB14-02
**Title:** Structural / functional models of HLA for data mining of permissive mismatching in allogeneic hematopoietic stem cell transplantation  
**Study Chair:** Loren Gragert (National Marrow Donor Program)  
**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)  
**PhD Statistician:** TBD  
**Study Status:** Analysis in progress

### Study # IB14-03
**Title:** The prognostic impact of somatic mutations and levels of CXC chemokine ligands on post hematopoietic cell transplantation outcomes in patients with myelodysplastic syndromes  
**Study Chairs:** Wael Saber (Froedtert & Medical College of Wisconsin)  
Coleman Lindsley (Dana Farber Cancer Institute)  
Benjamin Ebert (Dana Farber Cancer Institute)  
**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development

### Study # IB14-04
**Title:** Assessing the similarity of the T cell receptor repertoire in allogeneic hematopoietic stem cell recipients with the same single human leukocyte mismatches  
**Study Chair:** Everett Meyer (Stanford Hospital & Clinics)  
**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development

### Study # IB14-05
**Title:** mtDNA haplotypes and unrelated donor transplant outcomes  
**Study Chairs:** Michael Verneris (University of Minnesota Medical Center)  
Julie Ross (University of Minnesota Medical Center)  
**MS Statistician:** Mike Haagenson (mhaagens@nmdp.org)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development

### Study # IB14-06
**Title:** Donor-specific anti HLA antibodies, allele and antigen level HLA mismatches in the outcomes of transplantation of non-malignant diseases with unrelated donors  
**Study Chairs:** Ann Woolfrey (Fred Hutchinson Cancer Research Center)  
Marcelo Fernandez-Viña (Stanford Hospital & Clinics)  
**MS Statistician:** Hai-Lin Wang (hwang@mcw.edu)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development
Study # IB14-07
Title: Indirectly recognizable HLA epitopes (PIRCHES): a retrospective validation study on the role of indirect recognition of mismatched HLA in hematopoietic stem cell transplantation outcome
Study Chair: Eric Spierings (University Medical Center Utrecht)
MS Statistician: Mike Haagenson (mhaagens@nmdp.org)
PhD Statistician: TBD
Study Status: Protocol development

PLANNED STUDIES

Study # IB06-10
Title: Evaluation of the impact of the exposure to non-inherited maternal antigens during fetal life and breast feeding and to the inherited paternal antigens during pregnancy on the clinical outcomes of hematopoietic cell transplantation from haploidentical family members
Study Chair: Jon Van Rood (Leiden University Medical Centre)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Deferred

Study # IB12-07
Title: Telomeres and incidence of leukemia recurrence and survival after hematopoietic cell transplantation
Study Chair: Mary Eapen (Froedtert & Medical College of Wisconsin)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Deferred

Study # IB13-06
Title: Role of the complement system in graft-versus-host disease
Study Chair: Vahid Afshar-Kharghan (The University of Texas MD Anderson Cancer Center)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Deferred

Study # IB13-07
Title: Impact of donor signal-regulatory protein alpha (SIRPα) polymorphism on outcome of allogeneic hematopoietic cell transplantation
Study Chair: Adam Gassas (Hospital for Sick Children)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Deferred
8.9 INFECTION AND IMMUNE RECONSTITUTION WORKING COMMITTEE

Co-Chair: Michael Boeckh, MD, Fred Hutchinson Cancer Research Center
Email: mboeckh@fredhutch.org

Co-Chair: Jeffery Auletta, MD, Nationwide Children’s Hospital
Email: jeffery.auletta@nationwidechildrens.org

Co-Chair: Caroline Lindemans, MD PhD, University Medical Center Utrecht, Pediatrics
Email: c.a.lindemans@umcutrecht.nl

Scientific Director: Marcie Riches, MD, MS, CIBMTR, H Lee Moffitt Cancer Center and Research Institute
Email: marcie.tomblyn@moffitt.org

PhD Statistician: Kwang Woo Ahn, PhD, CIBMTR Milwaukee
Email: kwooahn@mcw.edu

MS Statistician: Min Chen, MS, CIBMTR Milwaukee
Email: minchen@mcw.edu

PRELIMINARY RESULTS

Study # IN05-02

Title: Atypical mold infections in hematopoietic cell transplantation patients

Study Chairs: Marcie Riches (H. Lee Moffitt Cancer Center and Research Institute)
Steven Trifilio (Northwestern Memorial Hospital)

MS Statistician: Min Chen (minchen@mcw.edu)
PhD Statistician: Kwang Woo Ahn (kwooahn@mcw.edu)

Study Status: Manuscript preparation

Abstract: Purpose: To assess the impact of atypical mold infection (AMI) on transplant outcome and risk factors for AMI, which have not been well assessed in the current era of antifungal agents. Patients / Methods: All patients receiving allogeneic HCT from 1995 - 2008 for any indication are included. Cases (n=124) had a Zygomycetes [n=72 (58%)] or Fusarium [n=52 (42%)] AMI between day 0-365 after HCT. A control cohort (n=11,856) included all patients from the same 66 centers as cases. HCT indication was malignancy in 106 (85%) cases and 9,603 (81%) controls. Results: Cases were older [41 yrs (1-68) vs 34 yrs (1-79), p=0.004] and more likely to have a KPS <90% at HCT [cases=50 (40%), control=3,330 (28%), p=0.009]. Similar numbers of cases occurred before and after May 2002 [1995-Apr 2002=60 (48%), May 2002-2008=64 (52%)]. Systemic antifungal prophylaxis was similar between cases and controls (p=0.64). The median time from HCT to AMI was 48 days (0-363) with most occurring between day 0-100 [day 0-30=49 (40%), day 31-60=18 (15%); day 61-100=22 (18%)]. AMI diagnosis significantly impacted one-year OS with a probability (95% CI) for cases of only 22% (15-29) compared to 65% (64-65) for controls (p<0.001). Conclusions: Atypical mold infection occurs infrequently but appears similar in the current antifungal era and remains associated with high morbidity.
Study # IN06-01
Title: The rate of breakthrough of pneumocystis jiroveci pneumonia after transplant as a function of prophylaxis regimens
Study Chair: Kirsten Williams (Children's National Medical Center)
MS Statistician: Min Chen (minchen@mcw.edu)
PhD Statistician: Kwang Woo Ahn (kwooahn@mcw.edu)
Study Status: Manuscript preparation
Abstract: Pneumocystis jiroveci pneumonia (PJP) is associated with high morbidity and mortality after HCT. Little is known about PJP infections after HSCT because of the rarity of this complication following the routine implementation of prophylaxis. We report results of a CIBMTR study evaluating the incidence, timing, prophylaxis agents, risk factors, and mortality of PJP in autoHCT and alloHCT recipients. For recipients of first HCT captured between 1995 and 2005, PJP infection was documented in 0.63% (177 of 27,934) alloHCTs and 0.28% (52 of 18,525) autoHCTs. Cases occurred both early and late after alloHCT. A nested case control study using supplemental data (n=68 allo cases, n=111 allo controls) revealed that PJP infection was higher among recipients who were not Caucasian; received peripheral blood stem cells (versus marrow); were exposed to Campath or ATG; received less well-matched grafts; and had lymphopenia, neutropenia, or recent steroid exposure after alloHCT. Lymphopenia, neutropenia, and concurrent autoimmune disease were risk factors after autoHCT. Prophylaxis agents varied but fewer cases received Trimethoprim/sulfamethoxazole was lower occurring later after alloHCT. There were more cases with grade 3-4 acute GVHD and chronic GVHD compared to controls. After alloHCT or autoHCT, overall survival was significantly poorer among cases vs controls [at 1 year: 41% vs 73% (p<0.0001) and 42% vs 86% (p=0.0004), respectively]. After controlling for significant variables, proportional hazards model revealed that PJP cases were 6.87 times more likely to die vs matched controls (p<0.0001, CI 4.84-9.75). Thus, these data reveal that: PJP infection is rare after HSCT; PJP occurs both early and late after HCT; mismatch, GVHD prophylaxis, GVHD and steroids are risk factors for PJP; and PJP infection is associated with higher mortality rate after HCT. Furthermore, our data suggest opportunities to improve supportive care, starting PJP prophylaxis early post-HCT and continuing for those with these newly identified risk factors: GVHD, steroid exposure, or poor immune reconstitution.

Study # IN09-01
Title: Outcomes of allogeneic hematopoietic cell transplantation for patients with hematologic malignancies with and without pre-existing fungal infections
Study Chair: Richard Maziarz (Oregon Health and Science University)
MS Statistician: Min Chen (minchen@mcw.edu)
PhD Statistician: Ruta Brazauskas (ruta@mcw.edu)
Study Status: Manuscript preparation
Abstract: Invasive fungal infections (IFI) are associated with high mortality rates in patients undergoing allogeneic HCT. However, with availability of novel antifungal agents with lower toxicity profiles and implementation of reduced-intensity transplants (RIT), patients with previously documented, proven, or probable IFI are increasingly undergoing HCT. Recognizing these practice changes, the clinical outcomes of patients with pre-transplant IFI (n=825) were compared to a similar cohort of patients from the same HCT centers over the past decade without proven or probable pre-transplant IFI (n=10,247). Specifically, outcomes of NRM, malignant disease relapse rates, OS, DFS, and the development of post-transplant IFI were compared between patient groups. Primary analysis focused on outcomes between 2001-2009, with a secondary analysis limited to AML and ALL patients receiving myeloablative conditioning extending from 1995 to 2009, as a surrogate for availability of novel antifungal agents and the emergence of PBSC allografts. Patients with pre-transplant IFI were older, had lower performance status, had advanced disease, and were more likely to have AML. Additionally, they were more likely to have received a cord blood transplant, RIT, mold-active fungal prophylaxis, and have been more recently transplanted. Aspergillus and Candida were the most commonly identified pathogens associated with pre-transplant IFI, and 68% of patients with IFI presented with pulmonary involvement. Univariable outcomes analysis revealed lower 1-, 3-, and 5-year DFS and OS for patients with pre-transplant IFI. Relapses were higher in this cohort, whom also had a trend toward increased TRM. The probability of post-HCT IFI was 24% for the study group and 17% for the control group (p<0.001). Interestingly, cause of death was associated with a greater likelihood of having recurrent / persistent malignant disease. Infectious mortality causes were only slightly increased (13 vs 9%) between the study group and the control group. With regard to the secondary analysis comparing patients with pre-transplant IFI diagnosed between 1995-2000 vs 2001-2009, NRM at 1-, 3-, and 5-years were significantly higher with associated reduction in OS and DFS for the early cohort. However, no observable differences were identified in post-HCT IFI and in relapse rates. Conclusions: Documentation of pre-HCT IFI is associated with lower DFS and OS after allogeneic HCT. However, mortality is most influenced by patients with more advanced disease status than infectious etiologies. Treated pre-transplant IFI does not appear to be a contraindication to allogeneic HCT.

Study # IN12-01
Title: Cytomegalovirus infection and relapse after hematopoietic cell transplantation
Study Chairs: Minoo Battiwalla (National Heart Lung and Blood Institute - NIH)
A. John Barrett (National Heart Lung and Blood Institute - NIH)
Muthalagu Ramanathan (UMass Memorial Medical Center)
Pierre Teira (Centre Hospitalier Universitaire Sainte-Justine)
MS Statistician: Min Chen (minchen@mcw.edu)
PhD Statistician: Kwang Woo Ahn (kwooahn@mcw.edu)
Study Status: Manuscript preparation
Abstract: Several single center studies have recently reported an association between early CMV reactivation (before day 100) and a decreased incidence of relapse for AML after alloHCT. The CIBMTR conducted a retrospective large scale study to assess the impact of CMV serology and CMV reactivation in the current era. Data from 11,153 patients undergoing initial HCT between 2003 and 2010 were analyzed for 6 disease-stem cell source categories: AML transplanted with BM/PBSC (n=5,310), AML transplanted with CB (n=925), ALL with BM/PBSC (n=1,883), ALL with CB (n=759), CML with BM/PBSC (n=1,079) and MDS with BM/PBSC (n=1,197). The median time to CMV reactivation was 40 days (range: 1–362 days) after HCT, and 98% of reactivations occurred before day 100. In multivariable analysis throughout the 6 identified groups, positive serology (D+/R+, D+/R-, D-/R+) versus negative serology (D-/R-) had no effect on the risk of acute or chronic GVHD or the risk for malignant disease relapse. However, positive serology was associated with higher TRM and poorer OS. Specifically, CMV reactivation after HCT was associated with higher TRM for MDS (RR 1.61, p=0.0002), CML (RR 1.86, p=0.0004), AML (RR 1.68; p<0.0001), and ALL (RR 1.95; p<0.0001) and lower OS (range of RR from 1.27 to 1.49; p value from 0.003 to <0.0001). Only among AML patients following CB transplantation was CMV reactivation not associated with lower OS. Moreover, CMV reactivation had no effect on the incidence of relapse irrespective of the diagnosis or the source of stem cells. In conclusion, positive D/R CMV serology is still associated with increased TRM and decreased OS in the current era. Early CMV reactivation did not prevent hematologic malignant disease relapse in patients with AML, MDS, CML, or ALL after initial HCT.

STUDIES IN PROGRESS

Study # IN07-01 / IN11-01
Title: Early bacterial infection in patients undergoing allogeneic hematopoietic cell transplantation
Study Chairs: Mark Robien (University of Minnesota Medical Center)
Celalettin Ustun (University of Minnesota Medical Center)
Jo-Anne Young (University of Minnesota Medical Center)
MS Statistician: Min Chen (minchen@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # IN10-01
Title: Comparison of infectious rates among alternative graft sources: single and double cord blood, matched unrelated donor, and mismatched unrelated donor
Study Chair: Karen Ballen (Massachusetts General Hospital)
MS Statistician: Min Chen (minchen@mcw.edu)
PhD Statistician: Kwang Woo Ahn (kwooahn@mcw.edu)
Study Status: Analysis in progress
Study # IN13-01
Title: Bacterial and fungal infections in patients undergoing allogeneic hematopoietic cell transplantation following nonmyeloablative and myeloablative regimens
Study Chair: Celalettin Ustun (University of Minnesota Medical Center)
MS Statistician: Min Chen (minchen@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # IN14-01
Title: Post allogeneic hematopoietic transplant Ebstein Barr Virus related lymphoproliferative disorder following conditioning with antithymocyte globulin or alemtuzumab
Study Chairs: Carlos Bachier (Texas Transplant Institute)
Rammurti Kamble (Baylor College of Medicine Center for Cell and Gene Therapy)
Paul Shaughnessy (Texas Transplant Institute)
Seema Naik (Texas Transplant Institute)
Parameswaran Hari (Froedtert & Medical College of Wisconsin)
MS Statistician: Min Chen (minchen@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development
8.10 LATE EFFECTS AND QUALITY OF LIFE WORKING COMMITTEE

Co-Chair: Christine Duncan, MD, Dana-Farber Cancer Institute  
Email: christine_duncan@dfci.harvard.edu

Co-Chair: Bipin Savani, MD, Vanderbilt University Medical Center  
Email: bipin.savani@vanderbilt.edu

Co-Chair: Mary Flowers, MD, Fred Hutchinson Cancer Research Center  
Email: mflowers@fredhutch.org

Scientific Director: Bronwen Shaw, MD, PhD, CIBMTR Milwaukee  
Email: beshaw@mcw.edu

PhD Statistician: Ruta Brazauskas, PhD, CIBMTR Milwaukee  
Email: ruta@mcw.edu

MS Statistician: Heather Millard, MPH, CIBMTR Milwaukee  
Email: hmillard@mcw.edu

RECENTLY COMPLETED STUDIES

Study # LE07-01


Abstract: We examined risk of second solid cancers after alloHCT using RIC / NST. RIC / NST recipients with leukemia / MDS (n=2,833) and lymphoma (n=1,436) between 1995-2006 were included. In addition, RIC / NST recipients 40-60 years of age (n=2,138) were compared with patients of the same age receiving MAC (n=6,428). The cumulative incidence of solid cancers was 3.35% at 10-years. There was no increase in overall cancer risk compared to the general population (SIR 0.99, P=1.00 for leukemia / MDS and 0.92, P=0.75 for lymphoma). However, risks were significantly increased in leukemia / MDS patients for cancers of lip (SIR 14.28), tonsil (SIR 8.66), oropharynx (SIR 46.70), bone (SIR 23.53), soft tissue (SIR 12.92), and vulva (SIR 18.55) and skin melanoma (SIR 3.04). Lymphoma patients had significantly higher risks of oropharyngeal cancer (SIR 67.35) and skin melanoma (SIR 3.52). Among RIC / NST recipients, age >50 years was the only independent risk factor for solid cancers (HR 3.02, P<0.001). Among patients age 40-60 years, when adjusted for other factors, there was no difference in cancer risks between RIC / NST and MAC in leukemia / MDS patients (HR 0.98, P=0.905). In lymphoma patients, risks were lower after RIC / NST (HR 0.51, P=0.047). The overall risks of second solid cancers in RIC / NST recipients are similar to the
8.10 LATE EFFECTS AND QUALITY OF LIFE WORKING COMMITTEE  CIBMTR Progress Report 2014

general population, although there is an increased risk of cancer at some sites. Studies with longer follow-up are needed to realize the complete risks of solid cancers after RIC / NST alloHCT.

Study # LE09-03b


Abstract: With broadening indications, more options for HCT and improvement in survival, the number of long-term HCT survivors is expected to increase steadily. Infertility is a frequent problem that long-term HCT survivors and their partners face, and it can negatively impact quality of life. The most optimal time to address fertility issues is before the onset of therapy for the underlying disease; however, fertility preservation should also be addressed prior to HCT in all children and patients of reproductive age, with referral to a reproductive specialist for patients interested in fertility preservation. In vitro fertilization and embryo cryopreservation, oocyte cryopreservation, and ovarian tissue banking are acceptable methods for fertility preservation in adult women / pubertal females. Sperm banking is the preferred method for adult men / pubertal males. Frequent barriers to fertility preservation in HCT recipients may include the perception of lack of time to preserve fertility given an urgency to move ahead with transplant, lack of patient-physician discussion due to several factors (e.g., time constraints, lack of knowledge), inadequate access to reproductive specialists, and costs and lack of insurance coverage for fertility preservation. There is a need to raise awareness in the medical community about fertility preservation in HCT recipients.

Study # LE10-01


Abstract: We conducted a nested case-control study within a cohort of 6,244 patients to assess risk factors for avascular necrosis (AVN) of bone in children and adolescents following alloHCT. Eligible patients were ≤21 years of age, received their first alloHCT between 1990 and 2008 in the US and had survived ≥6 months from transplantation. Overall, 160 cases with AVN and 478 controls matched by year of transplant, length of follow-up, and transplant center were identified. Cases and controls were confirmed via central review of radiology, pathology,
and/or surgical procedure reports. Median time from transplant to diagnosis of AVN was 14 months. On conditional logistic regression, increasing age at transplant (≥5 years), female gender, and chronic GVHD were significantly associated with increased risks of AVN. Compared to patients receiving MAC regimens for malignant diseases, lower risks of AVN were seen in patients with non-malignant diseases and those who had received RIC regimens for malignant diseases. Children at high risk for AVN include those within the age group where rapid bone growth occurs as well as those who experience exposure to MAC regimens and immunosuppression post-HCT for the treatment of GVHD. More research is needed to determine whether screening strategies specifically for patients at high risk for developing AVN with early interventions may mitigate the morbidity associated with this complication.

Study # LE10-G1e


Abstract: Advances in HCT technology and supportive care techniques have led to improvements in long-term survival after HCT. Emerging indications for transplantation, introduction of newer graft sources (eg, umbilical cord blood), and transplantation of older patients using less intense conditioning regimens have also contributed to an increase in the number of HCT survivors. These survivors are at risk for developing late complications secondary to pre-, peri-, and post-HCT exposures and risk factors. Guidelines for screening and preventive practices for HCT survivors were published in 2006. An international group of transplantation experts was convened in 2011 to review contemporary literature and update the recommendations while considering the changing practice of transplantation and international applicability of these guidelines. This review provides the updated recommendations for screening and preventive practices for pediatric and adult survivors of autologous and allogeneic HCT.

Study # LE11-01

Abstract: Little is known about long-term outcomes in survivors of 2nd alloHCT performed for patients who have relapsed following a previous alloHCT. We analyzed outcomes of 1-year survivors following 2nd allo HCT who were reported to the CIBMTR between 1980 and 2009. Overall, 1,285 patients received a 2nd HCT for relapsed acute leukemia or MDS; 325 1-year survivors were eligible for this study (children=146, adults=179). Rate of 1-year survival was 35% for all patients. The corresponding rates for children and adults were 30% and 46%. The majority of grafts (61%) used the same donor for the 2nd transplant. The median age at 2nd HCT was 9 (range: 1- 17) years and 38 (range 19-66) years for children and adults, respectively. MAC regimen was used in 89% for 1st and 62% for 2nd HCT in children and in 79% and 45% of adults. 16% of children and 32% of adults had a history of chronic GVHD prior to 2nd HCT. In the two age groups, median time from 1st HCT to relapse was 14 mos and 18 months, and median time from 1st to 2nd HCT was 17 mos and 24 mos, respectively. Chronic GVHD developed in 43% and 75% of children and adults following 2nd HCT. Relapse was the major cause of death (43/56 for children and 54/96 for adults, respectively). In proportional hazard models, only disease status (relapse / progression) prior to second HCT was associated with statistically significant higher risk for mortality [HR 1.71 (95% CI 1.22-2.38) vs remission; P<0.01). Other pre-transplant characteristics had no impact on survival including age, interval between 1st and 2nd HCT, chronic GVHD, 1st-2nd HCT donor pair, or conditioning intensity for 2nd HCT. The CIBMTR collects information on selected late complications. The cumulative incidence of developing at least one late effect for which data were collected at 10-years following 2nd HCT was 63% in children and 55% in adults. In children, notable late effects were growth disturbance (10-year cumulative incidence after 2nd HCT 22%), cataracts (20%), gonadal dysfunction (16%), and hypothyroidism (13%). In adults, cataracts (20%), avascular necrosis (13%) and hypothyroidism (5%) were commonly reported late effects after 2nd HCT. In summary, 1-year survivors of 2nd allo HCT for relapsed acute leukemia or MDS have favorable long-term outcomes. Attaining remission prior to HCT is the single favorable predictive factor for long-term survival. Majority of late failures are due to relapse, and late effects are frequently encountered. Future trials focusing on reducing risks of relapse and implementing systematic surveillance for long-term toxicities are warranted.

PRELIMINARY RESULTS

Study # LE13-04
Title: Mortality rates after second malignancy
Study Chair: Matthew Ehrhardt (St. Jude Children’s Research Hospital)
MS Statistician: Matthew Ehrhardt (matthew.ehrhardt@stjude.org)
PhD Statistician: Ruta Brazauskas (ruta@mcw.edu)
Study Status: Manuscript preparation
Abstract: AlloHCT is a curative treatment for many benign and malignant conditions. Cure is often associated with late occurring adverse effects of therapy, including development of secondary solid cancers. Outcomes for individuals who develop secondary solid cancers are incompletely described in that most reports address risk factors contributing to the second malignancy but not survival after the occurrence of this potentially life threatening complication. The objective of this study was to estimate the probability of OS in alloHCT recipients who develop secondary solid cancers and to describe the proportion of patients surviving within specific secondary solid cancer subtypes. All consecutive transplant recipients reported to the CIBMTR between 1964 and 1994 were evaluated. Age, sex, primary disease, treatment, secondary cancers, geographic region, and donor type were denoted for patients who developed secondary solid cancers. Descriptive statistics were generated. Probability of OS was calculated using the Kaplan-Meier estimator. There were 146 individuals who developed secondary solid cancers. After exclusion of basal cell carcinomas (n=28) and those diagnosed at the time of autopsy (n=6), 112 individuals with invasive or in situ secondary solid cancers were retained for survival analysis. The median duration of follow-up from the time of secondary cancer development for survivors was 11.9 years (range 0.8-23.4), and 75% of patients were followed for more than 7.0 years. The 5- and 10-year overall survival probabilities after development of a secondary solid cancer were 50% (95% CI 41-60%) and 46% (95% CI 37-57%), respectively. The median survival from the time of secondary cancer diagnosis was less than 6 months for patients diagnosed with central nervous system, lung, liver, and other tumors and less than 2.5 years for those diagnosed with lower gastrointestinal tract, bone, soft tissue, or female reproductive tumors. Secondary cancer was the cause of death in the majority of patients who died following the development of melanoma, central nervous system, oral cavity, thyroid, lung, lower gastrointestinal tract, bone, and other secondary solid cancers. This large cohort allowed for more representative longitudinal evaluation of an otherwise uncommon condition. These findings will enhance the ability of clinicians to predict outcomes for transplant survivors who develop secondary solid cancers and support the need to prioritize the reduction of risk factors associated with those secondary solid cancers with worse overall outcomes.

Study # LE14-G1
Title: Risks and outcomes of therapy related myeloid neoplasms after autologous hematopoietic cell transplantation
Study Chairs: Nirali Shah (NIH - National Cancer Institute)
Yoshihiro Inamoto (Fred Hutchinson Cancer Research Center)
MS Statistician: Navneet Majhail (majhain@ccf.org)
PhD Statistician: N/A
Study Status: Manuscript preparation
Abstract: Survivors after HCT have a substantial risk of secondary solid cancers. To facilitate implementation of cancer screening appropriate to HCT recipients, a working group has been established through the CIBMTR with the goal of
developing clinical guidelines for screening for secondary solid cancers. The working group reviewed cancer screening guidelines applicable to the general population, and reviewed the incidence and risk factors of individual secondary cancers after HCT. A consensus approach was used to establish recommendations for screening and prevention of individual secondary solid cancers. The incidence of secondary cancer is increased particularly beyond five years after HCT without reaching a plateau overtime. The most common sites include oral cavity, skin, female breast, and thyroid. Risks of cancers are increased after HCT compared to the general population in the skin, thyroid, oral cavity, esophagus, liver, nervous system, bone, and connective tissues. High-dose TBI, young age at HCT, chronic GVHD, and prolonged immunosuppressive treatment beyond 24 months were well-documented risk factors for many types of secondary cancers. All HCT recipients should be advised of the risks of secondary cancers annually and encouraged to perform recommended screening based on their predisposition. These recommendations will serve as the first step in establishing consensus guidelines for screening and prevention of secondary cancers among HCT recipients.

**STUDIES IN PROGRESS**

**Study # LE99-01**

**Title:** Quality of life in late hematopoietic cell transplant survivors  
**Study Chair:** John Wingard (University of Florida)  
**MS Statistician:** TBD  
**PhD Statistician:** Ruta Brazauskas (ruta@mcw.edu)  
**Study Status:** Ongoing

**Study # SC09-05**

**Title:** Stem Cell Therapeutic Outcomes Database assessment of quality of life data  
**Study Chair:** J. Douglas Rizzo (Froedtert & Medical College of Wisconsin)  
**MS Statistician:** TBD  
**PhD Statistician:** TBD  
**Study Status:** Supplemental form / data collection

**Study # LE11-02**

**Title:** Risk factors for development of secondary central nervous system tumors in survivors of pediatric hematopoietic cell transplantation  
**Study Chairs:** Melissa Gabriel (The Children’s Hospital at Westmead)  
Peter Shaw (The Children’s Hospital at Westmead)  
**MS Statistician:** Min Chen (minchen@mcw.edu)  
**PhD Statistician:** TBD  
**Study Status:** Supplemental form / data collection
Study # LE12-02
Title: Late effects of children undergoing allogeneic hematopoietic cell transplantation at a young age
Study Chairs: Lynda Vrooman (Dana Farber Cancer Institute)
Christine Duncan (Dana Farber Cancer Institute)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Protocol development

Study # LE12-03
Title: Solid organ transplantation after hematopoietic cell transplantation
Study Chairs: Meera Gupta (Abramson Cancer Center University of Pennsylvania Medical Center)
Peter L Abt (Abramson Cancer Center University of Pennsylvania Medical Center)
Matthew Levine (Abramson Cancer Center University of Pennsylvania Medical Center)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Analysis in progress

Study # LE12-04
Title: The hematopoietic cell transplant-recovery index: identifying patients at risk for poor outcomes based upon hematologic recovery at day +100
Study Chairs: Shernan Holtan (University of Minnesota Medical Center)
Rekha Chandran (Legacy Health Systems, Legacy Salmon Creek Hospital)
Luis Porrata (Mayo Clinic Rochester)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Protocol development

Study # LE13-01
Title: Late cardiovascular morbidity and mortality following pediatric allogeneic hematopoietic cell transplantation
Study Chairs: Christine Duncan (Dana Farber Cancer Institute)
K. Scott Baker (Fred Hutchinson Cancer Research Center)
Michael Pulsipher (University of Utah)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Supplemental form / data collection
Study # LE13-02

Title: Cancer risk in hematopoietic cell transplant recipients followed in the recent transplant era

Study Chair: Eric Engels (NIH - National Cancer Institute)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Protocol development

Study # LE13-03

Title: The rate of aging in hematopoietic stem cells transplant patients: A frailty survival model analysis

Study Chair: Yuhui Lin (Max Planck Institute for Demographic Research)
MS Statistician: TBD
PhD Statistician: Ruta Brazauskas (ruta@mcw.edu)
Study Status: Analysis in progress

Study # LE14-01

Title: Risks and outcomes of therapy related myeloid neoplasms after autologous hematopoietic cell transplantation

Study Chairs: Shahrukh Hashmi (Mayo Clinic Rochester)
Robert Dean (Cleveland Clinic Taussig Cancer Institute)
Kenneth R. Cooke (Johns Hopkins School of Medicine)
Matt Kalaycio (Cleveland Clinic Taussig Cancer Institute)
Betty Hamilton (Cleveland Clinic)
Robert Peter Gale (Imperial College London)
Mark R. Litzow (Mayo Clinic)

MS Statistician: TBD
PhD Statistician: TBD
Study Status: Protocol development
8.11 LYMPHOMA WORKING COMMITTEE

Co-Chair: David Maloney, MD, PhD, Fred Hutchinson Cancer Research Center
Email: dmaloney@fredhutch.org

Co-Chair: Sonali Smith, MD, University of Chicago Hospitals
Email: smsmith@medicine.bsd.uchicago.edu

Co-Chair: Anna Sureda, MD,
Email: asureda@iconcologia.net

Scientific Director: Mehdi Hamadani, MD, MS, CIBMTR Milwaukee
Email: mhamadani@mcw.edu

PhD Statistician: Kwang Woo Ahan, PhD, CIBMTR Milwaukee
Email: kwooahn@mcw.edu

MS Statistician: Alyssa DiGilio, MS, CIBMTR Milwaukee

RECENTLY COMPLETED STUDIES

Study # LY07-02


Abstract: We describe outcomes after alloHCT for mycosis fungoides and Sezary syndrome (MF/SS). Outcomes of 129 subjects with MF/SS reported to the CIBMTR from 2000-2009. Median time from diagnosis to transplant was 30 (4-206) months and most subjects were with multiply relapsed / refractory disease. Majority (64%) received NST/RIC. NST/RIC recipients were older in age compared to myeloablative recipients (median age 51 vs. 44 y p=0.005) and transplanted in recent years. NRM at 1 and 5 years was 19% (95% CI 12-27%) and 22% (95% CI 15-31%) respectively. Risk of disease progression was 50% (95% CI 41-60%) at 1 year and 61% (95% CI 50-71%) at 5 years. PFS at 1 and 5 years was 31% (95% CI 22-40%) and 17% (95% CI 9-26%), respectively. Overall survival at 1 and 5 years was 54% (95% CI 45-63%) and 32% (95% CI 22-44%), respectively. AlloHCT in MF/SS results in 5 year survival in approximately one-third of patients and, of those, half of them remain disease-free.

Study # LY09-01


Abstract:
There are limited data on the outcomes of autologous or allogeneic HCT in DLBCL transformed from follicular lymphoma. We analyzed transplant outcomes in 141 subjects with biopsy-proven DLBCL transformed from follicular lymphoma reported to the CIBMTR from 1990-2009. Two groups were identified: autoHCT (N=108) and alloHCT (N=33). Fewer autoHCTs were done for transformed follicular lymphoma in 2003-2009, with a shift favoring alloHCTs. AutoHCT had 1 year NRM of 8% (95% CI 4-14), 5 year PFS of 35% (95% CI 26-45), and 5 year OS of 50% (95% CI 40-50). AlloHCT had 1 year NRM of 41% (95% CI 23-58), 5 year PFS of 18% (95% CI 6-35), and 5 year OS of 22% (95% CI 8-41). In univariate analysis, age, pre-transplant rituximab, or transformation <1 year or >1 year from diagnosis of follicular lymphoma had no influence on outcomes. AutoHCT is beneficial for transformed follicular lymphoma and achieves sustained remission in a high proportion of subjects. The high NRM of alloHCT obscured any benefit that might be associated with this transplant modality.

Study # LY10-02


Abstract: Alternative donor transplantation is increasingly used for high risk lymphoma patients. We analyzed 1593 transplant recipients (2000 to 2010) and compared transplant outcomes in recipients of 8/8 allele HLA-A, -B, -C, and DRB1 MUD; n=1176, 7/8 allele MMUD; n=275 and UCB (1 or 2 units; n=142). Adjusted 3-year non-relapse mortality of MMUD (44%) was higher as compared to MUD (35%; p=0.004), but similar to UCB recipients (37%; p=0.19), although UCB had lower rates of neutrophil and platelet recovery compared to unrelated donor groups. With a median follow-up of 55 months, 3-year adjusted cumulative incidence of relapse was lower after MMUD compared with MUD (25% vs 33%, p=0.003) but similar between UCB and MUD (30% vs 33%; p=0.48). In multivariate analysis UCB recipients had lower risks of acute and chronic graft versus host disease compared with adult donor groups (UCB vs MUD: HR=0.68, p=0.05; HR=0.35; p<0.001). Adjusted 3-year overall survival was comparable (43% MUD, 37% MMUD and 41% UCB). Data highlight that patients with lymphoma have acceptable survival after alternative donor transplantation. MMUD and UCB can expand the curative potential of allotransplant to patients who lack suitable HLA-matched sibling or MUD.
Study # LY13-01


Abstract: The poor prognosis of DLBCL patients relapsing within one year of initial diagnosis after first-line rituximab-based chemoimmunotherapy has created controversy about the role of autoHCT in this setting. We compared autoHCT outcomes of chemosensitive DLBCL patients between 2000 and 2011 in two cohorts based on time to relapse from diagnosis. The early rituximab failure (ERF) cohort consisted of patients with primary refractory disease or those with first relapse within 1 year of initial diagnosis. The ERF cohort was compared with those relapsing >1 year after initial diagnosis [late rituximab failure (LRF) cohort]. ERF and LRF cohorts included 300 and 216 patients, respectively. NRM, progression / relapse, PFS, and OS of ERF vs LRF cohorts at 3 years were 9% (95% CI 6-13) vs 9% (95% CI 5-13), 47% (95% CI 41-52) vs 39% (95% CI 33-46), 44% (95% CI 38-50) vs 52% (95% CI 45-59), and 50% (95 CI 44-56) vs 67% (95% CI 60-74), respectively. On multivariate analysis, ERF was not associated with higher NRM (RR 1.31, p=0.34). ERF cohort had a higher risk of treatment failure (progression / relapse or death) (RR 2.08, p<0.001) and overall mortality (RR 3.75, p<0.001) within the first 9 months post autoHCT. Beyond this period, PFS and OS were not significantly different between ERF and LRF cohorts. AutoHCT provides durable disease control to a sizeable subset of DLBCL despite ERF (3-year PFS 44%) and remains the standard-of-care in chemosensitive DLBCL regardless of the timing of disease relapse.

PRELIMINARY RESULTS

Study # SC10-06

Title: Efficacy of a pharmacokinetics-directed busulfan, cyclophosphamide, and etoposide conditioning and autologous stem cell transplantation for lymphoma: A comparison of a multi-center Phase II study and CIBMTR outcomes

Study Chairs: Christopher R. Flowers (Winship Cancer Institute, Emory University)
Marcelo Pasquini (Froedtert & Medical College of Wisconsin)

MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)
PhD Statistician: Jennifer LeRademacher (jlerade@mcw.edu)
Study Status: Manuscript preparation
Abstract: AutoHCT is the standard therapy for patients with lymphoma who relapse after initial therapy because it improves PFS and OS. BEAM is the most frequently utilized regimen but other regimens, such as those incorporating intravenous Bu, are now being investigated. This study compares outcomes from BuCyE in patients enrolled in a phase II multicenter clinical trial from 2010 to 2012 to recipients of BEAM registered with the CIBMTR from 2008 to 2011. After an interim analysis, the clinical trial protocol was amended to enroll patients 65 years and younger due to excess TRM with BuCyE in older patients. 184 recipients of BuCyE with lymphoma in CR or PR were matched to a maximum of 4:1 with 729 controls based on age, performance status, disease status prior to transplant, and lymphoma histology. 177 cases had 4 matched controls, and 97% of controls had an age difference from controls of 5 years or less. Median age is 50 years, 76% with performance status greater than 90%, 35% with HL, 34% DLBCL, 16% mantle cell, 12% follicular, and 3% other NHL histologies; 43% were in PR, and median follow up was 22 months in both cohorts. Two-year cumulative incidences of TRM were 3.3% (95% CI 1.4-6.6%) and 3.9% (95% CI 2.4-5.7%) for BuCyE and BEAM, respectively. Corresponding two-year probabilities of OS were 76% (95% CI 68-82%) and 78% (95% CI 74-82%). Multivariate analysis demonstrated a significant interaction between disease and conditioning regimen in evaluation of disease progression and treatment failure outcomes. Analyses by histology demonstrated that among patients with DLBCL and other NHL histologies, there were no differences in outcomes between conditioning groups. Among patients with HL, the two-year cumulative incidence of progression were 66% (95% CI 53-77%) and 38% (95% CI 31-45%) and two-year PFS were 33% (95% CI, 21-46%) and 59% (95% CI, 52-66%) for BuCyE and BEAM, respectively with no difference in TRM or OS. BuCyE were associated with comparable outcomes after an autoHCT with BEAM conditioning among patients younger than 65 years with NHL. In a subset of patients with HL, BuCyE was associated with higher progression and shorter PFS compared to BEAM conditioning.

Study # LY12-02 / GV11-01

Title: Analysis of graft-versus-lymphoma effect after allogeneic hematopoietic cell transplantation

Study Chairs: Alvaro Urbano-Ispizua (University of Barcelona, IDIBAPS, and Institute of Research Josep Carreras)
Steven Pavletic (NIH - NCI Experimental Transplantation and Immunology Branch)
Mary Flowers (Fred Hutchinson Cancer Research Center)

MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)
PhD Statistician: John P. Klein / Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Submitted

Abstract: To analyze the impact of GVHD on relapse rate of different lymphoma subtypes after alloHCT. Adult patients with a diagnosis of HL, DLBCL, FL, PTCL, or MCL undergoing HLA-identical sibling or unrelated donor HCT between 1997 and 2009 were included. 2,611 cases were included. RIC regimen was used in 62.8% of
the transplants. In multivariate analysis of myeloablative cases (n=970), acute GVHD nor chronic GVHD were significantly associated with a lower incidence of relapse / progression in any lymphoma subtype. In contrast, the analysis of RIC cases (n=1,641) showed that both acute and chronic GVHD were associated with a lower incidence of relapse / progression in FL (RR 0.33, p=0.01; and RR 0.47, p=0.02, respectively), and chronic GVHD was associated with a lower incidence of relapse / progression in MCL (RR 0.31, p<0.001). Patients with FL or MCL developing both acute and chronic GVHD had the lowest risk of relapse (RR 0.12, p=0.003; and RR 0.14, p=0.0019, respectively). Unfortunately, both acute and chronic GVHD had a deleterious effect on OS and PFS in FL cases and did not impact OS or PFS in MCL. This study reinforces the use of RIC alloHCT as a platform for immunotherapy in indolent lymphoma patients.

STUDIES IN PROGRESS

**Study # LY06-03**

**Title:** Human leukocyte antigen-identical sibling transplantation versus human leukocyte antigen-matched unrelated donor transplantation in patients with follicular lymphoma

**Study Chairs:** Anna Sureda (Hospital Duran i Reynals)  
Harry Schouten (Academische Ziekenhuis)

**MS Statistician:** Jeanette Carreras (jcarrera@mcw.edu)

**PhD Statistician:** Mei-Jie Zhang (meijie@mcw.edu)

**Study Status:** Data file preparation

**Study # LY12-01**

**Title:** Role of positron emission tomography (PET) imaging prior to allogeneic hematopoietic cell transplantation in predicting outcomes for non- hodgkin and hodgkin lymphoma

**Study Chairs:** Veronika Bachanova (University of Minnesota Medical Center)  
Linda Burns (University of Minnesota Medical Center)

**MS Statistician:** Jeanette Carreras (jcarrera@mcw.edu)

**PhD Statistician:** Mei-Jie Zhang (meijie@mcw.edu)

**Study Status:** Analysis in progress

**Study # LY13-02**

**Title:** Outcome of autologous hematopoietic cell transplantation for children, adolescents, and young adults with relapsed / refractory Hodgkin lymphoma

**Study Chair:** Prakash Satwani (Columbia University Medical Center)

**MS Statistician:** Jeanette Carreras (jcarrera@mcw.edu)

**PhD Statistician:** Kwang Woo Ahn (kwooahn@mcw.edu)

**Study Status:** Analysis in progress
Study # LY13-03
Title: Comparison of autologous versus allogeneic hematopoietic cell transplantation after reduced / non-myeloablative conditioning for relapsed / refractory patients with follicular lymphoma
Study Chairs: Evgeny Klyuchnikov (Interdisciplinary Clinic for Stem Cell Transplantation, University Cancer Center Hamburg)  
Ulrike Bacher (MLL Munich Leukemia Laboratory)  
Nicolaus Kröger (Interdisciplinary Clinic for Stem Cell Transplantation, University Cancer Center Hamburg)  
Parameswaran Hari (Froedtert & Medical College of Wisconsin)
MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)  
PhD Statistician: Kwang Woo Ahn (kwoohn@mcw.edu)  
Study Status: Analysis in progress

Study # LY14-02
Title: Outcome of patients with relapsed diffuse large B cell lymphoma treated with allogeneic hematopoietic cell transplantation following a failed autologous HCT
Study Chairs: Timothy S. Fenske (Froedtert & Medical College of Wisconsin)  
Tara Graff (Medical Oncology Hematology Associates)
MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)  
PhD Statistician: TBD  
Study Status: Protocol development
8.12 PEDIATRIC CANCER WORKING COMMITTEE

Co-Chair: Carrie Kitko, MD, University of Michigan
Email: ckitko@med.umich.edu
Co-Chair: Gregory Hale, MD, All Children’s Hospital
Email: ghale4@jhmi.edu
Co-Chair: Parinda Mehta, MD, Cincinnati Children’s Hospital Medical Center
Email: parinda.mehta@cchmc.org
Scientific Director: Elizabeth Thiel, MD, MS, CIBMTR Milwaukee
Email: ethiel@mcw.edu
PhD Statistician: Jennifer Le-Rademacher, PhD, CIBMTR Milwaukee
Email: jlerade@mcw.edu
MS Statisticians: Heather Millard, MPH, CIBMTR Milwaukee
Email: hmillard@mcw.edu

RECENTLY COMPLETED STUDIES

Study # PC10-01


Abstract: The safety and efficacy of RIC regimens for the treatment of pediatric acute myeloid leukemia is unknown. We compared the outcome of alloHCT in children with AML using RIC regimens to those receiving MAC regimens. 180 patients were evaluated (39 with RIC and 141 with MAC regimens). Results of univariate and multivariate analysis showed no significant differences in the rates of acute and chronic GVHD, LFS and OS between treatment groups. The 5-year probabilities of OS with RIC and MAC regimens were 45% and 48%, respectively (p=0.99). Moreover, relapse rates were not higher with RIC compared to MAC regimens (39% vs. 39%, p=0.95), and recipients of MAC regimens were not at higher risk for TRM compared to recipients of RIC regimens (16% vs. 16%, p=0.73). In this relatively modest study population and after carefully controlled analyses, the data support a role for RIC regimens for AML in children undergoing alloHCT. The data also provide justification for designing a carefully controlled randomized clinical trial that examines the efficacy of regimen intensity in this population.
Study # PC10-02b


Abstract: We report on 27 patients with DS and ALL who received alloHCT between 2000 and 2009. 78% of patients received myeloablative conditioning and 52% underwent transplantation in second remission. DFS was 24% at a median of 3 years. Post-transplant leukemic relapse was more frequent than expected for children with DS-ALL (54%) than for non-DS ALL. These data suggest leukemic relapse rather than transplant toxicity is the most important cause of treatment failure. Advancements in leukemia control are especially needed for improvement in HCT outcomes for DS-ALL.

Preliminary Results

Study # PC10-03

Title: Transplantation in children with hypodiploid acute lymphoblastic leukemia

Study Chairs: Parinda Mehta (Cincinnati Children’s Hospital Medical Center)
Sonata Jodele (Cincinnati Children’s Hospital Medical Center)

MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)

Study Status: Manuscript preparation

Abstract: Children with hypodiploid ALL have inferior outcomes with chemotherapy despite intensive risk adapted treatment. A case series of pediatric hypodiploid ALL (n=139) with <45 chromosomes treated by 10 different national ALL study groups (Nachman et al; 2007), reported an 8-year EFS of 38.5% and OS of 49.8%. Patients with fewer than 44 chromosomes fared significantly worse than those with 44 chromosomes (EFS of 30% vs. 52%, p=0.01). A similar report from the Medical Research Council (MRC) included 226 children and adults treated with chemotherapy (Harrison et al, 2004). Patients with 42-45 chromosomes (n=153) had a 3-year survival of 66% compared to 29% in those with 25-39 chromosomes. We conducted a retrospective study of 78 children with hypodiploid ALL who underwent HCT between 1990 and 2010 and reported to the CIBMTR, to determine whether outcomes might be improved with transplant. Median age at HCT was 10 years (range 3-18). 39 (50%) patients had ≤43 chromosomes, 12 (15%) had 44 chromosomes, and 27 (35%) had 45 chromosomes. 43 (55%) patients were transplanted in CR1 while 35 (45%) were transplanted in ≥CR2. 29 (37%) patients received a graft from a related donor, 34 (44%) an unrelated donor, and 15 (19%) cord blood. Demographics and transplant characteristics were similar in those with chromosomes ≤43 or ≥44 and those transplanted with early or late disease (CR1 or CR2 and beyond). All patients received a MAC regimen. Multivariate
analysis confirmed both disease status and number of chromosomes were independently associated with mortality; mortality risks were higher for transplants in CR2 (HR 2.16, p=0.05) and when chromosomes were ≤43 (HR 2.15, p=0.05). In the group with ≥44 chromosomes (n=13), 3 patients died and 10 were alive at last contact (9 disease free and 1 with relapsed disease). Despite the obvious limitation of small numbers of patients and the retrospective nature of our study, our results suggest that compared to historical results from chemotherapy only treatment, pediatric patients with hypodiploid ALL, may have improved outcomes when transplanted in CR1, and benefit may be most notable in those with ≤43 chromosomes.

**STUDIES IN PROGRESS**

**Study # PC09-01**

**Title:** Outcomes in children with T cell acute lymphoblastic leukemia following allogeneic hematopoietic cell transplantation  
**Study Chair:** Michael Burke (Medical College of Wisconsin)  
**MS Statistician:** Wensheng He (vhe@mcw.edu)  
**PhD Statistician:** Jennifer Le-Rademacher (jlerade@mcw.edu)  
**Study Status:** Analysis in progress

**Study # PC14-01**

**Title:** Auto transplantation for children with Wilms’ tumor  
**Study Chair:** Marcio Malogolowkin (Children’s Hospital of Wisconsin)  
**MS Statistician:** Michael Hemmer (mhemmer@mcw.edu)  
**PhD Statistician:** TBD  
**Study Status:** Data file preparation

**Study # PC14-02**

**Title:** The CIBMTR experience in pediatric autologous transplantation: trends over the past 5 years  
**Study Chair:** Elizabeth Thiel (Medical College of Wisconsin)  
**MS Statistician:** Wensheng He (vhe@mcw.edu)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development

**Study # PC14-03**

**Title:** Personalized prognostic information for pediatric leukemia survivors  
**Study Chair:** Stella Davies (Cincinnati Children’s Hospital Medical Center)  
**MS Statistician:** Wensheng He (vhe@mcw.edu)  
**PhD Statistician:** TBD  
**Study Status:** Protocol development
RECENTLY COMPLETED STUDIES

Study # ST06-01


Abstract: Desmoplastic small round cell tumor of the peritoneum (DSRCTP) is a rare, frequently fatal tumor. This retrospective study, based on CIBMTR registry data, describes the largest reported cohort of DSRCTP patients who have undergone autoHCT. The probabilities of DFS at 1 year for patients in CR and not in CR were 75% (95% CI 48-94%) and 35% (15-59%), respectively. The probability of OS at 3 years was 57% (29-83%) and 28% (9-51%) for patients in CR and not in CR, respectively. Median survival for the entire cohort was 31 months (36 months and 21 months for those in CR and not in CR, respectively). Engraftment at 42 days was 97% (88-100%). Treatment-related mortality was low, with only one death in the first 100 days. AutoHCT is a tolerable approach in patients with DSRCTP, with the greatest benefit seen in those patients who obtain CR. For those not in CR, the median OS in this series is greater than previously reported.
(21 months vs 17 months), suggesting autoHCT is useful in prolonging DFS and OS, even in patients with residual or persistent disease pre-transplant.

**Study # MM06-04**


**Abstract:** Patients with MM who are eligible for autoHCT typically receive a finite period of initial therapy prior to autoHCT. It is not clear if patients with suboptimal (less than a partial) response to initial therapy benefit from additional alternative therapy with intent to maximize pre-transplant response. We identified 539 patients with MM who had an autoHCT after having achieved less than a PR to first line induction chemotherapy between 1995 and 2010. These patients were then divided into two groups: those who received additional salvage chemotherapy prior to autoHCT (n=324) and those who had no additional salvage chemotherapy immediately prior to autoHCT (n=215). Additional pre-transplant chemotherapy resulted in deepening responses in 68% (complete response in 8% and PR in 60%). On multivariate analysis there was no impact of pre-transplant salvage chemotherapy on TRM, risk for relapse, PFS or OS. In conclusion, for patients achieving a less than PR to initial induction therapy including with novel agent combinations, additional pre-autoHCT salvage chemotherapy improved the depth of response and pre-autoHCT disease status but was not associated with survival benefit.

**Study # MM11-01**


**Abstract:** AutoHCT for plasma cell myeloma (PCM) is performed less often in >70 year olds. We analyzed 11,430 autoHCT recipients for PCM prospectively reported to the CIBMTR between 2008 and 2011 representing the majority of US autoHCT activity during this period. OS was compared in 3 cohorts: ages 18-59 years (N=5,818), 60-69 years (N= 4,666) and >70 years (N=946). Median OS was not
reached for any cohort. In multivariate analysis, increasing age was associated with mortality (p=0.0006). Myeloma specific mortality was similar at 12% indicating age related effect on non-myeloma mortality. Analyses were performed in a representative subgroup comparing RR, PFS, and NRM. 1-year NRM was 0% for age >70 years and 2% for other ages (p=NS). 3-year RR were 56% in age 18-59 years, 61% in age 60-69 years, and 63% age >70 (p=NS). 3-year PFS was similar at 42% in age 18-59 years, 38% in age 60-69 years, and 33% in age >70 years (p=NS). Post-relapse survival was significantly worse for the older cohort (p=0.03). Older subjects selected for autoHCT derived similar anti-myeloma benefit without worse NRM, RR, or PFS.

PRELIMINARY RESULTS

Study # MM08-02
Title: HLA polymorphism and MM risk in black and white individuals
Study Chair: Meral Beksac (Ankara University Medical School / Ibni Sina Hospital)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Submitted
Abstract: Higher incidence of MM in African Americans (AFA) and within first-degree family members suggests a genetic basis for MM susceptibility. 4-digit allele level HLA A/B/DRB1 typing was performed on 2,887 US Caucasian (CAU) and 509 AFA MM patients and compared with 500,000 CAU and 438,873 AFA controls randomly selected from a pool of all 2,141,439 DNA-typed US Caucasian and 438,873 AFA volunteer donors registered at the NMDP. ORs and p-values estimating the association of HLA type and MM risk were calculated using multivariable logistic regression models and adjusted for age, sex, geographical region and multiple testing using a false discovery rate method with a threshold of 5%. HLA specificities B*07:02 (O:1.22, p=5.15E-05) and C*07:02 (OR 1.19, p=0.012), and the haplotype A*03:01~B*07:02 (OR 1.23, p=0.008) were modestly associated with MM among CAU. An inverse association between MM risk and A*02:01~B*44:02 (OR 0.82, p=0.026); DRB1*04 (OR 0.88, p=0.029), and A*02:01~B*44:02~DRB1*04:01 (OR 0.69, p= 0.019) was also observed among CAU. Associations were stronger among AFA: HLA-A*30~DRB1*11 (OR 1.85 p=0.043), A*02~DRB1*07 (OR 1.72 p=0.044), DRB1*07+DRB1*13 (OR 1.88 p=0.009), DRB1*07:01+DRB1*11:01 (OR 2.14, p=0.023). Race-specific HLA alleles / haplotypes impact the risk for MM, and this may partially explain racial and familial variability in MM susceptibility.

Study # MM10-01
Title: Second primary malignancies after autologous hematopoietic cell transplants for plasma cell myeloma
Study Chairs: Paulette Mehta (University of Arkansas for Medical Sciences)
Anuj Mahindra (University of California San Francisco Medical Center)
Study # ST10-01

Title: The value of high-dose chemotherapy and autologous hematopoietic cell transplantation as adjuvant treatment in patients with high-risk inflammatory breast cancer after neoadjuvant chemotherapy

Study Chairs: Naoto Ueno (The University of Texas MD Anderson Cancer Center)
Yee Cheng (Medical College of Wisconsin)
Yushu Shi (Medical College of Wisconsin)

MS Statistician: Michael Hemmer (mhemmer@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Manuscript preparation

Abstract: Introduction: Inflammatory breast cancer (IBC) is a rare aggressive form of breast cancer. The outcomes of IBC are usually worse than that of non-IBC in the non-transplant setting. The role of high-dose chemotherapy (HDC) with autoHCT in IBC is unclear. The objective of this study was to determine the outcomes of IBC vs that of non-IBC in the setting of HDC/autoHCT. Long term effect of HDC in secondary malignancy was also determined.

Methods: We reviewed registry data from the CIBMTR to identify all patients with IBC and non-IBC who had undergone HDC/autoHCT between 1990 and 2002. Causes of death, TRM rates, relapse rates, and DFS and OS rates were determined. A univariate and multivariate analysis were used to determine the HR of different outcomes.

Results: We identified 527 patients with IBC and 2,860 patients with non-IBC from the registry; 84% of IBC and 80% of non-IBC patients did not have...
metastatic disease at transplantation; the median age at transplantation (47 vs 46 years old) and median follow-up period in the 2 groups (167 vs 168 months) were similar. The most commonly used conditioning regimen was cyclophosphamide, carboplatin, and others in both groups (54% in IBC and 50% in non-IBC). The most common cause of death was disease progression (81% in IBC and 75% in non-IBC). A univariate analysis revealed that the TRM rate at 1 year was 2% for IBC and 3% for non-IBC (p=0.16), the relapse rate at 10 years was 67% for IBC and 69% for non-IBC (p=0.36), the DFS rate at 10 years was 27% for IBC and 24% for non-IBC (p=0.21), and the OS rate at 10 years was 31% for IBC and 28% for non-IBC (p=0.16). A multivariate analysis revealed that stage III IBC patients at transplantation had a poorer outcome than did stage III non-IBC patients at transplantation in terms of relapse rate (HR 1.24, p=0.0082), DFS rate (HR 1.17, p=0.0339), and OS rate (HR 1.16, p=0.0459). These poor outcomes were also shown even though they had no active diseases at transplant. Both groups presented with very low incidence of second malignancy on long term follow-up (<2%).

Conclusions: Our study confirmed that the long term outcomes of stage III IBC patients who underwent HDC / auto HCT were poorer than that in non-IBC patients even though they had no active diseases at transplant; however, the difference in the survival HR was smaller (1.16) than that reported previously (1.43) in non-transplant setting.

**Study # MM11-03**

**Title:** Outcomes of hematopoietic cell transplantation for amyloidosis  
**Study Chairs:** Baldeep Wirk (Stony Brook University Medical Center)  
Anita D’Souza (Medical College of Wisconsin)  
**MS Statistician:** Jiaxing Huang (jiaxhuang@mcw.edu)  
**PhD Statistician:** Mei-Jie Zhang (meijie@mcw.edu)  
**Study Status:** Manuscript preparation  
**Abstract:** Background: Light chain (AL) amyloidosis is a rare plasma cell neoplasm associated with systemic amyloid deposition leading to organ dysfunction and death without treatment. The use of autoHCT in AL amyloidosis remains controversial as a prospective randomized control trial suggested inferior outcomes when compared with standard chemotherapy, driven primarily by high peri-TRM up to 24%. Improved patient selection criteria, supportive care, and risk-adapted therapy have reduced TRM in recent single center studies. We analyzed trends and prognostic factors associated with AHCT outcomes in AL amyloidosis patients.  
Methods: We identified 1,532 AL amyloidosis patients who underwent autoHCT following high dose MEL within 24 months of diagnosis between 1995 and 2012 from the CIBMTR database. A subset of patients with more complete level of research data reported between 2001 and 2012 was analyzed for multivariate analysis (n=354). The primary endpoints were Day 30 and Day 100 mortality, hematologic PFS, hematologic relapse / progression, and OS. Data regarding
cardiac, renal, hepatic, and neurologic amyloid involvement was collected. Hematologic and organ response and progression were defined based on the 2004 uniform consensus criteria.

Results: The median age at transplant was 57 years, with 61% males. AutoHCT was performed within 6 months of diagnosis in 66% patients. KPS was <80 in 14%, HCT-CI was ≥3 in 20%, and 69% had a lambda isotype. Organ involvement included renal, cardiac, hepatic, and autonomic nervous system involvement in 74%, 38%, 16%, and 11%, respectively. Coexistent myeloma (>10% bone marrow plasma cells) was seen in 14%. Progressively higher numbers of patients received autoHCT from 1995-2000 (n=140) to 2001-2006 (n=595) and 2007-2012 (n=800). The majority were untreated pre-transplant (77%) while 8% received MEL, 6% thalidomide, and 4% each received lenalidomide and bortezomib based pre-AHCT therapy. The median CD34 cell dose infused was 4.4 X 10^6/kg cells (IQR 3.3-6.2). MEL dose reduction was common (60% received < MEL 180 mg/m² and 38% < MEL 140 mg/m²). The median length of hospital stay was 17 days (IQR 13-23). The median follow-up of patients from the time of transplant was 61 months (range 3-145). Day 100 response included hematologic CR (12%), PR (26%), stable disease (23%), and renal response (12%) with an ultimate best response of hematologic CR (33%), PR (28%), stable disease (19%), and renal response in 31%. Day 30 and Day 100 mortality and OS at 1, 3, and 5 years show steady declines in mortality rates and improvements in survival in successive time cohorts. On multivariate analysis, albumin ≥3 g/dl at diagnosis, KPS ≥80, pre-transplant anti-plasma cell therapy and MEL ≥180 mg/m² were associated with lower hematologic relapse / progression. KPS ≥80 and predominant renal involvement were associated with superior hematologic PFS while KPS≥80 and <2 organ involvement correlated with OS.

Conclusions: There has been a significant improvement in survival of AL patients after autoHCT driven primarily by a reduction in early peri-transplant mortality. Limited organ involvement, higher KPS, use of pre-transplant therapy, and higher dose melphalan conditioning contributed to superior outcomes.

**Study # MM11-04**

**Title:** High-dose intravenous busulfan and melphalan followed by bortezomib (BUMELVEL) vs high-dose melphalan (MEL) as conditioning regimen for autologous peripheral blood stem cell transplantation for patients with multiple myeloma

**Study Chair:** Tulio Rodriguez (Loyola University Medical Center)

**MS Statistician:** Jiaxing Huang (jiaxhuang@mcw.edu)

**PhD Statistician:** Tulio Rodriguez (trodriguez@lumc.edu)

**Study Status:** Manuscript preparation

**Abstract:** Introduction: For more than two decades, high dose chemotherapy followed by autoHCT has been an effective therapy for selected patients newly diagnosed multiple myeloma. Single agent melphalan, at a dose of 200 mg/m² (MEL 200) is widely used around the world and continues to be the standard of care for
patients with MM with relatively predictable results. Other chemotherapy and chemo-radiotherapy regimens are generally associated with increased hematologic and non-hematologic toxicities. However, there is emerging evidence demonstrating the clonal heterogeneity of multiple myeloma at diagnosis and at different stages of disease progression. Moreover, during the course of the disease and especially in high risk or advanced patients, sub-clones of myeloma cells appear to compete for dominance. Based on this phenomenon, a partial response to therapy might represent just the suppression of a sensitive clone while refractory clones remain stable and thus becoming proportionally more dominant. These observations support the rationale of developing preparative chemotherapy regimens combining synergistic systemic agents with diverse mechanism of actions in order to circumvent the possibility of heterogeneous resistant clones while maintaining an acceptable therapeutic index. Considering that BuMel is associated with superior PFS compared to MEL200 on patients who do not achieve a CR prior to autoHCT and that the combination of bortezomib and melphalan appears to be synergistic, especially when bortezomib is administered after MEL200, we proceeded to study a conditioning regimen combining high dose busulfan and melphalan followed by bortezomib (BUMELVEL) in an open label phase II study aimed at improving PFS after autoHCT for MM patients and compared the results against a cohort of patients who received single agent MEL 200.

Patients and Methods: Between July 2009 and May 2012, 43 eligible patients received BuMelVel conditioning followed by HCT. Outcomes were compared with a contemporaneous North American cohort (n=162) from the CIBMTR Research Database that received single agent MEL 200 conditioning. Controls were matched on age, sex, KPS, stage, and interval from diagnosis to HCT. Multivariate analysis of relapse, PFS, and OS was performed. Median follow up of survivors was 25 months. Planned maintenance therapy was not used.

Results: Age, gender, KPS, isotype, and stage were similar between groups. The MEL200 cohort had more standard risk patients per Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) (78% vs. 40% in BuMelVel, p <0.0001) and more patients with only one prior line of therapy pre-HCT (67% vs. 47%, p=0.02). Platelet and neutrophil engraftment kinetics were similar. Veno-occlusive disease was not observed in the BuMelVel group, and there was no NRM. The incidence of relapse at and PFS at 1 year were superior in the BuMelVel cohort, but OS was similar between cohorts. In multivariate analysis, PFS was superior in the BuMelVel cohort (HR for relapse / death in MEL 200 was 1.87, p=0.04). BuMelVel therapy was not significant for OS or relapse. Lack of a very good partial response (>VGPR) prior to HCT was associated with inferior PFS, whereas lower KPS (<80) and higher international stage were associated with mortality.

Conclusions: PK directed dosing of Bu can be safely combined with Mel 140 and bortezomib (BUMELVEL) without higher risk of non-hematologic toxicity or non-relapse mortality. In the absence of maintenance therapy, BUMELVEL
appears to deliver better PFS to MM patients in comparison to single agent MEL 200. Within the constraints of a short follow up and uncontrolled post-transplant salvage therapies on both groups, no difference in OS has been observed.

Study # MM13-01

Title: Contribution of chemotherapy mobilization to disease control in multiple myeloma treated with autologous transplantation

Study Chairs: Luciano Costa (University of Alabama at Birmingham)
Geoffrey Uy (Washington University School of Medicine)

MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)

Study Status: Manuscript preparation

Abstract: Background: Autologous hematopoietic progenitor cells (auto-HC) can be mobilized either by hematopoietic growth factors (GF) alone or cytotoxic chemotherapy + GF (CC+GF). The latter is associated with higher CD34+ yields, but is associated with increased costs and risks of infection and hospitalization. In patients with MM undergoing autoHCT, it is uncertain whether mobilization with CC+GF affects post transplant outcomes.

Methods: We conducted a retrospective analysis of patients with MM undergoing their first AHPCT following high dose melphalan (≥140 mg/m2) between 2007 and 2012 in US and Canada and registered with the CIBMTR. Patients who had a planned subsequent allogeneic transplant, received VAD or similar induction therapy, had disease progression prior to transplant, or were mobilized with plerixafor were excluded from the analysis. The primary endpoint was PFS, and the main secondary end-points were TRM, relapse, and OS.

Results: There were 519 patients in GF and 449 in CC+GF with median follow-up of 42 and 46 months, respectively. The most common mobilizing CC regimen was single agent cyclophosphamide (71%). GF and CC+GF groups were similar, but there were more patients in GF with only one prior line of therapy, lenalidomide exposure, and CR at the time of transplant and more patients in CC+GF with low HCT co-morbidity index, prior thalidomide exposure, and planned second autologous transplant. Median number of days for auto-HC collection was 2 (IQR 1-3) in GF and 1 (IQR 1-3) in CC+GF (P<0.001). There were fewer days between collection and transplant (median 16 vs. 18, P<0.001) and fewer CD34+ cells (x 106/kg) infused at transplant (median 3.9, IQR=3.1-4.8, vs. 5.1, IQR 3.5-6.9, P<0.001) in GF than in CC+GF. Kinetics of neutrophil engraftment (>0.5 x 10^9/L) was similar between groups (13 vs. 13 days, P=0.69) while platelet engraftment (>20 x 10^9/L) was faster in CC+GF (median 19 vs. 18 days, P=0.006). There was no difference between groups in number of hospitalization days (14 vs. 14, P=0.7). In univariate analysis, there was no significant difference between the two groups in OS, PFS, or TRM. In multivariate analysis, stage III at diagnosis and Karnofsky status <90 but not modality of mobilization were associated with worse PFS. Similarly HCT-CI > 2, Stage III at diagnosis and immunoglobulin isotype (IgG/IgA/Others), but not mobilization were associated with OS. Adjusted 3-year
PFS was 43% (95% CI 38-48) in GF and 40% (95% CI 35-45) in CC+GF, P=0.33. Adjusted 3-years OS was 82% (95% CI 78-86) vs 80% (95% CI 75-84), P=0.43, and adjusted 5-year OS was 62% (95% CI 54-68) vs. 60% (95% CI 52-67), P=0.76, for GF and CC+GF, respectively. Conclusions: MM patients undergoing AHPCT have similar outcomes irrespective of the use of cytotoxic chemotherapy mobilization. We found no evidence that chemotherapy mobilization contributes to disease control in MM.

STUDIES IN PROGRESS

Study # MM09-03
Title: Comparison of outcomes after initial upfront autologous peripheral blood stem cell transplant with delayed initial autologous peripheral blood stem cell transplant in multiple myeloma patients
Study Chairs: Leona Holmberg (Fred Hutchinson Cancer Research Center)
Sergio Giralt (Memorial Sloan Kettering Cancer Center)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # MM11-02
Title: Waldenstrom's macroglobulinemia: retrospective analysis with hematopoietic cell transplantation
Study Chairs: Robert Cornell (Vanderbilt University Medical Center)
Veronika Bachanova (University of Minnesota Medical Center)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # MM13-02
Title: Outcome of tandem autologous hematopoietic cell transplantation in patients with abnormality in chromosome 1 and high-risk multiple myeloma
Study Chairs: Manish Sharma (Thomas Jefferson University)
Emma Scott (Oregon Health and Science University)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # MM14-01
Title: High dose chemotherapy and autologous stem cell transplantation for germ cell tumors
Study Chairs: Muna Qayed (Emory University Hospital)
Deepak Kilari (Medical College of Wisconsin)
Study # MM14-02
Title: Autologous hematopoietic cell transplantation in patients with renal insufficiency
Study Chair: Anuj Mahindra (University of California San Francisco Medical Center)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # MM14-03
Title: Trends in survival outcomes among patients relapsing early after autologous stem cell transplantation for multiple myeloma
Study Chairs: Angela Dispenzieri (Mayo Clinic Rochester)
Shaji Kumar (Mayo Clinic Rochester)
MS Statistician: Jiaxing Huang (jiaxhuang@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development
RECENTLY COMPLETED STUDIES

Study # AA10-02


Abstract:  A proportion of patients with aplastic anemia who are treated with immunosuppressive therapy develop clonal hematologic disorders, including MDS (post-aplastic anemia MDS). Many will proceed to alloHCT. We identified 123 patients with post-aplastic anemia MDS who from 1991 through 2011 underwent alloHCT, and in a matched-pair analysis compared outcomes to that in 393 patients with de novo myelodysplastic syndrome. There was no difference in OS. There were no significant differences in regards to 5-year probabilities of relapse, NRM, RFS, and OS, which were 14%, 40%, 46%, and 49% for post-aplastic anemia MDS and 20%, 33%, 47%, and 49% for de novo myelodysplastic syndrome, respectively. Cytogenetic risk was independently associated with OS in both groups. Thus, transplant success in patients with post-aplastic anemia MDS was similar to that in patients with de novo MDS and cytogenetic risk was the only significant prognostic factor for post-aplastic anemia MDS patients.
8.14 PRIMARY IMMUNE DEFICIENCIES, INBORN ERRORS OF METABOLISM, AND NON-MALIGNANT MARROW DISORDERS WORKING COMMITTEE

Study # ID11-02


Abstract: Mucolipidosis type II (MLII), or I-cell disease, is a rare but severe disorder affecting localization of enzymes to the lysosome, generally resulting in death before the 10th birthday. Although HCT has been used to successfully treat some lysosomal storage diseases, only two cases have been reported on the use of HCT to treat MLII. For the first time, we describe the combined international experience in the use of HCT for MLII in 22 patients. Although 95% of the patients engrafted, OS was low, with only 6 patients (27%) alive at last follow-up. The most common cause of death post-transplant was cardiovascular complications, most likely due to disease progression. Survivors were globally delayed in development and often required complex medical support, such as gastrostomy tubes for nutrition and tracheostomy with mechanical ventilation. Although HCT has demonstrated efficacy in treating some lysosomal storage disorders, the neurologic outcome and survival for patients with MLII were poor. Therefore, new medical and cellular therapies should be sought for these patients.

PRELIMINARY RESULTS

Study # ID98-05

Title: Hematopoietic cell transplantation for infantile osteopetrosis
Study Chairs: Paul Orchard (University of Minnesota Medical Center)
Anders Fasth (Sahlgrenska University Hospital)
MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Manuscript preparation
Abstract: We examined long-term survival associated with alloHCT in 160 children with infantile osteopetrosis transplanted in 1990-2011 at 57 centers. The majority of the patients were transplanted from 1990-1999 (n=89; 56%). Eighty-two patients (51%) of the cohort were male. In 55 patients (34%), an HLA sibling allograft was utilized while an additional 24 patients (15%) received grafts from other family members. Unrelated donor transplants were performed in 44 patients (28%), but in only 8 cases were these from well-matched donors. In 37 (23%) of transplants, unrelated cord blood grafts were used. Busulfan and cyclophosphamide was the most commonly used conditioning regimen (81%) and bone marrow the predominant graft source (71% of all transplants, 92% of non-cord blood grafts). The overall cumulative incidence of neutrophil recovery at 28 days was
decreased in the recipients of cord blood grafts (46%) as compared to matched and mismatched related grafts as well as unrelated transplants (p<0.05). Overall survival at 1 and 3 years was 54 and 53%, respectively. This did not vary significantly between graft sources. Early mortality (death by day +100) rates were high (32%) regardless of donor type but were not significantly different depending on graft type. The proportion of patients that were recipients of manipulated grafts was 11% (n=17), and the majority of these were in the setting of unrelated transplantation (11 of 26 grafts; 42%). Twelve patients received a second transplant because of graft-failure. Severe acute grade GVHD (grade 3-4) rates were lowest with related donor grafts (6%, 95% CI 1-13%, p<0.05). The proportion of patients with chronic GVHD was not significantly different between donor groups; the 3-year probability of chronic GVHD was 11%.

Study # ID99-02
Title: The role of hematopoietic cell transplantation in Langerhans cell histiocytosis
Study Chair: Paul Veys (Great Ormond Street Hospital for Children)
MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: N/A
Study Status: Submitted
Abstract: Patients with Langerhans cell histiocytosis (LCH) refractory to conventional chemotherapy have a poor outcome. There are currently two promising treatment strategies for high-risk patients: the first involves the combination of 2-clorodeoxyadenosine and cytarabine; the other approach is alloHCT. Here we evaluated 87 patients with high-risk LCH who were transplanted between 1990-2013. Prior to the year 2000, most patients underwent HCT following MAC: only 5 of 20 patients (25%) survived with a high rate of TRM: 55%. After the year 2000, an increasing number of patients underwent HCT with RIC: 49/67 (73%) patients survived; however, the improved survival was not overtly achieved by the introduction of RIC regimens with similar 3-year probability of survival after MAC (77%) and RIC transplantation (71%). There was no significant difference in TRM by conditioning regimen intensity but relapse rates were higher after RIC compared to MAC regimens (28% vs 8%, p=0.02), although most patients relapsing after RIC transplantation could be salvaged with further chemotherapy. HCT may be a curative approach in 3 out of 4 patients with high risk LCH refractory to chemotherapy: the optimal choice of HCT conditioning remains uncertain.

Study # ID10-02
Title: Outcomes of hematopoietic cell transplantation for DNA repair disorders
Study Chair: Andrew Gennery (Newcastle General Hospital / The Royal Victoria Infirmary)
MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: N/A
Study Status: Manuscript preparation
Abstract: Introduction: Patients with DNA-dsb repair defects often present with recurrent infection, BM failure, and predisposition to lymphoid malignancy. The systemic nature of the repair defect may cause patients not to tolerate MAC. We report multi-center outcomes of HCT in patients with Nijmegen Breakage Syndrome (NBS), DNA ligase 4 deficiency (LIG4), Cernunnos deficiency (XLF), and Ataxia Telangietasia (AT).

Materials and Methods: Centres were contacted through the EBMT, IEWP, and CIBMTR. Retrospective data were collected via a questionnaire, including conditioning regimen, outcome post-HCT, incidence of GVHD. Conditioning regimens were classified as MAC (busulfan or treosulphan) or RIC (typically a combination of fludarabine and melphalan or very low dose cyclophosphamide, including combinations of targeted antibodies and alemtuzumab).

Results: 23 patients identified from 17 transplant centers in 11 countries, including NBS (8), LIG4 (7), XLF (4), and AT (4). Median age at HCT was 52 months (range 22-240), median follow-up 13.5 months (range 2-102). 8 received MFD, 11 MUD, 4 mis-matched donors; 3 UCBT, 12 BM, 8 PBSC. 16/23 (70%) received RIC, of whom 14 (88%) are alive; 7 underwent MAC, of whom 2 (29%) are alive. Acute GVHD (grade 1-3) was common, occurring in 14/23 (61%) cases, 12 ≥ grade 2 skin+/ girt/liver; 5 died. Acute GVHD occurred in 4/4 XLF, 4/8 NBS, 2/7 LIG4, and 3/4 AT patients. Five developed chronic GVHD; two died.

Discussion: HCT can be successful for patients with DNA-dsb repair defects. A good short-term outcome can be achieved, particularly if RIC is used. Irradiation is not necessary as part of conditioning, and should be avoided. GVHD is common and not well tolerated. Long-term follow-up will be required to determine whether these patients are at greater risk of developing secondary malignancies.

Study # ID11-01
Title: Outcomes in allogeneic hematopoietic cell transplantation for adrenoleukodystrophy
Study Chair: Paul Orchard (University of Minnesota Medical Center)
MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: Jennifer Le-Rademacher (jlerade@mcw.edu)
Study Status: Manuscript preparation
Abstract: Cerebral adrenoleukodystrophy (cALD) is an X-linked, rapidly progressive neuroinflammatory disorder affecting school-aged boys. Demyelination is observed, most commonly in the occipital area of the brain. Progression is characteristically rapid, and if untreated, death ensues within several years after onset. The only current therapy proven to mitigate disease progression is alloHCT. Historically, patients identified and treated early in the course of their disease have been shown to experience good rates of survival and preservation of function. In contrast, those with more advanced disease have had inferior outcomes. We describe the characteristics of disease and transplant-related outcomes in 67 boys transplanted at 4 institutions from 2000 to 2009. The majority
of patients were identified as having cALD due to clinical, neurologic manifestations of their disease (N=38, 57%). The median age at the time of transplantation was 8.7 years (range 2-18 years), with a median time from diagnosis of cALD to transplantation of 4 months (<1-73 months). An MA preparative regimen was used in the majority of transplants (N=52, 78%), and BM or PBSC were used as a graft source in 35 cases (52%), while 31 patients received CB grafts (46%). The extent of disease was characterized based on the Loes MRI severity score and a neurologic functional score (NFS). At transplant, 42 patients (63%) had MRI scores <9, and 30 (45%) were asymptomatic neurologically (NFS score of 0). In 54 cases, information was available on the presence of gadolinium enhancement prior to transplant. Of these, enhancement was observed in 47 MRI’s (87%). OS at 1 and 5 years was 82% (CI 72-90%) and 75% (CI 62-85%), respectively. The most common cause of death was disease progression (7/16, 44%). In patients with available data regarding MRI severity scores, those with a score <10, survival at 5 years was 91% (N=46, CI 82-98%). In patients with more advanced disease (>10, N=13) overall survival at 5 years was 69% (CI 43-90%, p=0.04). Analysis of survival based on the presence or absence of neurologic symptoms (NFS=0 vs >1) did not achieve significance (92% vs 78%, p=0.06).

Study # AA12-01

Title: Outcome of second allogeneic hematopoietic cell transplantation in patients with fanconi anemia

Study Chair: Mouhab Ayas (King Faisal Specialist Hospital & Research Center)

MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)

PhD Statistician: Jennifer Le-Rademacher (jlerade@mcw.edu)

Study Status: Manuscript preparation

Abstract: Purpose: AlloHCT can cure bone marrow failure in Fanconi anemia (FA) patients. For those who fail, a second HCT is still the only potential salvage option. Data on outcomes of second HCT in FA patients are scarce.

Patients and Methods: We analyzed data on 81 FA patients who underwent second HCT for graft failure and were reported to the CIBMTR from 1990 to 2012.

Results: The median time from the 1st to the 2nd HCT was 2 months; neutrophil recovery occurred in 45% and 51% of patients, at days 28 (95% CI 33-56) and 100 (95% CI 39-62). The cumulative incidence of acute GVHD grades 2-4 at day 100 was 16% (95% CI 9-26) and that of chronic GVHD at 1, 3, and 5 years 11% (95% CI 5-19). The median follow up of survivors of the 2nd HCT was 62 months (range 3-117 months). Survival probabilities at 1, 3, and 5 years were 37% (95% CI 26-47), 29% (95% CI 19-39), and 27% (95% CI 18-37). In univariate analysis, the 5-year survival was superior when the 2nd HCT was done using the same donor, 37% (95% CI 25-50) vs 7% (95% CI 1-21) when a different donor was used (P<0.001); in patients with a KPS of ≥90 % at the time of the 2nd HCT, 72% (95% CI 46-87) vs 13% (95% CI 6-23) in those with KPS of <90% (P<0.001); in patients who had their 2nd HCT at a time period of ≥3 months from the 1st HCT, 45% (95% CI 27-61) vs
16% (95% CI 8-28) in those who had their 2nd HCT earlier (P=0.006); and in patients who had fludarabine containing regimens for the 2nd HCT, 42% (95% CI 23-60) vs 20% (95% CI 10-32) in those who did not (P=0.046).

Conclusion: Our analysis indicates that 2nd HCT after graft failure can lead to long-term survival in FA patients. Certain variables appear to significantly improve survival: use of the same donor, a better performance score, longer period between the two transplants, and fludarabine containing conditioning.

STUDIES IN PROGRESS

Study # ID12-01
Title: Allogeneic hematopoietic cell transplantation for combined immunodeficiency and common variable immunodeficiency
Study Chairs: Geoff Cuvelier (CancerCare Manitoba / University of Manitoba)
Greg Guilcher (Alberta Children's Hospital)
Nicola Wright (Alberta Children's Hospital)
MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: TBD
Study Status: Supplemental form / data collection

Study # AA13-01
Title: Correlation of levels of donor cell chimerism with hemoglobinopathy symptoms following allogeneic hematopoietic cell transplantation
Study Chairs: Allistair Abraham (Children's National Medical Center)
Shalini Shenoy (St. Louis Children's Hospital)
MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # ID13-01
Title: Second and subsequent hematopoietic cell transplants for congenital neutropenia / kostmann agranulocytosis
Study Chairs: Steven Keogh (The Children's Hospital at Westmead)
James Connelly (University of Michigan Cancer Centre)
MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development
Study # AA13-02
Title: Malignancies in patients with fanconi anemia
Study Chair: John Wagner (Thomas Jefferson University Hospital)
MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # NM14-01
Title: An investigation of the long term neurological outcomes of hematopoietic stem cell transplant in boys with X-linked adrenoleukodystrophy
Study Chairs: Paul Orchard (University of Minnesota Medical Center)
           : Jaap-Jan Boelens (University Medical Center Utrecht)
           : Robert Wynn (Royal Manchester Children’s Hospital)
MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: TBD
Study Status: Draft protocol received

Study # NM14-02
Title: Outcomes of allogeneic hematopoietic cell transplant in patients with Shwachman diamond syndrome
Study Chair: Kasiani Myers (Cincinnati Children’s Hospital Medical Center)
MS Statistician: Wensheng He (vhe@mcw.edu)
PhD Statistician: TBD
Study Status: Draft protocol received

Study # NM14-04
Title: Outcomes in allogeneic stem cell transplantation for sickle cell disease
Study Chairs: Eliane Gluckman (Hopital Saint Louis)
           : Mary Eapen (Froedtert & Medical College of Wisconsin)
MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)
PhD Statistician: TBD
Study Status: Analysis in progress

Study # NM14-05
Title: Descriptive report of congenital dyserythropoietic anemia
Study Chair: Hermann Heimpel (Universitätsklinikum Ulm Klinik für Kinder)
MS Statistician: Jeanette Carreras (jcarrera@mcw.edu)
PhD Statistician: TBD
Study Status: Analysis in progress
8.15 REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE WORKING COMMITTEE

Co-Chair:  Philip McCarthy, MD, Roswell Park Cancer Institute  
Email: philip.mccarthy@roswellpark.org
Co-Chair:  Andrew Artz, MD, MS, University of Chicago Hospitals 
Email: aartz@medicine.bsd.uchicago.edu
Co-Chair:  Alison Loren, MD, MS, Abramson Cancer Center University of Pennsylvania Medical Center  
Email: alison.loren@uphs.upenn.edu
Scientific Director:  Marcelo Pasquini, MD, MS, CIBMTR Milwaukee  
Email: mpasquini@mcw.edu
PhD Statistician:  Brent Logan, PhD, CIBMTR Milwaukee  
Email: blogan@mcw.edu
MS Statistician:  Xiaochun Zhu, MS, CIBMTR Milwaukee  
Email: xzhu@mcw.edu

RECENTLY COMPLETED STUDIES

Study # RT09-02


Abstract:  The rising incidence of pediatric obesity may significantly affect BMT outcomes. We analyzed outcomes in 3,687 children worldwide who received cyclophosphamide-based BMT regimens for leukemias between 1990 and 2007. Recipients were classified according to age-adjusted BMI percentiles as underweight (UW), at risk of UW (RUW), normal, overweight (OW), or obese (OB). Median age and race were similar in all groups. Sixty-one percent of OB children were from the United States / Canada. Three-year relapse-free and overall survival ranged from 48% to 52% (P=0.54) and 55% to 58% (P=0.81) across BMI groups. Three-year leukemia relapses were 33%, 33%, 29%, 25%, and 21% in the UW, RUW, normal, OW, and OB groups, respectively (P<0.001). Corresponding cumulative incidences for TRM were 18%, 19%, 21%, 22%, and 28% (P<0.01). Multivariate analysis demonstrated a decreased risk of relapse compared with normal BMI (RR 0.73, P<0.01) and a trend toward higher TRM (RR 1.28, P=0.014). BMI in children is not significantly associated with different survival after BMT for hematologic malignancies. Obese children experience less relapse post-transplant compared with children with normal BMI; however, this benefit is offset by excess in TRM.
8.15 REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE WORKING COMMITTEE

Study # RT12-04


Abstract: HCT with NMA conditioning for lymphoproliferative diseases (LD) includes fludarabine with and without low-dose TBI. Transplant outcomes were compared among patients ≥40 years with LD who received a HCT with TBI (N=382) and no-TBI (N=515) NMA from 2001 to 2011. The groups were comparable except for donor, graft, prophylaxis for GVHD, disease status, and year of HCT. Cumulative incidences of grades II-IV GVHD at 100 days were 29% and 20% (p=0.001), and chronic GVHD at 1 year were 54% and 44% (p=0.004) for TBI and no-TBI, respectively. Multivariate analysis of progression / relapse, treatment failure, and mortality showed no outcome differences by conditioning. Full donor chimerism at day 100 was observed in 82% vs. 64% in the TBI and no-TBI groups, respectively (p=0.006). Subset of four most common conditioning / GVHD prophylaxis combinations demonstrated higher rates of grades II-IV acute (p<0.001) and chronic GVHD (p<0.001) among recipients of TBI-MMF compared to other combinations. TBI-based NMA conditioning induces faster full donor chimerism but overall survival outcomes are comparable to no-TBI regimens. Combination of TBI and MMF are associated with higher rates of GVHD without impact on survival outcomes in patients with LD.

PRELIMINARY RESULTS

Study # RT07-01a

Title: Prospective validation of the impacts of the hematopoietic cell transplantation co-morbidity index, alone and combined with aging, on hematopoietic cell transplantation outcomes for malignant diseases

Study Chair: Mohamed Sorror (Fred Hutchinson Cancer Research Center)

MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)

PhD Statistician: Brent Logan (blogan@mcw.edu)

Study Status: Submitted

Abstract: Prospective validation of the HCT-CI using contemporary patients transplanted across the US is necessary to confirm its widespread applicability. We performed a prospective observational study including all patients (8,115 recipients of allogeneic and 11,652 recipients of autologous HCT) who underwent first HCT reported to the CIBMTR between 2007 and 2009. In proportional hazards models, increased HCT-CI scores were independently associated with increases in hazard ratios for NRM (p<0.0001) and overall mortality (p<0.0001) among recipients of allogeneic HCT. HCT-CI scores of ≥3 were uniformly associated with higher risks for outcomes in both allogeneic and autologous HCT, and all subgroups regardless of diagnoses, age, and conditioning intensity. Recipients of allogeneic HCT with scores of 1-2 who were aged <18 or were treated with lower intensity
conditioning regimens had similar outcomes compared to those with score 0. Higher risks for overall mortality, but not for NRM, were observed among recipients of autologous HCT with scores of 1-2 versus 0. Our results confirm the validity the HCT-CI in both allogeneic and autologous HCT. The index should be used as a valid standard-of-care health measure in counseling patients for HCT, in clinical trial design, and in adjusting outcome analyses.

**Study # RT07-01b**

**Title:** Prospective validation of the impacts of the hematopoietic cell transplantation comorbidity index, alone and combined with aging, on hematopoietic cell transplantation outcomes for non-malignant diseases

**Study Chairs:**
Mohamed Sorror (Fred Hutchinson Cancer Research Center)
Monica Thakar (Medical College of Wisconsin)

**MS Statistician:** Xiaochun Zhu (xzhu@mcw.edu)

**PhD Statistician:** Brent Logan (blogan@mcw.edu)

**Study Status:** Manuscript preparation

**Abstract:**
The HCT-CI was developed to summate the effect of 17 weighted comorbidities on nonrelapse mortality and OS in the allogeneic HCT setting. However, only 3% of patients included in the initial HCT-CI study had non-malignant diseases (Sorror M. et al, Blood 2005). In an attempt to broaden the application of HCT-CI by assessing its prognostic effect on overall mortality in patients with nonmalignant diseases, we conducted a prospective observational study collecting comorbidities on all patients reported to the CIBMTR from December 2007 to December 2009. A total of 853 patients with non-malignant diseases were identified, including SAA (n=404); inherited disorders of erythrocytes (n=180), histiocytes (n=68), metabolism (n=41), and platelets (n=6); primary immune deficiencies (n=149); and autoimmune diseases (n=5). Patients were transplanted at a median of 12 (<1-70) years of age (72% of patients were less than 20 years of age at HCT), and a median of 10 (<1-500) months from diagnosis. Donors were unrelated (n=414), HLA-matched siblings (n=356), other relatives (n=76), or syngeneic (n=7). Transplant regimens were predominantly Flu and TBI (n=144); Flu and melphalan (n=140); busulfan and cyclophosphamide (CY, n=138); CY and antithymocyte globulin (n=137) for conditioning, and methotrexate with cyclosporine (n=279) or tacrolimus (n=160) for post-grafting immunosuppression, respectively. Karnofsky / Lansky scores were ≥90% in 77% of patients. HCT-CI scores were 0 (64%), 1 (13%), 2 (6%), 3 (8%), 4 (5%), and ≥5 (4%). The top three HCT-CI comorbidities reported were active infection (8%) and pulmonary disease (severe 8% and moderate 7%). With a median follow-up of 27 (1-51) months, the OS for HCT-CI 0 (n=546), 1-2 (n=161), and ≥3 (n=144) at 3 years was 85%, 81%, and 63%, respectively (p<0.001). Multivariate analyses were adjusted for age, conditioning regimen, donor type, and HLA-match status. In these analyses, higher HCT-CI scores were associated with increased overall mortality as judged by increasing HR (p<0.001) compared to patients with HCT-CI of 0. This was mostly a result of the effect of HCT-CI scores of ≥3 (HR 2.54,
95% CI 1.68-3.83, p<0.0001) than from HCT-CI scores of 1-2 (HR 1.15, 95% CI 0.72-1.82, p=0.56). The negative effect of HCT-CI scores ≥ 3 on OS was preserved in subgroup analyses of pediatric (<20 years old; HR 2.43, 95% CI 1.30-4.54, p<0.005) and adult patients (≥20 years old; HR 2.91, 95% CI 1.56-5.41, p<0.001), and in SAA (HR 2.91, 95% CI 1.56-5.41, p<0.001). In conclusion, in a relatively large sample size, this study demonstrates that HCT-CI can also be used to predict OS in patients with non-malignant diseases. In particular, patients with HCT-CI scores of ≥3 experienced higher overall mortality independent of age group, conditioning regimen, donor type and HLA matching. HCT-CI is an important instrument to assist in patient counseling and transplant associated risk assessment in patients with nonmalignant diseases.

Study # RT09-01

Title: Primary graft failure following allogeneic hematopoietic cell transplantation for the treatment of hematological malignancies

Study Chairs: Richard Olsson (Karolinska University Hospital, Centre for Allogeneic Stem Cell Transplantation)
Sonali Chaudhary (Ann & Robert H. Lurie Children’s Hospital of Chicago)
Jeffrey Schriber (Virginia G. Piper Cancer Center)
Olle Ringdén (Karolinska University Hospital, Centre for Allogeneic Stem Cell Transplantation)

MS Statistician: Xiaochun Zhu (xzh@mcw.edu)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Submitted

Abstract: Purpose: Investigate risk factors for primary graft failure (PGF) in a large population undergoing alloHCT with myeloablative conditioning. Patients and Methods: All patients with leukemia, myelodysplasia, or MPD who underwent their first myeloablative alloHCT and reported to the CIBMTR between 1995-2008 (n=23,272) were included. A multivariate logistic risk model for PGF (absolute neutrophil count <0.5x10^9/l by day +28) was performed. Results: PGF was reported in 1,278 (5.5%) patients. PGF was markedly lower in recipients of PBSC compared to BM (2.5 vs. 7.3%; P<0.001). In the multivariate model, a 4-fold increased risk of PGF was observed in MPD (P<0.001), whereas chronic leukemia and myelodysplasia only slightly increased the risk. Other factors associated with higher incidence of PGF included HLA-mismatched unrelated grafts, female donors to male recipients, major ABO-incompatibility, recipient age below 30, and cryopreservation. Among recipients of BM, total nucleated cell doses >2.4 x10^9/kg decreased the rate of PGF (OR 0.72; P<0.001). Moreover, tacrolimus-based immunosuppression, cyclophosphamide / total body irradiation conditioning, or planned granulocyte colony-stimulating factor decreased the risk for PGF. A risk score by day 21 predicted PGF in 34% of patients.

Conclusion: The present analysis reports important risk factors, which allow more informed choices with respect to graft source, donor selection, ABO
matching, and immune suppressive regimens, and the novel risk score by day 21 may support an early initiation of a rescue transplant.

Study # RT09-04 / IB09-06a

Title: Genetic susceptibility to transplant-related mortality after unrelated donor stem cell transplant: Determination of causes of death within first year of transplantation

Study Chair: Theresa Hahn (Roswell Park Cancer Institute)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: Lara Sucheston-Campbell (lara.sucheston@roswellpark.org)
Study Status: Manuscript preparation

Abstract:

Purpose: Clinical trials use adjudication committees to determine study endpoints; however, these are rarely applied to genome-wide association studies (GWAS) despite the risk of over / under-estimation of genetic effects due to misclassification. Using an expert consensus panel, we adjudicated cause-specific death (CSD), which is the primary endpoint for an on-going GWAS of URD-HCT outcomes.

Patients and Methods: Through document review and consensus, three physicians and a clinical epidemiologist adjudicated CSD of T-replete URD-HCT AML, ALL, and MDS patients reported to the CIBMTR. Two cohorts included 3,532 >8/8 HLA-matched URD-HCT recipients from 2000-2011. Concordance was measured between CSD: Disease-related mortality (DRM) and TRM, including GVHD, infection, organ failure, other, reported by the transplant centers and determined by the consensus panel.

Results: Internal and external validity of 1,484 adjudicated cases yielded >95% agreement. For both cohorts, the consensus panel agreed with >99% of deaths reported by transplant centers as DRM and 80% reported as TRM. Hence 20% of TRM deaths reported by transplant centers were reclassified as DRM by the consensus panel. Cohort effects, disease status, and age significantly influenced agreement.

Conclusion: Standard pre-defined criteria for adjudicating CSD led to consistent application of CSD to similar clinical scenarios and clearer delineation of CSD categories. Without adjudication, the TRM category would have been diluted by DRM cases, generated a false genetic correlation between these two outcomes, and reduced the total detectable genetic variance by approximately 30%. Carefully conducted phenotype adjudication is essential prior to GWAS.

Study # RT10-01

Title: C-reactive protein to predict non-relapse mortality after allogeneic hematopoietic cell transplantation

Study Chair: Andrew Artz (University of Chicago School of Medicine)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Manuscript preparation
Abstract: Introduction: HCT entails substantial TRM, justifying continued efforts to better risk stratify patients. Single institutional studies have suggested several clinically available biomarkers of CRP, ferritin, and albumin influence TRM if not OS. We sought to confirm the independent prognostic value of these biomarkers in a large multi-institutional cohort.

Methods: The study population consisted of 784 adults with AML in remission (80%) or MDS (20%) undergoing unrelated donor HCT between 2008 and 2010 and available cryopreserved samples through the CIBMTR repository. CRP and ferritin were quantified by ELISA from cryopreserved plasma whereas albumin levels obtained from center reported data. Correlation studies for biomarkers required log transformation of CRP and ferritin to produce a normal distribution. Multivariate models were fitted separately for each biomarker applying protocol specified thresholds generated from the literature of CRP >10 mg/L, ferritin >2500 ng/mL, albumin <3.5 g/dL on TRM. Further analysis explored optimal cutpoints for this cohort for all significant clinical variables for TRM.

Results: HCT characteristics included a median age of 50 (range 18-78) years, HCT-CI 3 or more in 35%, single allele / antigen mismatch (7/8) in 23%, PB as stem cell source in 83%, and myeloablative conditioning in 72%. Biomarker data were available in 783, 781, and 695 cases for CRP, ferritin, and albumin, respectively. The median values and ranges for each biomarker were as follows: 5.0 mg/L (0.3 - 316) for CRP, 1,148 ng/mL (51 – 14,298) for ferritin, and 3.6 g/dL (0.6-5.3) for albumin. Log transformed CRP and ferritin showed a modest correlation (r=0.35, P<0.001), and log CRP was marginally associated with albumin (r=-0.12, P=0.002). HCT-CI had no correlation to CRP and albumin. Higher ferritin was associated with HCT-CI (P=0.014) and disease (P<0.001). In the entire population, TRM and OS at 2 years were 23% and 54%, respectively. Ferritin had no association with these outcomes, but only 12% had levels above 2,500 by ELISA. The optimal cutpoints for TRM were defined as follows: CRP > 3.67 (HR 1.75, P=0.001); albumin < 3.4 (HR 1.70, P <0.001); and ferritin as a continuous variable (HR 1.30, P=0.008). A risk score was created modeling optimal biomarker thresholds to predict TRM based on the following formula: risk score = 0.44633*I(CRP>3.67)+0.18330*ln(Ferritin)+0.44730*I(albumin<3.4), where “I” is an indicator function and represent 1 or 0 depending on the presence of the abnormal biomarker level in parenthesis. The risk score included adjustment for HCT-CI. The biomarkers did not influence the incidence of relapse or acute GVHD (2-4 or 3-4) with any of these models.

Conclusions: Elevated CRP and ferritin and decreased albumin prior to HCT were associated with impaired transplant survival, primarily through higher TRM. Integration of a biomarker panel in clinical practice once validated can enhance risk-stratification, improve adjustment for comparative studies, and point towards the design of biomarker driven trials.
Study # RT11-01
Title: Risk factors for the development of idiopathic pneumonitis after autologous hematopoietic cell transplantation for lymphoma using BCNU-containing regimens

Study Chairs:
Andrew Lane (Dana Farber Cancer Institute)
Yi-Bin Chen (Massachusetts General Hospital)

MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: Brent Logan (blogan@mcw.edu)
Study Status: Submitted

Abstract:
There are limited data to guide choice of specific high-dose therapy (HDT) regimen prior to autoHCT for patients with HL and NHL. Using the CIBMTR, we studied 4,917 patients (NHL=3,905, HL=1,012) who underwent autoHCT from 1995-2008 using the most common HDT platforms: BEAM (n=1,730), CBV (n=1,853), BuCy (n=789), and TBI-containing (n=545). CBV was divided into CBVhigh and CBVlow based on a BCNU cutoff of 375 mg/m2. We analyzed the impact of regimen on relapse, TRM, PFS, and OS. 1-year TRM ranged from 4-8% and was similar between regimens. Multivariate analysis showed that for NHL, outcomes were similar with BEAM, CBVlow, and BuCy; however, CBVhigh had shorter PFS. 3-year OS for NHL was: BEAM 64%, CBVlow 60%, CBVhigh 52%, BuCy 59% and TBI 59%, with CBVhigh and TBI being inferior. For HL, BuCy and TBI were associated with increased progression. 3-year OS for HL was BEAM 79%, CBVlow 73%, CBVhigh 68%, BuCy 65%, and TBI 47% with BEAM superior to other regimens. The impact of specific autoHCT regimen is different in NHL and HL, and BEAM can be considered the standard based on these results.

Study # RT12-01
Title: Sequence of cyclophosphamide and total body irradiation in evaluation of relapse, mortality, and graft-versus-host disease in patients with acute myeloid leukemia and acute lymphoblastic leukemia undergoing hematopoietic cell transplantation

Study Chairs:
Jennifer Holter Chakrabarty (University of Oklahoma)
George Selby (University of Oklahoma)
Robert Epstein (University of Oklahoma)

MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: Mei-Jie Zhang (meijie@mcw.edu)
Study Status: Submitted

Abstract:
Limited clinical data are available to assess whether the sequencing of Cy and TBI changes outcomes. We, therefore, evaluated the sequence in 1,769 (CyTBI=948, TBICy=821) recipients of related or unrelated HCT who received TBI (1200-1500cGY) for acute leukemia from 2003 to 2010. The two cohorts were comparable for median age, performance score, type of leukemia, first complete remission, Ph+ ALL, HLA matched siblings, bone marrow stem cell source, anti-thymocyte globulin use, TBI dose, and type of GVHD prophylaxis. The sequence of TBI did not significantly affect TRM (24% vs. 23% at 3 years, p=0.67; RR 1.01,
8.15 REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE WORKING COMMITTEE

p=0.91), leukemia relapse (27% vs. 29% at 3 years, p=0.34; RR 0.89, p=0.18), leukemia-free survival (49% vs. 48% at 3 years, p=0.27; RR 0.93, p=0.29), chronic GVHD (45% vs. 47% at 1 year, p=0.39; RR 0.9, p= 0.11) or overall survival (53% vs. 52% at 3 years, p=0.62; RR 0.96, p=0.57) for CyTBI and TBICy, respectively. Corresponding cumulative incidences of veno-occlusive disease (VOD) were 4% and 6% at 100days (p=0.08). This study demonstrates that the sequence of Cy and TBI does not impact transplant outcomes and complications in patients with acute leukemia undergoing HCT with myeloablative conditioning.

STUDIES IN PROGRESS

Study # RT09-04 / IB09-06b
Title: Genetic susceptibility to transplant-related mortality after unrelated donor stem cell transplant
Study Chair: Theresa Hahn (Roswell Park Cancer Institute)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: Lara Sucheston-Campbell (lara.sucheston@roswellpark.org)
Study Status: Analysis in progress

Study # RT12-03
Title: Transplant in older adults: is it feasible in those 70 years and older?
Study Chairs: Lori Muffly (University of Chicago School of Medicine)
Andrew Artz (University of Chicago School of Medicine)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: TBD
Study Status: Data file preparation

Study # RT13-01
Title: In-hospital mortality among allogeneic hematopoietic cell transplant recipients that develop critical illness in the early post-transplantation period: a nationwide temporal trend analysis (1998 - 2010)
Study Chair: Sameer Kadri (National Heart Lung and Blood Institute - NIH)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # RT13-02
Title: Safety of high-dose total body irradiation followed by an allogeneic hematopoietic cell transplant for hematologic malignancies
Study Chair: Mitchell Sabloff (University of Ottawa and Ottawa Hospital Research Institute)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development
Study # RT14-01
Title: Trends and risk factors for infant mortality following allogeneic hematopoietic cell transplant: case-control study
Study Chairs: Prakash Satwani (Columbia University Medical Center)
Suhag Parikh (Duke University Medical Center)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # RT14-02
Title: Endothelial injury complications after allogeneic hemotapoietic cell transplantation
Study Chairs: Stella Davies (Cincinnati Children’s Hospital Medical Center)
Wichai Chinratanalab (Vanderbilt University Medical Center)
Sonata Jodele (Cincinnati Children’s Hospital Medical Center)
Muthalagu Ramanathan (UMass Memorial Medical Center)
Benjamin Laskin (Cincinnati Children’s Hospital Medical Center)
MS Statistician: Xiaochun Zhu (xzhu@mcw.edu)
PhD Statistician: TBD
Study Status: Protocol development

Study # RT14-03
Title: Multicenter cohort identification of transplant-related risk-factors for infection, organ failure, and mortality among pediatric hematopoietic stem cell transplant patients requiring intensive care unit admission
Study Chairs: Christopher Dvorak (University of California San Francisco Medical Center)
Matthew Zinter (University of California San Francisco Medical Center)
Anil Sapru (University of California San Francisco Medical Center)
MS Statistician: TBD
PhD Statistician: TBD
Study Status: Protocol development
APPENDIX A: CIBMTR 2014 FACTS

The following data provide a numerical listing of the CIBMTR’s 2014 information.

CIBMTR Research Database
• ~350 participating centers
• >390,000 HCT recipients
• ~20,500 new HCT recipients annually

Clinical Outcomes Research Program Studies
• >1,700 researchers participate in Working Committees
• 209 Working Committee studies in progress
• 156 proposals submitted, 88 presented, and 40 accepted for the 2014 Working Committee meetings
• 156 proposals submitted for the 2015 Working Committee meetings

Clinical Trials Support Program
BMT CTN
• 1 new trial opened to accrual, bringing the total number of launched trials to 34
• 1,316 patients accrued to trials, increasing the total number of accrued patients to 7,303
• 11 open protocols managed with overall accrual for open studies at about 175% of projections

RCI BMT
• 2,477 patients accrued to 5 open protocols
• 3 protocols completed accrual
• 12 protocols completed analysis and submitted abstracts

Immunobiology Research Program – Research Repository
• 1,815,832 aliquots
• 18,901 cell lines
• 54,556 samples from unrelated donors and 3,870 from related donors
• 52,626 samples from unrelated recipients and 4,113 from related recipients
• 9,643 samples from unrelated cord blood units
• 31,464 samples from complete unrelated adult donor-recipient pairs, 3,483 from complete related donor-recipient pairs, and 3,322 from unrelated cord-recipient pairs

Publications and Presentations
• 81 CIBMTR publications
  o 48 Clinical Outcomes Research Program Scientific Working Committee publications
  o 10 BMT CTN publications
  o 2 RCI BMT publications
  o 2 Health Services Research Program publications
  o 4 Statistical Methodology Research Program publications
  o 2 Bioinformatics publications
  o 13 Coordinating Center publications
• 46 presentations by CIBMTR and BMT CTN principal investigators
  o 16 abstracts (13 oral and 3 poster) presented at the 2014 BMT Tandem Meetings
  o 23 abstracts (15 oral and 8 poster) presented at the 2014 ASH Annual Meeting
### APPENDIX B1: US CENTERS

The following table lists the US-based transplant centers that submit data to the CIBMTR Research Database for matched unrelated donor (MUD), related donor, and autologous transplants. Centers submit data at two levels: TED and CRF (Section 2.1.2).

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<th>State</th>
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<th>REALTED</th>
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## APPENDIX B2: INTERNATIONAL CENTERS

The following table lists the international transplant centers that submit data to the CIBMTR Research Database for matched unrelated donor (MUD), related donor, and autologous transplants. Centers submit data at two levels: TED and CRF (Section 2.1.2).

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APPENDIX C3: COORDINATING CENTER PERSONNEL

The CIBMTR Coordinating Center resides on two campuses: one is located at MCW in Milwaukee, WI, and the other is located at NMDP / Be The Match in Minneapolis, MN. The Coordinating Center provides administrative, statistical, data management, clinical trials, IT, and personnel support for CIBMTR activities, and it benefits from a unique, collegial partnership with the Division of Biostatistics of MCW.

CIBMTR Milwaukee has approximately 70 employees and is an academic division of the MCW Department of Medicine. The Milwaukee office receives administrative support from the MCW departments of Grants and Contracts, Development, Office of Technology Development, Public Affairs, Human Resources and the Department of Medicine Administration. CIBMTR Minneapolis has approximately 120 employees, and several NMDP / Be The Match departments provide substantial support for CIBMTR activities, including Finance, Contracts, Bioinformatics, and Marketing and Communications.

Scientific Directors

CIBMTR Scientific Directors provide scientific and clinical leadership for the organization's research activities. In 2014, Bronwen Shaw, MD, PhD, joined the Milwaukee campus and Linda Burns, MD, joined the Minneapolis campus.

Milwaukee Campus Scientific Directors

- Mary M. Horowitz, MD, MS, is Chief Scientific Director of the CIBMTR, the Robert A. Uihlein Professor of Hematologic Research at MCW, Chief of the Division of Hematology and Oncology at MCW, and an attending physician in the MCW HCT program. She is Principal Investigator for the Data and Coordinating Center of the BMT CTN and Research Director for the SCTOD. Dr. Horowitz received an MD from MCW in 1980 and an MS in biostatistics and clinical epidemiology from MCW in 1991. She has been with the IBMTR / CIBMTR since 1985.
- J. Douglas Rizzo, MD, MS, is Professor of Medicine at MCW, Senior Scientific Director and Principal Investigator for the SCTOD, Associate Director of Clinical Operations for the Froedtert and MCW Cancer Center, and an attending physician in the MCW HCT program. Dr. Rizzo received an MD from Johns Hopkins University Hospital in 1990 and an MS in epidemiology from MCW in 2005. He completed a Robert Wood Johnson fellowship in epidemiology and cost-effectiveness research at Johns Hopkins University in 1998. He has been with the IBMTR / CIBMTR since 2003.
- Mary Eapen, MBBS, MS, is Professor of Medicine at MCW, Senior Scientific Director of CIBMTR Research, and an attending physician in the MCW HCT program. She is Scientific Director for the Graft Sources and Manipulation Working Committee as well as the Primary Immune Deficiencies, Inborn Errors of Metabolism and Other Non-Malignant Marrow Disorders Working Committee. Dr. Eapen is also Protocol Officer for several BMT CTN trials. She received an MBBS from Ahmadu Bello University, School of Medicine in Zaria, Nigeria in 1986, completed a residency in pediatrics at the University of Minnesota in 1997, and completed a fellowship in pediatric hematology/oncology and an MS in Clinical Research at the University of Minnesota in 2000. She has worked with the IBMTR / CIBMTR since 2000.
- **Parameswaran Hari, MD, MS,** is Professor of Medicine in the Division of Hematology and Oncology, and in November 2012, he was named the first Armand J. Quick / William F. Stapp Professor in Hematology at MCW. Dr. Hari is Section Head of Hematologic Malignancies and BMT as well as Clinical Director of the Adult Blood and Marrow Transplant Program at MCW. He is also Scientific Director of the Plasma Cell Disorders and Adult Solid Tumors Working Committee. Dr. Hari received an MD from the Jawaharlal Institute of Post Graduate Medicine, India, in 1995 and an MS in epidemiology from MCW in 2006. He completed fellowships in internal medicine and hematology at the Royal College of Physicians and the Royal College of Pathologists in the United Kingdom in 1997 and medical oncology and transplantation at MCW in 2004. He has worked with the CIBMTR since 2004.

- **Bronwen Shaw MD, PhD,** is Professor of Medicine at MCW and Scientific Director of the Late Effects and Quality of Life Working Committee as well as the Donor Health and Safety Working Committee. Dr. Shaw received an MBChB from the University of Cape Town, South Africa, in 1993. All of her subsequent postgraduate hematology specialist training was completed in London, UK, where she also received her PhD in Clinical Sciences and Immunology from University College London in 2004. Her PhD was entitled, “Understanding the immunogenetic and clinical factors which influence the outcome of haematopoietic stem cell transplantation using unrelated donors.” She joined the CIBMTR in 2014.

- **Marcelo Pasquini, MD, MS,** is Associate Professor of Medicine at MCW, Senior Scientific Director of CIBMTR Clinical Trials Support – BMT CTN, and an attending physician in the MCW HCT program. He is Scientific Director for the Autoimmune Diseases and Cellular Therapies Working Committee as well as the Regimen-Related Toxicity and Supportive Care Working Committee. He is also Protocol Officer and Medical Monitor for the BMT CTN and CIBMTR representative to the Worldwide Network for Blood and Marrow Transplantation. Dr. Pasquini received an MD from the State University of Londrina in Brazil in 1997 and an MS degree in epidemiology from MCW in 2006. He completed a residency in internal medicine at the University of Miami / Jackson Memorial Hospital in 2001, a fellowship in hematology/oncology at the University of Utah in 2004, and a fellowship in blood and marrow transplantation at MCW in 2005, after which he joined the CIBMTR Coordinating Center.

- **Mehdi Hamadani, MD,** is Associate Professor of Hematology / Oncology at MCW and an attending physician in the MCW HCT program. He is Scientific Director of the Lymphoma Working Committee. Dr. Hamadani received his MBBS from Kin Edward Medical College in Lahore, Pakistan, in 2001. He completed a residency in internal medicine at the University of Oklahoma in 2006 and a fellowship in hematology/oncology at Ohio State University in 2009. Dr. Hamadani has worked with the CIBMTR since 2013.

- **Elizabeth Thiel, MD, MS,** is Associate Professor of Hematology / Oncology at MCW and an attending physician in the MCW Palliative Care program. She is Scientific Director of the Pediatric Cancer Working Committee. Dr. Thiel received an MD from the MCW in 2004 and an MS in epidemiology from MCW in 2010. She completed a residency in pediatrics from MCW in 2007, a fellowship in pediatric hematology/oncology at MCW in 2010, and a fellowship in palliative medicine at MCW in 2011. Dr. Thiel has worked with the CIBMTR since 2013.

- **Anita D’Souza, MD,** is Assistant Professor of Hematology / Oncology at MCW and an attending physician in the MCW HCT program. She is Assistant Scientific Director of the
Plasma Cell Disorders and Adult Solid Tumors Working Committee. Dr. D’Souza received her MBBS from Goa Medical College, Goa, India, in 1995. She completed residencies in internal medicine at Goa Medical College, Goa, India, in 2001 and William Beaumont Hospital, Royal Oak, MI, in 2010, and a fellowship in hematology / oncology at Mayo Clinic, Rochester, MN, in 2010. Dr. D’Souza has worked with the CIBMTR since 2013.

- **Wael Saber, MD, MS**, is Assistant Professor of Hematology / Oncology at MCW and an attending physician in the MCW HCT program. He is Scientific Director for the Chronic Leukemia and Health Services and International Issues Working Committees and Assistant Scientific Director for the Acute Leukemia Working Committee. Dr. Saber received an MBBCh from Ain Shams University, Egypt, in 1995 and an MS in epidemiology from the University of Wisconsin in 2008. He completed a residency in internal medicine at the Cleveland Clinic Foundation in 2001 and a hematology fellowship at the University of Wisconsin in 2009. Dr. Saber has worked with the CIBMTR since 2009.

**Minneapolis Campus Scientific Directors**

- **Dennis Confer, MD**, is Chief Medical Officer of NMDP / Be The Match and Associate Scientific Director of the CIBMTR. He is Co-PI of the Data and Coordinating Center of the BMT CTN and Scientific Director of the Donor Health and Safety Working Committee. He is also Treasurer of the Executive Board of the Worldwide Network for Blood and Marrow Transplantation. In 1977, Dr. Confer received an MD from, and in 1980 he completed a residency at, the University of Nebraska Medical Center. In 1983, he completed a fellowship in hematology/oncology at the University of Minnesota Medical School. He has worked with the NMDP / Be The Match and the CIBMTR since 1993.

- **Daniel Weisdorf, MD**, is Professor of Medicine; Chief of the Division of Hematology, Oncology, and Transplant; Director of the Adult Blood and Marrow Transplant Program; and Associate Chair of Clinical Research in the Department of Medicine at the University of Minnesota. He is Senior Research Advisor to the CIBMTR and Scientific Director of the Acute Leukemia Working Committee. Dr. Weisdorf is Immediate Past President of the American Society for Blood and Marrow Transplantation. He received an MD from Chicago Medical School in 1975, completed a residency at Michael Reese Hospital in Chicago in 1978, and completed a fellowship in hematology / oncology at the University of Minnesota in 1981. Dr. Weisdorf has worked with the NMDP / Be The Match and the CIBMTR since 2000.

- **Linda Burns, MD**, is Vice President of NMDP / Be The Match and Senior Scientific Director of the Health Services Research Program of the CIBMTR. She served as the President of the American Society for Blood and Marrow Transplantation from 2010-2013 and President of the American Society of Hematology in 2014. Dr. Burns received an MD from the University of Missouri – Columbia in 1981. She completed a residency and chief residency in internal medicine as well as a fellowship in hematology / oncology at the University of Iowa from 1981-1988. Dr. Burns joined the CIBMTR in December 2014.

- **Mukta Arora, MD, MBBS, MS**, is Associate Professor of Medicine at the University of Minnesota. She is Scientific Director of the Graft-versus-Host Disease Working Committee. Dr. Arora received an MD from the University of Kanpur, India, in 1997 and an MS in Clinical Research from the University of Minnesota in 2000. She completed residency and fellowship training in hematology, oncology, and transplantation at the University of Minnesota in 2003. Dr. Arora has worked with the CIBMTR since 2004.
Stephen Spellman, MBS, is Director of Immunobiology and Observational Research and Principal Investigator for the NMDP / Be The Match Research Sample Repository. He leads the CIBMTR Immunobiology and Observational Research team and oversees the NMDP / Be The Match Research Sample Repository for the CIBMTR and the BMT CTN. Mr. Spellman is also Co-Scientific Director of the Graft-versus-Host Disease and Immunobiology Working Committees and staff liaison to the NMDP / Be The Match Cord Blood Advisory Group Research subcommittee and Histocompatibility Advisory Group (also known as the CIBMTR Immunobiology Steering Committee). Additionally, he is Program Manager for the NMDP / Be The Match Office of Naval Research Grant. Mr. Spellman received an MBS in immunobiology and molecular biology in 2000 from the University of Minnesota. He has worked with the NMDP / Be The Match and the CIBMTR since 2000.

Other Scientific Directors

Stephanie J. Lee, MD, MPH, is Professor of Medicine at the University of Washington and a Member at Fred Hutchinson Cancer Research Center in Seattle, Washington. She is Senior Scientific Director of CIBMTR Immunobiology Research and Scientific Director of the Immunobiology Working Committee. Dr. Lee received an MD from Stanford University in 1990 and an MPH from Harvard School of Public Health in 1996. She completed a fellowship at Brigham Women’s Hospital in hematology/oncology in 1996. She has worked with the CIBMTR since 2008.

Marcie Riches, MD, MS, is Associate Member in the Department of Blood and Marrow Transplantation and Director of BMT Clinical Research at Moffitt Cancer Center in Florida. She is Scientific Director of the Infection and Immune Reconstitution Working Committee and Protocol Officer and Medical Monitor for several BMT CTN trials. Dr. Riches received an MD from the University of Kentucky in 1997 and an MS in clinical investigation from Northwestern University in 2004. She completed fellowships in hematology/oncology and hematopoietic stem cell transplantation at Northwestern University in 2003 and 2004, respectively. She has worked with the CIBMTR since 2004.

Biostatistics Staff

CIBMTR Biostatisticians provide statistical support and analyses for all CIBMTR research activities.

Mei-Jie Zhang, PhD, is Professor of the Institute for Health and Society and Interim Chief Statistical Director for the CIBMTR. He is also Biostatistician for the Acute Leukemia and Graft Sources and Manipulation Working Committees. Dr. Zhang received an MS and PhD from Florida State University in 1989 and 1991, respectively. His primary research interests are survival analysis and analysis of HCT transplant data that involve censored and/or truncated time-to-event data and competing risk events. Dr. Zhang has worked with the IBMTR/CIBMTR since 1991.

Brent Logan, PhD, is Professor of Biostatistics at MCW and Biostatistician for the Donor Health and Safety Working Committee and the Regimen-Related Toxicity and Supportive Care Working Committee. Dr. Logan is also Lead Statistician for the BMT CTN and Statistical Consultant to the NMDP / Be The Match. He received an MS and PhD from Northwestern University in 1998 and 2001, respectively. Dr. Logan’s expertise is in clinical trial design and analysis of multiple endpoints. He led the development of the statistical approach for Center-
Specific Outcomes Analysis (now the purview of the CIBMTR through the SCTOD). Dr. Logan has worked with the IBMTR/CIBMTR since 2001.

- **Tao Wang, PhD**, is Associate Professor of Biostatistics at MCW and Biostatistician for the Graft-versus-Host Disease and Immunobiology Working Committees. Dr. Wang received an MS from Southeastern University in Nanjing, China, in 1990 and a PhD from North Carolina State University in 2001. His research focus is statistical genetics. He has worked with the IBMTR/CIBMTR since 2001.

- **Kwang Woo Ahn, PhD**, is Associate Professor of Population Health and Biostatistics at MCW and Biostatistician for the Chronic Leukemia, Infection and Immune Reconstitution, and Lymphoma Working Committees. Dr. Ahn received an MS and PhD from the University of Iowa in 2005 and 2008, respectively. He has worked with the CIBMTR since 2008.

- **Ruta Brazauskas, PhD**, is Assistant Professor of Biostatistics at MCW and Biostatistician for the Health Services and International Issues Working Committee as well as the Late Effects and Quality of Life and Autoimmune Disorders and Cellular Therapies Working Committees. Dr. Brazauskas received an MS from the University of Texas at Dallas in 1999 and a PhD from MCW in 2003. She has worked with the CIBMTR since 2008.

- **Jennifer Le-Rademacher, PhD**, is Assistant Professor of Biostatistics at MCW and Biostatistician for the Pediatric Cancer Working Committee as well as the Primary Immune Deficiencies, Inborn Errors of Metabolism, and Non-Malignant Marrow Disorders Working Committee and Plasma Cell Disorders and Adult Solid Tumors Working Committee. She also provides statistical support to the BMT CTN and the RCI BMT. Dr. Le-Rademacher received an MS from Georgia State University in 2004 and a PhD from University of Georgia in 2008. She has worked with the CIBMTR since 2009.

The following Master’s-level biostatisticians work in the CIBMTR Coordinating Center on the Milwaukee campus:

- Waleska S. Pérez, MPH (Associate Statistical Director; joined IBMTR in 1998)
- Jeanette Carreras, MPH (since 2003)
- Wensheng He, MS (since 2006)
- Min Chen, MS (since 2008)
- Xiaochun Zhu, MS (since 2009)
- Xiaobo Zhong, MS (since 2010)
- Sandra Tomany Korman, MS (since 2011)
- Junfang Chen, MS (since 2012)
- Mingwei Fei, MS (since 2012)
- Michael Hemmer, MS (since 2012)
- Hailin Wang, MS (since 2012)
- Jiaxing Huang, MS (since 2013)
- Naya He, MPH (since 2014)
- Heather Millard, MPH (since 2014)
- Alyssa DiGilio, MS (starting in 2015)

The following Master’s-level biostatisticians work in the CIBMTR Coordinating Center on the Minneapolis campus:

- Michael Haagenson, MS (since 2000)
- Pintip Chitphakdithai, PhD (since 2004)
• Deidre Kiefer, MPH (since 2013)
• Rachel Fonstad, MS (since 2013)

Other Key CIBMTR Milwaukee Staff

• **Patricia Steinert, PhD, MBA,** is Research Administrator of CIBMTR Milwaukee. Dr. Steinert is responsible for oversight of the administrative, scientific, and statistical support activities on the Milwaukee campus of the CIBMTR, which include data operations, development, observational research and prospective research, IT and meetings. She works in close collaboration with her counterpart on the Minneapolis campus, Roberta King. Dr. Steinert received her PhD in Health Sciences and Health Economics from the University of Wisconsin-Milwaukee in December 2012 and her MBA from the University of Illinois at Chicago in 1987. She has worked with the CIBMTR since 2006.

• **Erik Bergman, MBA, MS,** is Director of the Milwaukee-based IT team. He works closely with his counterpart on the Minneapolis campus, Colleen O’Neill. Mr. Bergman leads the Milwaukee-based staff, which is organized in four teams: Database, Applications Development, Technology Services, and Project Management. He oversees management of the Observational Research Database, including extraction of data from source systems, and their transformation and loading to the Database. He is also responsible for data retrievals from the Database as well as key solutions for sharing data with our many stakeholders. Mr. Bergman received an MS in Biotechnology from the University of Wisconsin-Madison School of Medicine and Public Health in 2006 and an MBA from Marquette University in 1999. Before joining the CIBMTR in 2013, he served as Manager of Information Systems at the Blood Center of Wisconsin, its Blood Research Institute, and its Medical Sciences Institute. Mr. Bergman has many years of experience developing and operationalizing business and technology strategies in the research environment.

• **Janet Brunner-Grady, PA-C,** is Program Director of Data Operations at the CIBMTR Milwaukee campus. She works closely with her counterpart on the Minneapolis campus, Marie Matlack. Ms. Brunner manages the CIBMTR CRCs, develops training programs, and monitors transplant center CPI. She also assists CRC staff on both campuses with clinical transplant-related questions. Ms. Brunner is Six Sigma Green Belt-certified and facilitates process reviews using Six Sigma and Lean techniques. Her experience includes many years of clinical practice as an HCT Physician’s Assistant, and she continues to work as a staff Physician Assistant on the MCW inpatient BMT Unit. She has worked with the CIBMTR since 2009.

• **Sue Lorenz** is Business Manager for CIBMTR. She is responsible for overseeing the program’s financial, personnel, and office practices to ensure compliance with institutional and federal policies and procedures. Ms. Lorenz works closely with her counterparts in the Contracts and Finance Departments on the Minneapolis campus to coordinate inter-institutional CIBMTR grants and contracts, and she represents the CIBMTR in all financial matters to the NIH and other contracted organizations. Ms. Lorenz has worked with MCW since 1988, and her roles include Administrative Coordinator for a Clinical Department, Budget Analyst for central Finance and Administration, and Center Administrator for the General Clinical Research Center. She has worked with the CIBMTR since 2006.

• **Waleska S. Pérez, MPH,** is Associate Statistical Director of CIBMTR, working under the direction of the Chief Scientific Director and Chief Statistical Director. She works closely with
her counterpart on the Minneapolis campus, Stephen Spellman. Ms. Perez oversees the Master’s-level biostatisticians and provides administrative oversight of the Clinical Outcomes Research Program. She received her MPH in Biostatistics in 1996 from the University of Puerto Rico Graduate School of Public Health. Ms. Perez has worked with the IBMTR / CIBMTR since 1998.

Other Key CIBMTR Minneapolis Staff

- **Roberta King, MPH**, is Vice President of CIBMTR Minneapolis. Ms. King is responsible for oversight of the administrative, scientific, and statistical support activities on the Minneapolis campus of the CIBMTR, which include research administration, human subject protection program, data management, auditing and monitoring, observational research, prospective research, and IT. She also serves as Staff Liaison to the NMDP / Be The Match Donor and Patient Safety Monitoring Advisory Group. Ms. King received her master’s in Public Health in 1988 from the University of Minnesota School of Public Health. She has worked with the National Marrow Donor Program since 1990 and served in its research area since 1993.

- **Debra Christianson** is Senior Manager of Auditing and Monitoring for CIBMTR Minneapolis. Her group is responsible for monitoring RCI BMT clinical trials and conducting on-site source document audits on data submitted to the research database as well as writing the FormsNet instruction manual. Ms. Christianson received Associate and Applied Science degrees from North Hennepin Community College/Anoka Vo-Tech School in 1985 and a BA in Independent Studies and Computer Science from Metropolitan State University in 1997. She is a certified Registered Health Information Technician through the American Health Information Management Association. Ms. Christianson has worked with the NMDP / Be The Match and the CIBMTR since 1997.

- **Rebecca Drexler** is Senior Manager of Prospective Research on the Minneapolis campus. She is responsible for activities of the RCI BMT, including the Survey Research Group, and she oversees the administration of the Clinical Trials Advisory Committee. Ms. Drexler has more than 25 years of experience in medical research as well as clinical and regulatory affairs. She joined the research department at NMDP / Be The Match in 2001 to manage clinical trials, and she has worked with the CIBMTR since 2004.

- **Marie Matlack** is Senior Manager of Data Management for the CIBMTR Minneapolis campus. She works closely with her counterpart on the Milwaukee campus, Janet Brunner. Ms. Matlack manages CRCs and Senior Research Programmers as well as data entry and imaging staff. She oversees form revision and development and the CPI program. She also works with the Minneapolis IT staff to develop enhancements to FormsNet. Ms. Matlack is Six Sigma Green Belt-certified and facilitates process reviews using Six Sigma and Lean techniques. She has worked with NMDP / Be The Match and the CIBMTR since 1990.

- **Colleen O’Neill** is Director of the Minneapolis-based IT staff. She works closely with her counterpart on the Milwaukee campus, Erik Bergman. Ms. O’Neill leads the CIBMTR IT Minneapolis staff, including project managers, programmer analysts, business systems and data analysts, quality assurance analysts, metadata analysts, and managers. She is responsible for development, implementation, and support for CIBMTR electronic data management, capture and messaging systems (FormsNet and AGNIS), data marts and data warehouses, infrastructure for these applications, and the curation of common data elements within the Cancer Data Standards Registry and Repository. Ms. O’Neill earned certification as a Project
Management Professional in 2002 and worked as a senior consultant for eight years before joining the CIBMTR in 2010.
APPENDIX D1: ADVISORY COMMITTEE MEMBERSHIP

The Advisory Committee provides oversight for CIBMTR policies and scientific agenda and also partners with the Working Committees to prioritize scientific studies. Members are elected to three-year terms by the CIBMTR Assembly and must be from qualifying CRF centers. All Advisory Committee terms begin on March 1. For more information, see Section 1.5.2.

**ELECTED MEMBERS**

*Chair*  
Paul Martin, MD, Fred Hutchinson Cancer Research Center, Seattle, WA

*Immediate Past Chair*  
Thomas Shea, MD, University of North Carolina at Chapel Hill, NC

**VICE CHAIRS**

*North America*  
Helen Heslop, MD, Baylor College of Medicine Center for Cell and Gene Therapy, Houston, TX

*Europe*  
David Marks, MD, PhD, University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom

*Central/South America*  
Carmem Bonfim, MD, Hospital de Clínicas – UFPR, Curitiba, Brazil

*Asia/Africa/Australia*  
Alok Srivastava, MD, Christian Medical College Hospital, Vellore, India

**MEMBERS AT LARGE**

*North America*  
Mitchell Horwitz, MD, Duke University Medical Center, Durham, NC

Michael Lill, MD, Cedars-Sinai Medical Center, Los Angeles, CA

Philip McCarthy, MD, Roswell Park Cancer Institute, Buffalo, NY

Joseph Pidala, MD, MS, H Lee Moffitt Cancer Center and Research Institute, Tampa FL

Michael Pulsipher, MD, Primary Children’s Hospital, Salt Lake City, UT

Bipin Savani, MD, Vanderbilt University Medical Center, Brentwood, TN

*Non-North America*  
Jan Cornelissen, MD, PhD, Dr. Daniel Den Hoed Cancer Center, Rotterdam, Netherlands

Ernst Holler, MD, Klinikum der Universitaet Regensburg, Germany

Shinichiro Okamoto, MD, PhD, Keio University, Shinjuku-ku Tokyo, Japan

Miguel Sanz, Hospital Universitario La Fe, Valencia, Spain

Jeffrey Szer, MD, Royal Melbourne Hospital City Campus, Victoria, Australia

Andre Tichelli, PhD, MD, University Hospital, Basel, Switzerland

**APPOINTED MEMBERS**

*ASBMT Representative*  
Christopher Bredeson, MD, MSc, The Ottawa Hospital Blood & Marrow Transplant Program, Ottawa, Canada
Bioethicist                        Steven Joffe, MD, MPH, Abramson Cancer Center University of Pennsylvania Medical Center, Philadelphia, PA

Business Representative          Theresa Franco, MSN, BSN, Nebraska Medicine, Omaha, NE

Collection Center Representative Lee Ann Weitekamp, MD, Michigan Blood Cord Blood Bank, Grand Rapids, MI

Cord Blood Bank Representative   Elizabeth Shpall, MD, MD Anderson Cord Blood Bank, Houston, TX

Donor Center Representative      Jason Gangewere, National Marrow Donor Program, Minneapolis, MN

Patient/Family Representatives    James Omel, MD, Co-Chair, Consumer Advocacy Committee
                                    Maureen Beaman, MBA, Co-Chair, Consumer Advocacy Committee

EX OFFICIO MEMBERS

Executive Director                Jeffrey Chell, MD, NMDP / Be The Match, Minneapolis, MN

Chief Scientific Director         Mary M. Horowitz, MD, MS, CIBMTR, Milwaukee, WI

Chief Statistical Director        Mei-Jie Zhang, PhD, CIBMTR, Milwaukee, WI

Senior Scientific Director Data Operations J. Douglas Rizzo, MD, MS, CIBMTR, Milwaukee, WI

Associate Scientific Director CIBMTR Minneapolis Dennis Confer, MD, CIBMTR, Minneapolis, MN

Senior Research Advisor           Daniel Weisdorf, MD, CIBMTR, Minneapolis, MN

Research Administrator CIBMTR Milwaukee Patricia Steinert, PhD, MBA, CIBMTR, Milwaukee, WI

Vice President CIBMTR Minneapolis Roberta King, CIBMTR, Minneapolis, MN

Vice President Patient Services   Elizabeth Murphy, EdD, RN, NMDP / Be The Match, Minneapolis, MN

NMDP/HRSA Project Officer         Shelley Grant, MHSA

NMDP/Navy Project Officer         Robert Hartzman, MD, Capt. MC, USN (ret)

MCW/HRSA Project Officer          Nawraz Shawir, MBBS

MCW/NCI Project Officer           Roy Wu, PhD

MCW/NHLBI Project Officer         Nancy DiFronzo, PhD

MCW/NIAID Project Officer         Linda Griffith, MD, PhD

Nominating Committee Chair        Stella Davies, PhD, MBBS, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
APPENDIX D2: EXECUTIVE COMMITTEE MEMBERSHIP

The CIBMTR Executive Committee, a subcommittee of the Advisory Committee, ensures that the organization carries out its mission and adheres to CIBMTR policies and procedures; it also provides advice and counsel to the CIBMTR Coordinating Center. All Executive Committee terms begin on March 1. For more information about the Executive Committee, see Section 1.5.2.1.

ELECTED MEMBERS

Chair          Paul Martin, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Immediate Past Chair  Thomas Shea, MD, University of North Carolina at Chapel Hill, NC

VICE CHAIRS

North America  Helen Heslop, MD, Baylor College of Medicine Center for Cell and Gene Therapy, Houston, TX
Europe         David Marks, MD, PhD, University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom
Central/South America  Carmem Bonfim, MD, Hospital de Clinicas – UFPR, Curitiba, Brazil
Asia/Africa/Australia  Alok Srivastava, MD, Christian Medical College Hospital, Vellore, India

APPOINTED MEMBERS

ASBMT Representative  Christopher Bredeson, MD, MSc, The Ottawa Hospital Blood & Marrow Transplant Program, Ottawa, Canada
Bioethicist            Steven Joffe, MD, MPH, Abramson Cancer Center University of Pennsylvania Medical Center, Philadelphia, PA
Business Representative  Theresa Franco, MSN, BSN, Nebraska Medicine, Omaha, NE
Collection Center Representative  Lee Ann Weitekamp, MD, Michigan Blood Cord Blood Bank, Grand Rapids, MI
Cord Blood Bank Representative  Elizabeth Shpall, MD, MD Anderson Cord Blood Bank, Houston, TX
Donor Center Representative  Jason Gangewere, National Marrow Donor Program, Minneapolis, MN
Patient/Family Representatives  James Omel, MD, Co-Chair, Consumer Advocacy Committee  Maureen Beaman, MBA, Co-Chair, Consumer Advocacy Committee

EX OFFICIO MEMBERS

Executive Director  Jeffrey Chell, MD, NMDP / Be The Match, Minneapolis, MN
Chief Scientific Director  Mary M. Horowitz, MD, MS, CIBMTR, Milwaukee, WI
Chief Statistical Director  Mei-Jie Zhang, PhD, CIBMTR, Milwaukee, WI
Senior Scientific Director Data Operations
J. Douglas Rizzo, MD, MS, CIBMTR, Milwaukee, WI

Associate Scientific Director CIBMTR Minneapolis
Dennis Confer, MD, CIBMTR, Minneapolis, MN

Senior Research Advisor
Daniel Weisdorf, MD, CIBMTR, Minneapolis, MN

Research Administrator CIBMTR Milwaukee
Patricia Steinert, PhD, MBA, CIBMTR, Milwaukee, WI

Vice President CIBMTR Minneapolis
Roberta King, CIBMTR, Minneapolis, MN

Vice President Patient Services
Elizabeth Murphy, EdD, RN, NMDP / Be The Match, Minneapolis, MN

NMDP/HRSA Project Officer
Shelley Grant, MHSA

NMDP/Navy Project Officer
Robert Hartzman, MD, Capt. MC, USN (ret)

MCW/HRSA Project Officer
Nawraz Shawir, MBBS

MCW/NCI Project Officer
Roy Wu, PhD

MCW/NHLBI Project Officer
Nancy DiFronzo, PhD

MCW/NIAID Project Officer
Linda Griffith, MD, PhD

Nominating Committee Chair
Stella Davies, PhD, MBBS, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
APPENDIX D3: CONSUMER ADVOCACY COMMITTEE MEMBERSHIP

The Consumer Advocacy Committee communicates CIBMTR research results and data to the non-medical community and provides patient and donor perspectives during the development of the CIBMTR research agenda. For more information, see Section 1.5.2.2.

CO-CHAIRS

James Omel, MD
Maureen Beaman, MBA

MEMBERS

Beatrice Abetti, MSW, Leukemia and Lymphoma Society
Jack Aiello, MS
Richard Boyajian, RN, ANP, MS, Dana-Farber Cancer Institute
Gerardo Camarillo, JD, MD Anderson Cancer Center
Jeffrey Haertling, ARK Air Express
Hilary Hall, Dana-Farber Cancer Institute
Barry Schatz, Cardinal Bernardin Cancer Center, Loyola University Medical Center

SCIENTIFIC DIRECTOR

J. Douglas Rizzo, MD, MS, CIBMTR Milwaukee

EX OFFICIO MEMBERS

Robyn Ashton, RN, MSN, HRSA
Jeffrey Chell, MD, NMDP / Be The Match
Dennis Confer, MD, NMDP / Be The Match
Ellen Denzen, (NMDP / Be The Match liaison) NMDP / Be The Match
Carol Doleysh, (CIBMTR liaison) CIBMTR Milwaukee
Rebecca Drexler, CIBMTR Minneapolis
Jessica Gillis-Smith, MPH, CIBMTR Milwaukee
Shelley Grant, MHSA, HRSA
Darlene Haven, NMDP / Be The Match
Mary Horowitz, MD, MS, CIBMTR Milwaukee
Elizabeth Murphy, EdD, RN, (NMDP / Be The Match liaison) NMDP / Be The Match
Nawraz Shawir, HRSA
APPENDIX D4: NOMINATING COMMITTEE MEMBERSHIP

The Nominating Committee consists of five members elected by the CIBMTR Assembly, and all terms begin on March 1. For more information about the Nominating Committee, see Section 1.5.3.

CHAIR

   Stella Davies, PhD, MBBS, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

MEMBERS

   Karen Ballen, MD, Massachusetts General Hospital, Boston MA
   Koen van Besien, MD, New York Presbyterian Hospital at Cornell, New York, NY
   Daniel Couriel, MD, University of Michigan, Ann Arbor, MI
   Richard Champlin, MD, MD Anderson Cancer Center, Houston TX
APPENDIX D5: SCIENTIFIC WORKING COMMITTEE LEADERSHIP

For information on Scientific Working Committee structure and organization, see Section 1.5.4. For information on Working Committee studies and associated contact information, see Section 8. The bolded name below identifies the coordinating statistician for that committee.

ACUTE LEUKEMIA WORKING COMMITTEE

Co-Chairs
- Steven Devine, MD, Ohio State University Medical Center, James Cancer Center
- Marcos de Lima, MD, University Hospitals Case Medical Center
- Brenda Sandmaier, MD, Fred Hutchinson Cancer Research Center

Scientific Director
- Daniel Weisdorf, MD, CIBMTR Minneapolis

Asst Scientific Dir
- Wael Saber, MD, MS, CIBMTR Milwaukee

Statisticians
- Hailin Wang, MPH, CIBMTR Milwaukee
- Mei-Jie Zhang, PhD, CIBMTR Milwaukee

AUTOIMMUNE DISEASES AND CELLULAR THERAPIES WORKING COMMITTEE

Co-Chairs
- Steven Pavletic, MD, MS, NIH NCI Experimental Transplantation and Immunology Branch
- Mitchell Cairo, MD, New York Medical College
- Ian Lewis, MBBS, PhD, Royal Adelaide Hospital
- David McKenna, MD, University of Minnesota Medical Center, Fairview
- Stefanie Sarantopoulos, MD, PhD, Duke University Medical Center

Scientific Director
- Marcelo Pasquini, MD, MS, CIBMTR Milwaukee

Statisticians
- Jiaxing Huang, MS, CIBMTR Milwaukee
- Ruta Brazauskas, PhD, CIBMTR Milwaukee

CHRONIC LEUKEMIA WORKING COMMITTEE

Co-Chairs
- Matt Kalaycio, MD, Cleveland Clinic Foundation
- Edwin Alyea, MD, Dana Farber Cancer Institute
- Uday Popat, MD, MD Anderson Cancer Center

Scientific Director
- Wael Saber, MD, MS, CIBMTR Milwaukee

Statisticians
- Zhenhuan Hu, MS, CIBMTR Milwaukee
- Kwang Woo Ahn, PhD, CIBMTR Milwaukee
DONOR HEALTH AND SAFETY WORKING COMMITTEE

Co-Chairs  
Paul O’Donnell, MD, PhD, Fred Hutchinson Cancer Research Center  
Michael Pulsipher, MD, Primary Children’s Hospital

Scientific Director  
Bronwen Shaw, MD, PhD, CIBMTR Milwaukee

Ex Officio SrAdvisor  
Dennis Confer, MD, CIBMTR Minneapolis

Statisticians  
Deidre Kiefer, MPH, CIBMTR Minneapolis  
Pintip Chitphakdiithai, PhD, CIBMTR Minneapolis  
Brent Logan, PhD, CIBMTR Milwaukee

Consumer Advocacy Committee Representatives  
Beatrice Abetti, Leukemia and Lymphoma Society  
Maureen Beaman  
Jeffrey Haertling

GRAFT SOURCES AND MANIPULATION WORKING COMMITTEE

Co-Chairs  
Daniel Fowler, MD, NIH NCI Experimental Transplantation and Immunology Branch  
Miguel-Angel Perales, MD, Memorial Sloan Kettering Cancer Center  
Vanderson Rocha, MD, PhD, Churchill Hospital

Scientific Director  
Mary Eapen, MBBS, MS, CIBMTR Milwaukee

Statisticians  
Junfang Chen, MS, CIBMTR Milwaukee  
Mei-Jie Zhang, PhD, CIBMTR Milwaukee

GRAFT-VERSUS-HOST DISEASE WORKING COMMITTEE

Co-Chairs  
Corey Cutler, MD, MPH, Dana Farber Cancer Institute  
Daniel Couriel, MD, University of Michigan  
Amin Alousi, MD, MD Anderson Cancer Center

Scientific Directors  
Mukta Arora, MD, MS, CIBMTR Minneapolis  
Stephen Spellman, MBS, CIBMTR Minneapolis

Statisticians  
Michael Hemmer, MS, CIBMTR Milwaukee  
Tao Wang, PhD, CIBMTR Milwaukee

Consumer Advocacy Committee Representatives  
Hilary Hall, Dana-Farber Cancer Institute  
James Omel, MD
HEALTH SERVICES AND INTERNATIONAL ISSUES WORKING COMMITTEE

Co-Chairs
Yoshiko Atsuta, MD, PhD, Nagoya University Graduate School of Medicine
Carmem Bonfim, MD, Hospital de Clinicas Curitiba
Jignesh Dalal, MD, The Children’s Mercy Hospitals and Clinics
Theresa Hahn, PhD, Roswell Park Cancer Institute

Scientific Director
Wael Saber, MD, MS, CIBMTR Milwaukee

Statisticians
Naya He, MPH, CIBMTR Milwaukee
Ruta Brazauskas, PhD, CIBMTR Milwaukee

Consumer Advocacy Committee Representatives
Jack Aiello
Gerardo Camarillo, MD

IMMUNOBIOLOGY WORKING COMMITTEE

Co-Chairs
Carlheinz Müller, MD, PhD, Zentrales Knochenmarkspender Register Deutschland
Michael Verneris, MD, University of Minnesota Medical Center, Fairview
Katharina Fleischhauer, MD, Universitätsklinikum Essen KMT

Scientific Directors
Stephanie J. Lee, MD, MPH, CIBMTR, Fred Hutchinson Cancer Research Center
Stephen Spellman, MBS, CIBMTR Minneapolis

Statisticians
Michael Haagenson, MS, CIBMTR Minneapolis
Tao Wang, PhD, CIBMTR Milwaukee

INFECTION AND IMMUNE RECONSTITUTION WORKING COMMITTEE

Co-Chairs
Michael Boeckh, MD, Fred Hutchinson Cancer Research Center
Jeffery Auletta, MD, Nationwide Children’s Hospital
Caroline Lindemans, MD, PhD, University Medical Center Utrecht

Scientific Director
Marcie Riches, MD, MS, CIBMTR, H Lee Moffitt Cancer Center and Research Institute

Statisticians
Min Chen, MS, CIBMTR Milwaukee
Kwang Woo Ahn, PhD, CIBMTR Milwaukee

LATE EFFECTS AND QUALITY OF LIFE WORKING COMMITTEE

Co-Chairs
Christine Duncan, MD, Dana-Farber Cancer Institute
Bipin Savani, MD, Vanderbilt University Medical Center
Mary Flowers, MD, Fred Hutchinson Cancer Research Center

Scientific Director
Bronwen Shaw, MD, PhD, CIBMTR Milwaukee

Statisticians
Heather Millard, MPH, CIBMTR Milwaukee
Ruta Brazauskas, PhD, CIBMTR Milwaukee

Consumer Advocacy Committee Representatives
Richard Boyajian, RN, Dana Farber Cancer Institute
Barry Schatz, Loyola University Medical Center
LYMPHOMA WORKING COMMITTEE

Co-Chairs
David Maloney, MD, PhD, Fred Hutchinson Cancer Research Center
Sonali Smith, MD, University of Chicago Hospitals
Anna Sureda, MD, PhD

Scientific Director
Mehdi Hamadani, MD, CIBMTR Milwaukee

Statisticians
Alyssa DiGilio, MS, CIBMTR Milwaukee
Kwang Woo Ahn, PhD, CIBMTR Milwaukee

PEDIATRIC CANCER WORKING COMMITTEE

Co-Chairs
Carrie Kitko, MD, University of Michigan
Gregory Hale, MD, All Children’s Hospital
Parinda Mehta, MD, Cincinnati Children’s Hospital Medical Center

Scientific Director
Elizabeth Thiel, MS, CIBMTR Milwaukee

Statisticians
Heather Millard, MPH, CIBMTR Milwaukee
Jennifer Le-Rademacher, PhD, CIBMTR Milwaukee

PLASMA CELL DISORDERS AND ADULT SOLID TUMORS WORKING COMMITTEE

Co-chairs
Amrita Krishnan, MD, City of Hope National Medical Center
Cristina Gasparetto, MD, Duke University Medical Center
Yago Nieto, MD, PhD, MD Anderson Cancer Center
Tomer Mark, MD, New York Presbyterian Hospital at Cornell

Scientific Director
Parameswaran Hari, MD, MS, CIBMTR Milwaukee

Asst Scientific Dir
Anita D’Souza, MD, CIBMTR Milwaukee

Statisticians
Jiaxing Huang, MS, CIBMTR Milwaukee
Jennifer Le-Rademacher, PhD, CIBMTR Milwaukee

Consumer Advocacy Committee Representative
James Omel, MD, retired

PRIMARY IMMUNE DEFICIENCIES, INBORN ERRORS OF METABOLISM, AND OTHER NON-MALIGNANT MARROW DISORDERS WORKING COMMITTEE

Co-Chairs
Harry Malech, MD, NIH NIAID Laboratory of Host Defenses
Shalini Shenoy, MD, Washington University / St. Louis Children’s Hospital
Paolo Anderlini, MD, MD Anderson Cancer Center
Neena Kapoor, MD, Children’s Hospital of Los Angeles
Jaap-Jan Boelens, MD, PhD, University Medical Center Utrecht
Vikram Mathews, MD, Christian Medical College Hospital

Scientific Director
Mary Eapen, MBBS, MS, CIBMTR Milwaukee

Statisticians
Wensheng He, MS, CIBMTR Milwaukee
Jennifer Le-Rademacher, PhD, CIBMTR Milwaukee
## REGIMEN-RELATED TOXICITY AND SUPPORTIVE CARE WORKING COMMITTEE

**Co-Chairs**
- Philip McCarthy, MD, Roswell Park Cancer Institute
- Andrew Artz, MD, MS, University of Chicago Hospitals
- Alison Loren, MD, MS, Abramson Cancer Center University of Pennsylvania Medical Center

**Scientific Director**
- Marcelo Pasquini, MD, MS, CIBMTR Milwaukee

**Statisticians**
- **Xiaochun Zhu, MS**, CIBMTR Milwaukee
- Brent Logan, PhD, CIBMTR Milwaukee
APPENDIX D6: IMMUNOBIOLGY STEERING COMMITTEE MEMBERSHIP

The NMDP / Be The Match Histocompatibility Advisory Group also serves as the CIBMTR Immunobiology Steering Committee. For more information, see Section 1.5.5.

CHAIR
Carolyn K. Hurley, PhD, Diplomate ABHI, Georgetown University Hospital

ADVISORY GROUP MEMBERS
Juliet Barker, MD, Memorial Sloan Kettering Cancer Center
Sarah Cooley, MD, University of Minnesota
Mary Eapen, MD, MS, Medical College of Wisconsin
Marcelo Fernandez Vina, PhD, Stanford Hospital and Clinics
Brent Logan, PhD, Medical College of Wisconsin
Carlheinz Mueller, MD, PhD, German National Bone Marrow Donor Registry (ZKRD)
Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center
David Porter, MD, Abramson Cancer Center University of Pennsylvania Medical Center
Raja Rajalingham, PhD, University of California, San Francisco
Bronwen Shaw, MD, PhD, Medical College of Wisconsin

EX OFFICIO MEMBERS
Daniel Arndt, MBA, NMDP / Be The Match Board Chair
James Bowman, MD, HRSA
Dennis Confer, MD, NMDP / Be The Match
Jason Dehn, MPH, NMDP / Be The Match
Karen Dodson, NMDP / Be The Match
Robert Hartzman, MD, Capt. MC, USN (Ret.), Navy Representative, C.W. Bill Young Marrow Donor Recruitment and Research Program
Martin Maiers, NMDP / Be The Match
Stephen Spellman, MBS, CIBMTR Minneapolis
APPENDIX D7: CLINICAL TRIALS ADVISORY COMMITTEE MEMBERSHIP

CHAIR

John Levine, MD, MS, University of Michigan

MEMBERS

Catherine Bollard, MD, MBChB, Children’s National Medical Center
Corey Cutler, MD, MPH, Dana Farber Cancer Institute
Colleen Delaney, MD, MSc, Fred Hutchinson Cancer Research Center
Marcos de Lima, MD, University Hospitals Case Medical Center
Steven Devine, MD, Ohio State Medical Center, James Cancer Center
Hugo Fernandez, MD, H Lee Moffitt Cancer Center and Research Institute
Mark Litzow, MD, Mayo Clinic Rochester
Margaret MacMillan, MD, MSc, University of Minnesota Medical Center, Fairview
Jan Storek, MD, PhD, University of Calgary

APPOINTED MEMBERS

Maureen Beaman, MBA
James Omel, MD

EX OFFICIO MEMBERS

Dennis Confer, MD, CIBMTR Minneapolis
Rebecca Drexler, BS, CIBMTR Minneapolis
Robert Hartzman, MD, Capt MC, USN (Ret.)
Mary Horowitz, MD, MS, CIBMTR Milwaukee
Roberta King, CIBMTR Minneapolis
Jennifer Le-Rademacher, PhD, CIBMTR Milwaukee
Brent Logan, PhD, CIBMTR Milwaukee
Nancy Poland, MA, NMDP / Be The Match Operations
Marcie Riches, MD, MS, H Lee Moffitt Cancer Center and Research Institute
Kevin Weber, NMDP / Be The Match Operations
Daniel Weisdorf, MD, CIBMTR Minneapolis
APPENDIX E: STAFF CONTINUING EDUCATION

CIBMTR staff members attended the following training and professional development activities in 2014.

Clinical Outcomes Research

- AABB Ex-Vivo Expansion of Cord Blood Derived HCT
- Anatomy and Physiology II
- Autoimmune Disease
- Biostatistics Lecture Series
- BMT for Sickle Cell Disease
- Chimeric Antigen Receptor T Cells with Marcela Maus
- Cord Blood Symposium
- Department of Medicine Core Education Sessions (autoHCT, alloHCT, sickle cell disease, AML, multiple myeloma, low and high grade lymphoma)
- Donor Availability Issues, Trends, and Strategies
- Ex-vivo Expansion of Cord Blood Derived Hematopoietic Stem Cells
- Fine Mapping of HLA Associations for Hematologic Diseases
- Genetics of HLA
- The Great Debate: Unrelated Cord vs Haplo Transplant
- HCT Coordinator Certification
- Hematopoietic Stem Cells: Understanding Clonal Expansion
- HLA Antibodies Presentation
- How to Report Adverse Events to the IRB / IEC (webinar)
- It’s Not Me – The Role of HLA in Tissue Compatibility
- Informed Consent (webinar)
- Next Generation Sequencing in Medicine
- NMDP / Be The Match and CIBMTR Research Lunch and Learn Series
- Orders vs Sources Training, Managing Postponed and Canceled CBU Orders Learning Series
- Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (webinar)
- Pathway to Transplant with Human Resources and Dr. Chell
- Permissible Mismatches and Mismatching Effects in HCT Transplant
- Plasma Cell Disorder eLearning
- Share the Science with Dr. Kurtzberg (webinar)
- Understanding GVHD Strategies to Prevent, Detect, and Treat

Health Services Research

- Defining Quality and Value in HCT
- Ethics in Donation and Transplantation
- Health Care Reform Educational Session
- How to Speed the Time to Transplant
- Impact of the Affordable Care Act on HCT
- Maintaining Patient and Donor Confidentiality
Information Technology

- Developer Conference

Management

- Agile Scaling Class
- Agile/Scrum Essentials for Practitioners
- Assertiveness Skills for Managers and Supervisors
- Beyond Scrum, Sprints, and Standups Webinar
- Book (personal study) – Smart Trust: The Defining Skill that Transforms Managers into Leaders by Steven Covey
- Book (personal study) – Seven Habits of Highly Effective People by Steven Covey
- Book (personal study) – Thinking on Purpose for Project Managers: Outsmarting Evolution by Bill Richardson
- Business Architecture Certificate Program
- Clinical Data Warehouse Training with Shawn Freeman
- Certified Scrum Master Training
- Certified Scrum Product Owner Training
- Crucial Conversations
- Customer Service: From Good to Great
- Examining 21CFR Part II and the Role of Technology
- Excel Training – Advanced (online)
- Excel Training – Basic
- Excel Training – Intermediate
- Excel Training – Pivot Tables
- Fissure Project Risk Management Webinar
- The Four Faces of Leadership through Fissure
- Good Clinical Practice: International Conference on Harmonisation (webinar)
- How to Prioritize ANY List Without Criteria
- International Institute for Business Analysis Professional Development Days
- InDesign Online Course
- IQ Leadership Seminars
- Jabber Roll-Out Training
- Leadership Learning Circle – Leading vs Managing
- Managing the Millennial Generation
- Managing Virtual Project Teams
- MasterControl Super User training
- No, That’s Not What I Meant! through Trissential
- Offering Rewards and Recognition
- OneNote Microsoft Virtual Academy
- Oracle Business Intelligence Enterprise Edition Training with Zubair Ahmed
- Project Communication
- Project Management Professional Development Days
- Project Management Institute Emotional intelligence and Leading Team Accountability
- Project Management Institute Global Congress
- Scrum Day Twin Cities
- ScrumMaster training
- Skillsoft eLearning: Business Skills, IT Skills, Desktop Skills
- SQL 101 with Naomi Goodnight
- SQL Advanced Online Training
- Strength Finder
- Team Foundation Server Administration
- Time Management Lecture
- Toastmasters
- Unanticipated Problems Involving Risks to Participate or Others
- University of Minnesota Leadership Series
- Women’s Leadership Conference
- Workplace Harassment Training - Manager Standard - California requirement: Darlene Kitajima

**Statistical Methodology**

- MS Statistician Retrieval Training
- MS Statistician Training Workshop
- SAS User Group Meetings
- University of Minnesota Bioinformatics and Computational Biology Journal Club Series

**Conferences**

- American Society of Hematology Annual Meeting
- American Society for Histocompatibility and Immunogenetics Annual Meeting
- American Statistical Association Meetings
- Bioinformatics and Computational Biology Industry Symposium
- BMT CTN State of the Science Symposium
- BMT Tandem Meetings
- Canadian Blood and Marrow Transplant Group GVHD Symposium
- EBMT Annual Meeting
- European Immunogenetics and Histocompatibility Annual Meeting
- International Conference on Survival Analysis (John P. Klein Memorial Conference)
- International Donor Registries Conference
- NMDP / Be The Match Council Meeting
- One Lambda Technical Workshop
- University of Minnesota Biopreservation Core Resource Workshop
- University of Minnesota Masonic Cancer Research symposium
### APPENDIX F: FORMS SUBMISSION PROCESS

**CIBMTR Forms Submission Process**

- Center submits CRID Assignment Form (Form 2804)
- CRID is generated – Stop here if autologous recipient declines consent for research participation
- Pre-TED (Form 2400) is added to Forms Due list
- Center completes and submits Pre-TED
- Pre-TED data are processed through the selection algorithm resulting in CRF or TED track

<table>
<thead>
<tr>
<th>CRF Track</th>
<th>TED Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forms 2004 and 2005 are due for each non-NMDP / Be The Match allogeneic donor.</td>
<td>Forms 2004 and 2006 are added if participating in related specimen repository and all non-NMDP / Be The Match cord blood units.</td>
</tr>
<tr>
<td>Form 2005 is due for each non-NMDP / Be The Match allogeneic recipient. Form 2006 is added for all products.</td>
<td>Form 2005 due for all allogeneic HCTs. Form 2006 due for all NMDP / Be The Match products and all cord blood units.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRF Track</th>
<th>TED Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline and Follow-up Forms are added to the Forms Due list.</td>
<td>Post-TED Follow-up Form 2450 is added to Forms Due list.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRF Track</th>
<th>TED Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center completes Baseline form after infusion.</td>
<td>Center completes designated Post-TED Forms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRF Track</th>
<th>TED Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center completes designated CRF Follow-up Forms.</td>
<td>Is recipient alive? If yes, go to Step 5. If no, go to Recipient Death Table.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRF Track</th>
<th>TED Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up Form entered.</td>
<td>Did recipient have a subsequent transplant? If yes, go to Step 6. If no, go to Step 3.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRF Track</th>
<th>TED Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is recipient alive? If yes, go to Step 7. If no, go to Recipient Death Table.</td>
<td>Subsequent transplant is reported on the next available follow-up form.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRF Track</th>
<th>TED Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did recipient have subsequent transplant? If yes, a Pre-TED (Form 2400) will be added for the center to complete. Then go to Step 8. If no, continue reporting at next time point (Step 4).</td>
<td>Center completes and submits Pre-TED (Form 2400) for subsequent transplant. Go to Step 2.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRF Track</th>
<th>TED Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>Future time points will be deleted for prior transplant from FormsNet when the form reporting the subsequent transplant is error free. Go to Step 2 for subsequent transplant.</td>
<td>Future time points will be deleted for prior transplant from FormsNet when the form reporting the subsequent transplant is error free.</td>
</tr>
</tbody>
</table>

**Recipient Death Table**

Death Form 2900 is completed to report the recipient’s death. If a follow-up form is received and reports the recipient’s death, and a form 2900 has not been submitted, one will be made due on the Forms Due list.

Recipient’s death is reported on the Post TED.

---

1. If the center has chosen to submit autologous forms without consent, follow the TED track.
2. Recipient has the option to withdraw consent at any time. If this happens, the Center CRC moves the allogeneic transplant record to the TED Track. If this is an autologous HCT and not on a BMT CTN study, the Center CRC does not switch the patient to the TED track; no further data needs to be collected. In either case, the consent status is updated so that the data will not be used for research other than as applicable for SCTOD reporting.
3. Designated time points are 100 days, 6 months, and annually post-transplant.
APPENDIX G: HUMAN SUBJECTS / HIPAA COMPLIANCE

All CIBMTR Coordinating Center personnel, including administrative and data entry staff, are trained in ethical conduct of clinical research, in compliance with policies of the MCW and NMDP / Be The Match IRBs. All Coordinating Center personnel are required to complete training through the CITI program. CITI completion certificates are on file for CIBMTR staff in administrative offices on the respective campuses and are renewed every two (Minneapolis) to three (Milwaukee) years. New employees are required to complete this training upon hire, and existing employees are required to maintain certification.

Institutional Review Board Approvals

The NMDP / Be The Match IRB, which is fully accredited by the Association for the Accreditation of Human Research Protection Programs, is responsible for reviewing all human subject research conducted by the CIBMTR, including research activities emanating from the CIBMTR Research Database. Since February 2011, an IRB Authorization Agreement between MCW and NMDP / Be The Match designates oversight for all CIBMTR human subject research to the NMDP / Be The Match IRB. From 1983 to February 2011, the MCW IRB had oversight for the CIBMTR Research Database.

The CIBMTR has an IRB-approved protocol that covers data submission to the CIBMTR Research Database and its research activities as well as a Research Sample Repository protocol that covers sample submission and research use. Both protocols and their associated consents are reviewed annually by the NMDP / Be The Match IRB. These protocols and consent documents are provided to participating US transplant centers, and centers are required to submit them to their local IRBs for review and approval.

US transplant centers are required to approach patients for participation in the CIBMTR Research Database. Only data from patients who provide written IRB-approved consent for research will have their data included in research studies. Because of the CIBMTR’s role with the SCTOD and its accompanying status as a Public Health Authority (PHA), essential patient data are collected for the Research Database, regardless of whether the patient provides consent to research use of their data. However, data from non-consenting patients are never used in research studies, only for government reporting purposes.

The CIBMTR tracks the IRB approval / renewal process for each center, monitors their IRB approval expiration dates, and sends timely reminders to transplant centers to renew their IRB approval. Centers are required to submit their initial and continuing review approvals to the CIBMTR. International centers are required to provide assurance to the CIBMTR, via a Data Transmission Agreement, that data submission from their site is in compliance with all relevant human subject protections and privacy regulations in place in their country.

Privacy Rule – HIPAA

The HIPAA Privacy Rule, enacted by the US Congress in 1996, applies to health care providers that transmit any health information in electronic form in connection with certain standard transactions, such as health care claims. It ensures the privacy of protected health care information for all patients. Historically, the CIBMTR has maintained compliance with HIPAA by collecting a limited dataset with a Data Use Agreement with participating centers. However, with receipt of the SCTOD contract, the
Office for Civil Rights and the Office of the General Counsel, US Department of Health and Human Services, determined that the CIBMTR meets the Privacy Rule’s definition of a PHA. As such, the CIBMTR is authorized by law to collect information necessary for the SCTOD to fulfill its statutory purpose and functions. HCT centers, regardless of their status as a “covered entity” are allowed to disclose protected health information to the CIBMTR without an individual’s written consent or authorization so that the CIBMTR can fulfill its statutory obligations as a PHA. In this context, Data Use Agreements are no longer required. All data collected between April 2003 and July 2007 are maintained in compliance with the regulations under which they were collected. Therefore, data submitted by centers during this time period that were not accompanied by a Data Use Agreement are not used by the CIBMTR.

**Gender and Minority Inclusion**

CIBMTR rules require that participating centers register all consecutive HCT recipients. The population available for study, therefore, includes women and minorities in the same proportion as they are found in the general HCT population. No patients are excluded on the basis of race or sex. In fact, the CIBMTR Research Database is a valuable resource for determining whether HCT recipients differ from the general population in race or sex and whether patients enrolled in clinical trials differ from the general HCT population in race, sex, or other characteristics.

**Inclusion of Children**

CIBMTR rules require that participating centers register all consecutive HCT recipients, regardless of age. Almost 18% of patients in the CIBMTR Research Database were younger than 18 years of age at time of transplantation. Children are included in most CIBMTR studies, unless the disease of interest (e.g. multiple myeloma) does not occur in the pediatric population or the technology to be studied has substantially different issues to be addressed in children and adults (e.g. comparisons of bone marrow versus peripheral blood grafts and bone marrow versus cord blood grafts were performed separately for children and adults). Additionally, the Pediatric Cancer Working Committee and the Primary Immune Deficiency, Inborn Errors of Metabolism, and Other Non-Malignant Marrow Disorders Working Committee are committed to facilitating studies focused on issues specific to pediatric HCT recipients.
APPENDIX H: PUBLICATIONS IN 2014

CLINICAL OUTCOMES RESEARCH PROGRAM PUBLICATIONS

The following publications were generated by Scientific Working Committees and related research programs, all of which use the CIBMTR Research Database. For more information about Scientific Working Committee studies, see Section 8. The PMCID number is assigned by PubMed Central, the NIH’s free digital archive of biomedical and life sciences journal literature, and is in compliance with the NIH policy on public access.

<table>
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<th>Authors</th>
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### Clinical Outcomes Research Program Scientific Working Committee Publications

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<td>JC, Dalal JD, Devine SM, Eames GM, Ferguson WS, Giller RH, He W, Kurtzberg</td>
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<td>J, Krance R, Katsanis E, Lewis VA, Sahdev I, Orchard PJ</td>
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<td>L, Hale GA, Halter J, Hayashi RJ, Hsu JW, Jacobsohn DA, Kamble RT,</td>
<td>using reduced intensity conditioning</td>
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<td>Kamani NR, Kasow KA, Khera N, Lazarus HM, Loren AW, Marks DI, Myers</td>
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<td>KC, Ramanathan M, Saber W, Savani B, Schouten HC, Socie G, Sorror ML,</td>
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<td>Steinberg A, Popat U, Wingard JR, Mattsson J, Majhail NS</td>
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<td>NS, Dispenzieri A, Freytes CO, Fung HC, Gale RP, Gasparetto C, Gibson</td>
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<td>J, Holmberg LA, Kindwall-Keller TL, Klumpp TR, Krishnan AY, Landau HJ,</td>
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<td>Lazarus HM, Lonial S, Maiolino A, Marks DI, Mehta P, Mikhail JR, Nishihori</td>
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<td>T, Olsson R, Ramanathan M, Roy V, Savani BN, Schouten HC, Scott E, Tay</td>
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<td>J, To LB, Vesole DH, Vogl DT, Hari P</td>
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<td>C, Frangouli HA, Freytes CO, Khera N, Lazarus HM, LeMaistre CF, Mehta</td>
<td>hematopoietic cell transplantation for acute leukemia in remission:</td>
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<td>P, Parsons SK, Szwajcer D, Ustun C, Wood WA, Majhail NS</td>
<td>comparison among alternative graft sources</td>
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## Clinical Outcomes Research Program Scientific Working Committee Publications

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<td>Ehnninger G, Egeland T, Fischer GF, Gervais T, Haagenson MD, Horowitz MM,</td>
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<td>Antin JH, Bolwell B, Cahn J-Y, Cairo MS, Cutler C, Flowers M, Gale R,</td>
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<td>Herzig R, Isola L, Jacobsohn D, Jagasia M, Klumpp T, Lee SJ, Petersdorf E,</td>
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<td>Santarone S, Spellman S, Schouten HC, Verdonck L, Wingard J, Weisdorf D,</td>
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<td>Horowitz M, Pavletic S</td>
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### Clinical Outcomes Research Program Scientific Working Committee Publications

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<th>Authors</th>
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## CLINICAL TRIALS SUPPORT PROGRAM PUBLICATIONS

### BMT CTN

The following publications were generated by the BMT CTN, a component of the Clinical Trials Support Program, which conducts multi-institutional phase II and III trials focused on HCT. The BMT CTN Data Coordinating Center maintains continuity of operations and facilitates effective communications. The Data Coordinating Center effort is a collaboration of the CIBMTR, NMDP / Be The Match, and the EMMES Corporation. For more information, see [Section 3.3.1](#).

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### Clinical Trials Support Program BMT CTN Publications

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<th>Authors</th>
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### RCI BMT

The following publications were generated by the RCI BMT, a component of the Clinical Trials Support Program, which conducts prospective research within the CIBMTR, providing researchers in the field of HCT with infrastructure and expertise in HCT clinical trial conduct and analysis. For more information, see Section 3.3.2.

### Clinical Trials Support Program RCI BMT Publications

<table>
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<tr>
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<th>Title</th>
<th>Citation</th>
<th>PMCID</th>
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</table>
**STATISTICAL METHODOLOGY RESEARCH PROGRAM PUBLICATIONS**

The following publications were generated by the Statistical Methodology Research Program, which develops and evaluates the statistical models used in HCT. For more information, see Section 3.7.

<table>
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<th>Title</th>
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<th>PMCID</th>
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**HEALTH SERVICES RESEARCH PROGRAM PUBLICATIONS**

The following publications were generated by the Health Services Research program, through which the CIBMTR conducts health policy and health services issues involving HCT. For more information, see Section 3.8.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Citation</th>
<th>PMCID</th>
</tr>
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<tbody>
<tr>
<td>Moore HK, Preussler J, Denzen EM, Payton TJ, Thao V, Murphy EA, Harwood E</td>
<td>Designing and operationalizing a customized internal evaluation model for cancer treatment support programs</td>
<td>Journal of Cancer Education. 2014 Sep 1; 29(3):463-472. doi:10.1007/s13187-014-0644-8. Epub 2014 Apr 24</td>
<td>N/A</td>
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</tbody>
</table>
BIOINFORMATICS PUBLICATIONS

The following publications were generated by the Bioinformatics program. Through its bioinformatics and HLA expertise, the program is a resource for researchers that facilitates collaboration, both within the US and internationally, for immunogenetic-focused research and NMDP / Be The Match operational bioinformatics. Clinical outcomes-focused research is facilitated through the CIBMTR.

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<th>Authors</th>
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<th>Citation</th>
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COORDINATING CENTER PUBLICATIONS

The following publications incorporated major contributions from the CIBMTR Coordinating Center and Scientific Directors.

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<tbody>
<tr>
<td>Pasquini MC, Wang Z, Horowitz MM, Gale RP</td>
<td>2013 report from the Center for International Blood and Marrow Transplant Research (CIBMTR): current uses and outcomes of hematopoietic cell transplants for blood and bone marrow disorders</td>
<td>Clinical Transplants. 2014 Jan 1; 2013:189-197</td>
<td>N/A</td>
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<tr>
<td>Authors</td>
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<tr>
<td>D'Souza A, Pasquini M, Spelley R</td>
<td>Is 'informed consent' an 'understood consent' in hematopoietic cell transplantation?</td>
<td>Bone Marrow Transplantation. doi:10.1038/bmt.2014.20. Epub 2014 Sep 22</td>
<td>N/A</td>
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## 2013 PUBLICATIONS NOT PREVIOUSLY REPORTED

The following publications were not presented in the 2013 CIBMTR Progress Report because they were published at the end of the year.

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<tr>
<th>Program</th>
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## 2013 Publications Not Previously Reported

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### APPENDIX I: PRESENTATIONS IN 2014

**2014 American Society of Hematology Annual Meeting**

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<thead>
<tr>
<th>Study</th>
<th>Title</th>
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<th>Principal Investigator</th>
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<tbody>
<tr>
<td>BMT CTN 0301</td>
<td>Optimized CY dosing in combination with fludarabine, TBI and ATG as conditioning for unrelated donor BMT in SAA: a Phase I/II study from BMT CTN</td>
<td>Oral</td>
<td>P Anderlini</td>
</tr>
<tr>
<td>BMT CTN 0302 / 0802</td>
<td>A biomarker algorithm defines onset grades of acute graft versus host disease with distinct non-relapse mortality</td>
<td>Oral</td>
<td>J Levine</td>
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<tr>
<td>BMT CTN 0302 / 0802</td>
<td>Circulating angiogenic factors as biomarkers of acute GVHD onset and response to therapy: repair and regeneration versus endothelial damage and inflammation</td>
<td>Poster</td>
<td>S Holtan</td>
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<tr>
<td>BMT CTN 0701</td>
<td>Reduced intensity conditioning (RIC) with rituximab yields excellent outcomes after allogeneic hematopoietic cell transplantation (alloHCT) for relapsed follicular lymphoma (FL): a Phase II multicenter trial from the Blood and Marrow Transplant Network (BMT CTN)</td>
<td>Oral</td>
<td>G Laport</td>
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<tr>
<td>BMT CTN 0703 (SWOG S0410)</td>
<td>A Phase II trial of tandem autologous stem cell transplantation (AHCT) for patients with primary progressive or recurrent Hodgkin lymphoma (HL)</td>
<td>Oral</td>
<td>E Smith</td>
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<tr>
<td>BMT CTN 0803</td>
<td>Autologous hematopoietic stem cell transplantation (AHCT) in patients with chemotherapy-sensitive, relapsed / refractory (CSRR) human immunodeficiency virus (HIV)-associated lymphoma (HAL)</td>
<td>Oral</td>
<td>J Alvarnas</td>
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<td>BMT CTN 0902</td>
<td>Patient-reported quality of life is an independent predictor of survival after allogeneic hematopoietic cell transplantation: a secondary analysis from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902</td>
<td>Oral</td>
<td>W Wood</td>
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<td>CK13-01</td>
<td>Outcomes of allogeneic hematopoietic cell transplantation in children (&lt;18y) and young adults (18-25y) with chronic myeloid leukemia: a CIBMTR cohort analysis</td>
<td>Poster</td>
<td>S Chaudhury</td>
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<td>DS05-02c</td>
<td>Baseline symptoms, female sex, and younger age are correlated with higher levels of peri-collection pain, symptoms, and persistent discomfort one year after related donor BM and PBSC donation: an analysis of the Related Donor Safety Study (RDSafe)</td>
<td>Poster</td>
<td>M Pulsipher</td>
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<td>GS13-01</td>
<td>Comparable 3-year disease-free survival regardless of anti-thymocyte globulin inclusion in pediatric myeloablative cord blood transplantation for acute lymphoblastic leukemia</td>
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<td>GV11-03</td>
<td>Comparison of tacrolimus versus cyclosporine with methotrexate for immunosuppression after allogeneic hematopoietic cell transplantation for severe aplastic anemia: a CIBMTR analysis</td>
<td>Poster</td>
<td>Yoshihiro Inamoto</td>
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<td>HS11-01</td>
<td>Do hematopoietic cell transplant patients treated on a clinical trial do better? Comparison of characteristics and outcomes of patients enrolled versus not enrolled on Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) 0201 Trial</td>
<td>Oral</td>
<td>N Khera / S Lee</td>
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<tr>
<td>IB08-06</td>
<td>Is there any effect of killer cell immunoglobulin-like receptor (KIR) on outcomes after single unrelated cord blood transplantation?</td>
<td>Oral</td>
<td>V Rocha</td>
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<tr>
<td>IB12-05/RT10-01</td>
<td>The prognostic value of YKL-40 in allogeneic hematopoietic cell transplantation</td>
<td>Poster</td>
<td>B Kornblit</td>
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<tr>
<td>IB12-06</td>
<td>Unrelated donor KIR B/X genotype reduces relapse and improves progression-free survival after HLA-matched allogeneic transplantation for relapse / refractory non-Hodgkin lymphoma</td>
<td>Oral</td>
<td>V Bachanova</td>
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<td>IB13-03</td>
<td>Clinical relevance of HLA supertype matching after myeloablative conditioning 7/8 unrelated donor hematopoietic cell transplantation: a CIBMTR study</td>
<td>Poster</td>
<td>A Lazaryan / D Weisdorf / M Arora</td>
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<td>IN12-01</td>
<td>Early CMV reactivation still remains a cause of increased transplant related mortality in the current era: a CIBMTR analysis</td>
<td>Oral</td>
<td>M Ramanathan</td>
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<td>LK12-01</td>
<td>Superiority of pediatric chemotherapy over allogeneic hematopoietic cell transplantation for Philadelphia chromosome negative adult ALL in first complete remission: A combined analysis of Dana-Farber ALL Consortium and CIBMTR cohorts</td>
<td>Oral</td>
<td>M Seftel / D Neuberg</td>
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<tr>
<td>LK12-02</td>
<td>FLT3 mutation increases relapse risk after allogeneic hematopoietic cell transplant for acute myeloid leukemia in first or second complete remission: a Center for International Blood and Marrow Transplant Research (CIBMTR) analysis</td>
<td>Oral</td>
<td>S Sengsayadeth / A Deol / B Savani / M Jagasia</td>
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<td>MM11-03</td>
<td>Improved outcomes of autologous hematopoietic cell transplantation (AHCT) for light chain (AL) amyloidosis: a Center for International Blood and Marrow Transplant Registry (CIBMTR) study</td>
<td>Oral</td>
<td>A D'souza / B Wirk</td>
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<tr>
<td>MM13-01</td>
<td>Contribution of chemotherapy mobilization to disease control in multiple myeloma treated with autologous transplantation</td>
<td>Poster</td>
<td>L Costa / G Uy</td>
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<td>RT10-01/IB12-05</td>
<td>Pre-transplant C-reactive protein (CRP), ferritin and albumin as biomarkers to predict transplant related mortality (TRM) after allogeneic hematopoietic cell transplant (HCT)</td>
<td>Oral</td>
<td>B Kornblit</td>
</tr>
<tr>
<td>Study</td>
<td>Title</td>
<td>Type</td>
<td>Principal Investigator</td>
</tr>
<tr>
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</tr>
<tr>
<td>DS05-02</td>
<td>RDSafe: a multi-institutional study of HCT donor safety and quality of life</td>
<td>Oral</td>
<td>M Pulsipher</td>
</tr>
<tr>
<td>HS11-02</td>
<td>Comparison of length of stay among alternative graft sources: single and double cord blood, matched unrelated donor, other related donor</td>
<td>Oral</td>
<td>K Ballen</td>
</tr>
<tr>
<td>IB10-01</td>
<td>Donor and recipient telomere length as predictors of outcomes after HCT in patients with acquired severe aplastic anemia</td>
<td>Oral</td>
<td>S Gadalla / S Savage</td>
</tr>
<tr>
<td>IB12-02</td>
<td>HLA in myeloablative conditioning allogeneic hematopoietic stem cell transplantation outcomes</td>
<td>Oral</td>
<td>J Pidala</td>
</tr>
<tr>
<td>IN06-01</td>
<td>The rate of breakthrough of pneumocystis jiroveci pneumonia after transplant as a function of prophylaxis regimens</td>
<td>Oral</td>
<td>K Williams</td>
</tr>
<tr>
<td>IN10-01</td>
<td>Comparison of infectious rates among alternative graft sources: single and double cord blood, matched unrelated donor, and mismatched unrelated donor</td>
<td>Oral</td>
<td>K Ballen</td>
</tr>
<tr>
<td>LE11-01</td>
<td>Long-term survival following second allogeneic HCT for hematologic malignancies</td>
<td>Oral</td>
<td>C Duncan / M Sorror</td>
</tr>
<tr>
<td>LK11-01</td>
<td>Impact of extramedullary disease on the outcome of allogeneic HCT in AML</td>
<td>Oral</td>
<td>S Goyal / G Uy</td>
</tr>
<tr>
<td>PC10-03</td>
<td>Transplantation in children with hypodiploid ALL</td>
<td>Oral</td>
<td>P Mehta / S Jodele</td>
</tr>
<tr>
<td>RT09-04</td>
<td>Genetic susceptibility to transplant-related mortality after unrelated donor stem cell transplant: determination of causes of death within first year of transplantation</td>
<td>Oral</td>
<td>T Hahn</td>
</tr>
<tr>
<td>RT11-01a</td>
<td>Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation (autoHCT)</td>
<td>Oral</td>
<td>A Lane / Y Chen</td>
</tr>
<tr>
<td>RT11-01b</td>
<td>Incidence and risk factors for the development of idiopathic pneumonitis syndrome (IPS) after autologous hematopoietic cell transplantation (autoHCT) for patients with lymphoma</td>
<td>Poster</td>
<td>Y Chen / A Lane</td>
</tr>
<tr>
<td>RT12-01</td>
<td>Sequence of cyclophosphamide and total body irradiation in evaluation of relapse, mortality, and graft versus host disease in patients with AML and ALL undergoing hematopoietic stem cell transplantation</td>
<td>Oral</td>
<td>J Holter Chakrabarty / G Selby / R Epstein</td>
</tr>
<tr>
<td>RT12-04</td>
<td>Impact of total body irradiation on non-myeloablative transplants for lymphoproliferative disorders</td>
<td>Poster</td>
<td>S Hong / M Pasquini</td>
</tr>
<tr>
<td>SC10-06</td>
<td>BuCyE vs BEAM for autologous transplants in lymphoma</td>
<td>Poster</td>
<td>M Pasquini</td>
</tr>
</tbody>
</table>
### 2014 American Society of Clinical Oncology Annual Meeting

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Type</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY13-01</td>
<td>Early rituximab failure (ERF) in relapsed diffuse large b-cell lymphoma (DLBCL) does not predict futility of autologous hematopoietic cell transplantation (AHCT)</td>
<td>Poster</td>
<td>M Hamadani</td>
</tr>
<tr>
<td>SC13-01</td>
<td>Impact of palifermin use on pediatric patient (PedPts) hematopoietic cell transplant (HCT) outcomes</td>
<td>Poster</td>
<td>W Saber</td>
</tr>
<tr>
<td>SC13-02</td>
<td>Comparison of University of Chicago haplo cord blood transplants with double cord bloods reported to the CIBMTR</td>
<td>Poster</td>
<td>K Besien</td>
</tr>
</tbody>
</table>

### 2014 European Group for Blood and Marrow Transplantation Annual Meeting

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Type</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMT CTN 0302 / 0802</td>
<td>A new Ann Arbor grading system uses biomarkers to risk stratify patients for non relapse mortality at the onset of acute graft versus host disease</td>
<td>Oral</td>
<td>J Levine</td>
</tr>
<tr>
<td>GS12-01</td>
<td>Role of stem cell dose in reduced-intensity conditioning transplants for AML and MDS</td>
<td>Poster</td>
<td>O Ringdén</td>
</tr>
</tbody>
</table>

### 2014 Interscience Conference on Antimicrobial Agents and Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Type</th>
<th>Principal Investigator</th>
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</thead>
<tbody>
<tr>
<td>BMT CTN 0101</td>
<td>Relationship between voriconazole concentrations and the probability of breakthrough fungal infections</td>
<td>Oral</td>
<td>W Hope</td>
</tr>
</tbody>
</table>

### 2014 Society for Clinical Trials Annual Meeting

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Type</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMT CTN Network</td>
<td>Leveraging resources to design, conduct and analyze hematopoietic stem cell transplant clinical trials: the ongoing collaboration between the Center for International Blood and Marrow Transplant Research and the Blood and Marrow Transplant Clinical Trials Network</td>
<td>Oral</td>
<td>A Mendizabal</td>
</tr>
</tbody>
</table>
APPENDIX J: STUDY DEVELOPMENT CYCLE

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

<table>
<thead>
<tr>
<th>Study Development Cycle</th>
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</thead>
<tbody>
<tr>
<td><strong>Planned</strong></td>
<td><strong>Protocol pending.</strong> Proposals remain in this preliminary stage until the PI creates a draft protocol.</td>
</tr>
<tr>
<td><strong>Draft protocol received.</strong></td>
<td>When a PI submits a draft protocol, Coordinating Center staff review it.</td>
</tr>
<tr>
<td><strong>Protocol development.</strong></td>
<td>During the development process, the Working Committee biostatisticians, Scientific Director, and Chairs refine the submission into a comprehensive study protocol. They add a table with a preliminary description of the proposed study population and present the draft protocol for discussion at a weekly Coordinating Center statistical meeting. When a protocol is approved, Coordinating Center personnel invite Working Committee members to participate in a Writing Committee.</td>
</tr>
<tr>
<td><strong>Sample typing.</strong></td>
<td>If applicable, the PIs perform laboratory tests (e.g., genotyping) on samples from the CIBMTR Research Repository. The testing data will be used in the analysis to determine any correlation with clinical outcome.</td>
</tr>
<tr>
<td><strong>Supplemental forms / data collection.</strong></td>
<td>Most studies use routinely-collected data. If necessary, Coordinating Center staff, in collaboration with the PI and relevant Working Committee Co-Chairs, develop a supplemental form, which is approved prior to soliciting centers for additional data. Use of supplemental data (e.g., data not collected on standard CIBMTR data collection forms) is discouraged unless it will result in a particularly meaningful publication and/or external funding can support the extra burden placed on transplant centers and supplement forms reimbursement costs.</td>
</tr>
</tbody>
</table>
| **Data file preparation.** | The objective of data file preparation is to create a file of eligible subjects who are consecutively treated at participating centers with adequate follow-up, with minimal missing data fields, and in large enough numbers to give the analysis sufficient statistical power to meet the stated study objectives. This process involves a series of steps by the MS Statistician, sometimes working with the CRC, to ensure data quality:  
  - Verifying selection criteria  
  - Assessing follow-up  
  - Determining the extent and nature of missing values and their potential effect on the study  
  - Resolving and reconciling data discrepancies / outliers by examining data collection forms and communicating with centers and the PI  
  - Including and excluding patients so that the investigators can determine whether the final study population is representative of the target population (unbiased sample) |
### In Progress

**Analysis in progress.** Analysis proceeds in several phases. The first generally includes a detailed description of the patient population and univariate and multivariate analyses of study endpoints. Coordinating Center personnel present these data for discussion at a weekly Coordinating Center statistical meeting and then distribute them to Writing Committee members for suggestions and comments. The PI works with Coordinating Center staff in an iterative process to review comments from the Writing Committee. The process repeats until final analysis, which serves as the basis for the manuscript.

**Ongoing.** A study in ongoing status is long-term and often involves multiple grants and/or renewals outside of the CIBMTR in order to reach its objectives. The study has its own PhD biostatisticians for analysis, but it requires data from the CIBMTR, usually each year.

### Preliminary Results

**Manuscript preparation.** The PI is primarily responsible for manuscript preparation and is expected to prepare a draft manuscript within 30 days of receiving analysis results. The Working Committee leadership review and revise the document, ensuring that the description and interpretation of the statistical analyses are accurate and contribute to the fundamental message of the manuscript. The Coordinating Center then distributes the approved first draft to the Writing Committee and solicits feedback. The PI incorporates comments from the Writing Committee and creates a revised draft, which is reviewed in an iterative process by the Writing Committee until reaching a reasonable consensus on a final manuscript.

**Submitted.** The Coordinating Center staff is responsible for submitting the manuscript and corresponding with the chosen journal. The Working Committee Scientific Director often serves as corresponding author, and the study statistician forwards all editor and reviewer comments to the PI and PhD statisticians. The PI is expected to prepare a response, working with Coordinating Center staff who provide additional analyses of data, as needed. Coordinating Center personnel communicate with the journal, including re-submissions, in most cases.

**In press.** A publication is in press when it has been approved but does not yet have a citation.

### Completed

**Published.** A manuscript is considered published when a citation is available, including a PMCID number, if applicable. For a list of 2014 publications, see Appendix H.
APPENDIX K1: BMT CTN CLINICAL TRIALS

The BMT CTN (Section 3.3.1) uses the CIBMTR Research Database to design, monitor, and analyze clinical trials. A status of its projects is included in this appendix. Support for BMT CTN clinical trials is provided by the NHLBI in partnership with the NCI.

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Title</th>
<th>Opened to Enrollment</th>
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</thead>
<tbody>
<tr>
<td>BMT CTN 0903</td>
<td>Allogeneic blood stem cell transplant for hematological cancers and bone marrow failure in HIV-infected individuals</td>
<td>Opened Sep 12, 2011</td>
</tr>
<tr>
<td>BMT CTN 1101</td>
<td>Phase III study comparing HLA-haploidentical related donor bone marrow versus double umbilical cord blood with reduced-intensity conditioning for patients with hematologic malignancies</td>
<td>Opened Jun 19, 2012</td>
</tr>
<tr>
<td>BMT CTN 1102</td>
<td>A multi-center biologic assignment trial comparing reduced intensity allogeneic hematopoietic cell transplant to hypomethylating therapy or best supportive care in patients aged 50-75 with intermediate-2 and high risk myelodysplastic syndrome</td>
<td>Opened Dec 16, 2013</td>
</tr>
<tr>
<td>BMT CTN 1202</td>
<td>Prospective multi-center cohort for the evaluation of biomarkers predicting risk of complications and mortality following allogeneic HCT</td>
<td>Opened Jun 11, 2013</td>
</tr>
<tr>
<td>BMT CTN 1203</td>
<td>A multi-center Phase II trial randomizing novel approaches for graft-versus-host disease prevention compared to contemporary controls</td>
<td>Opened Sep 16, 2014</td>
</tr>
<tr>
<td>BMT CTN 1204</td>
<td>Reduced-intensity conditioning for children and adults with hemophagocytic syndromes or selected primary immune deficiencies</td>
<td>Opened Nov 14, 2013</td>
</tr>
<tr>
<td>BMT CTN 1205</td>
<td>Easy-to-read informed consent (ETRIC) for hematopoietic cell transplantation clinical trials</td>
<td>Opened Nov 21, 2013</td>
</tr>
<tr>
<td>BMT CTN 1304</td>
<td>A randomized Phase III study comparing conventional dose treatment using a combination of lenalidomide, bortezomib, and dexamethasone (RVD) to high-dose treatment with peripheral stem cell transplant in the initial management of myeloma in patients up to 65 years of age</td>
<td>Opened by BMT CTN Nov 16, 2013</td>
</tr>
<tr>
<td>Protocol Number</td>
<td>Title</td>
<td>Accrual Dates</td>
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<tr>
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</tbody>
</table>
| BMT CTN 0101    | A randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infections in allogeneic blood and marrow transplant recipients                                      | • Opened Dec 1, 2003  
• Closed Sep 21, 2006                      |
| BMT CTN 0102    | A trial of tandem autologous stem cell transplants with or without post-second autologous transplant maintenance therapy versus single autologous stem cell transplant followed by matched sibling non-myeloablative allogeneic stem cell transplant for patients with multiple myeloma | • Opened Nov 15, 2003  
• Closed Mar 30, 2007                     |
| BMT CTN 0201    | A Phase III, randomized, multi-center trial comparing G-CSF mobilized peripheral blood stem cell with marrow transplantation from HLA-compatible, unrelated donors                                         | • Opened Jan 20, 2004  
• Closed Oct 16, 2009                     |
| BMT CTN 0202    | Autologous versus non-myeloablative allogeneic hematopoietic stem cell transplantation for patients with chemosensitive follicular non-Hodgkin lymphoma beyond first complete response of first partial response | • Opened Jul 28, 2004  
• Closed Mar 2, 2006                     |
| BMT CTN 0301    | Fludarabine-based conditioning for allogeneic marrow transplantation from HLA-compatible unrelated donors in severe aplastic anemia                                                                      | • Opened Jan 24, 2006  
• Closed Dec 2, 2013                      |
| BMT CTN 0302    | Initial systemic treatment of acute GVHD: a Phase II, randomized trial evaluating etanercept, mycophenolate mofetil, denileukin diftitox (ONTAK), and pentostatin                                                        | • Opened Aug 25, 2005  
• Closed Mar 24, 2008                     |
| BMT CTN 0303    | A single-arm, multi-center Phase II trial of transplants of HLA-matched, CD34+ enriched, T cell depleted peripheral blood stem cells isolated by the CliniMACS system in the treatment of patients with AML in first or second morphologic complete remission | • Opened Jun 5, 2005  
• Closed Dec 24, 2008                     |
| BMT CTN 0401    | Phase III Rituxan/BEAM versus Bexxar/BEAM with autologous hematopoietic stem cell transplantation for persistent or relapsed chemotherapy-sensitive diffuse large B cell non-Hodgkin lymphoma                     | • Opened Dec 5, 2007  
• Closed Jul 17, 2009                     |
| BMT CTN 0402    | A Phase III randomized, multi-center trial comparing sirolimus/tacrolimus with tacrolimus/methotrexate as GVHD prophylaxis after HLA-matched, related peripheral blood stem cell transplantation                         | • Opened Nov 20, 2006  
• Closed Oct 28, 2011                     |
| BMT CTN 0403    | A randomized, double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor Enbrel (etanercept) for the treatment of acute non-infectious pulmonary dysfunction (idiopathic pneumonia syndrome) following allogeneic stem cell transplantation | • Opened Aug 27, 2007  
• Closed Sep 14, 2011                     |
| BMT CTN 0501    | Multi-center, open label, randomized trial comparing single versus double cord blood transplantation in pediatric patients with leukemia and myelodysplasia                                                      | • Opened Oct 16, 2006  
• Closed Feb 29, 2012                     |
<table>
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<tr>
<th>Protocol Number</th>
<th>Title</th>
<th>Accrual Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMT CTN 0502</td>
<td>A Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first morphologic complete remission using a non-myeloablative preparative regimen</td>
<td>• CALGB opened Aug 29, 2006 &lt;br&gt;• BMT CTN opened Jan 29, 2007 &lt;br&gt;• Closed Dec 29, 2008 &lt;br&gt;• Re-opened Nov 10, 2009, to centers with IRB approval of NCI-approved amendment to increase accrual &lt;br&gt;• Closed Dec 29, 2011</td>
</tr>
<tr>
<td>BMT CTN 0601</td>
<td>Unrelated donor hematopoietic cell transplantation for children with severe sickle cell anemia using a reduced-intensity conditioning regimen</td>
<td>• Opened Jun 27, 2008 &lt;br&gt;• Closed Apr 24, 2014</td>
</tr>
<tr>
<td>BMT CTN 0603</td>
<td>A multi-center, Phase II trial of non-myeloablative conditioning and transplantation of partially matched HLA-mismatched bone marrow for patients with hematologic malignancies</td>
<td>• Opened Oct 17, 2008 &lt;br&gt;• Closed May 17, 2010</td>
</tr>
<tr>
<td>BMT CTN 0604</td>
<td>A multi-center, Phase II trial of non-myeloablative conditioning and transplantation of umbilical cord blood from unrelated donors in patients with hematologic malignancies</td>
<td>• Opened Dec 23, 2008 &lt;br&gt;• Closed Mar 31, 2010</td>
</tr>
<tr>
<td>BMT CTN 0701</td>
<td>Phase II trial of non-myeloablative allogeneic hematopoietic cell transplantation for patients with relapsed follicular non-Hodgkin lymphoma beyond first complete response</td>
<td>• Opened Apr 27, 2009 &lt;br&gt;• Closed Oct 22, 2012</td>
</tr>
<tr>
<td>BMT CTN 0702</td>
<td>Single autologous transplant with or without consolidation versus tandem autologous transplant with lenalidomide maintenance</td>
<td>• Opened Jun 1, 2010 &lt;br&gt;• Closed Nov 15, 2013</td>
</tr>
<tr>
<td>BMT CTN 0703</td>
<td>Tandem autologous stem cell transplantation for patients with primary progressive or recurrent Hodgkin disease (a BMT study), Phase I</td>
<td>• Opened Mar 18, 2008 &lt;br&gt;• SWOG 0410 opened Oct 15, 2005 &lt;br&gt;• Closed Feb 1, 2009</td>
</tr>
<tr>
<td>BMT CTN 0704</td>
<td>A Phase III, randomized, double-blind study of maintenance therapy with CC-55103 or placebo following autologous stem cell transplantation for multiple myeloma</td>
<td>• Opened May 15, 2007 &lt;br&gt;• CALGB 100104 opened Dec 15, 2004 &lt;br&gt;• Closed Jul 2, 2009</td>
</tr>
<tr>
<td>BMT CTN 0801</td>
<td>A Phase II/III randomized, multicenter trial comparing sirolimus plus prednisone, and sirolimus/calcineurin inhibitor plus prednisone for the treatment of chronic graft-versus-host disease</td>
<td>• Opened Apr 15, 2010 &lt;br&gt;• Closed Dec 9, 2013</td>
</tr>
<tr>
<td>BMT CTN 0802</td>
<td>A multi-center, randomized, double blind, phase III trial evaluating corticosteroids with mycophenolate mofetil versus corticosteroids with placebo as initial systemic treatment of acute GVHD</td>
<td>• Opened Feb 1, 2010 &lt;br&gt;• Closed Nov 14, 2011</td>
</tr>
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</table>
### BMT CTN Clinical Trials – Closed to Enrollment

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Title</th>
<th>Accrual Dates</th>
</tr>
</thead>
</table>
| BMT CTN 0803    | High-dose chemotherapy with autologous stem cell rescue for aggressive B cell lymphoma and Hodgkin lymphoma in HIV-infected patients | • Opened Jul 12, 2010  
• Closed May 15, 2013 |
| BMT CTN 0804    | Phase II study of reduced-intensity allogeneic stem cell transplant for high-risk chronic lymphocytic leukemia | • Opened Mar 16, 2011  
• Closed Jan 27, 2014 |
| (CALGB 100701)  |                                                                      |                                   |
| BMT CTN 0805    | Randomized Phase II trial of chemotherapy + dasatinib versus allogeneic HCT for adults with Ph+ acute lymphoblastic leukemia | • Opened Aug 9, 2010  
• Closed Oct 1, 2013 |
| (SWOG 0805)     |                                                                      |                                   |
| BMT CTN 0901    | Phase III study comparing myeloablative to non-myeloablative conditioning for transplantation in patients with MDS or AML | • Opened Jun 2, 2011  
• Closed Apr 18, 2014 |
| BMT CTN 0902    | A Phase III randomized, multi-center trial testing whether exercise or stress management improves functional status and symptoms of autologous and allogeneic HCT recipients | • Opened Jan 3, 2011  
• Closed Jun 1, 2012 |
The RCI BMT (Section 3.3.2) uses the CIBMTR Research Database to design, monitor, and analyze clinical trials. A status of its projects is included in this appendix. Support for RCI BMT projects is provided by a variety of external support sources.

<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Title</th>
<th>Status To Date</th>
</tr>
</thead>
</table>
| 05-DCB     | A phase II multi-center trial of myeloablative double unit umbilical cord blood transplantation in adults with hematologic malignancy | • Completed accrual Oct 2011  
• 56 of 55 targeted enrollment  
• Manuscript published in British Journal of Haematology Oct 2014 |
| 07-REV     | Revlimid as maintenance therapy post-transplant: evaluating the safety and tolerability of lenalidomide after allogeneic HCT | • Completed accrual Jan 2012  
• 30 of 30 targeted enrollment  
• Manuscript published in Biology of Blood and Marrow Transplantation July 2014 |
| 09-SQOL    | Pilot study to assess the feasibility of collecting quality of life data in collaboration with the Stem Cell Therapeutic Outcomes Database | • Closed to accrual Sep 2013  
• 301 adults and 89 pediatric recipients enrolled  
• Final subject follow-up expected by end of 2014  
• Data review in process |
| CTN 0201   | Peripheral blood versus bone marrow grafts from unrelated donors     | • Closed to accrual Oct 2009  
• 551 of 550 targeted enrollment  
• Performing 5 year recipient QOL assessment  
• Expect last assessment by May 2015 |
| 11-TREO    | Multi-center study evaluating treosulfan, fludarabine, and low-dose TBI in children with AML / MDS undergoing allogeneic HCT | • Closed to accrual April 2014, about one year earlier than expected  
• 40 of 40 targeted enrollment |
| COG-KIR    | A multi-center study examining donor NK-cell receptors and patient outcomes | • COG closed accrual May 2014  
• URD sample management  
• 609 of 1,200 samples collected  
• 145 out of 400 targeted enrollment |
| DS05-02, 06-DON | RDSafe: A multi-institutional study of hematopoietic stem cell donor safety and quality of life | • Closed to accrual July 2014  
• 1,812 donors enrolled  
• Follow up assessments continue through July 2015  
• One abstract accepted to ASH 2014, two at 2015 BMT Tandem Meetings, and one submitted to EBMT 2015 |
| PBMTC ONC 1001 / 09-MRD | A multi-center study to determine the role of minimal residual disease testing before and after HCT for pediatric acute myeloid leukemia | • Closed to accrual Oct 2014  
• 150 total enrollment  
• Follow-up continues |
<table>
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<tr>
<th>Protocol #</th>
<th>Title</th>
<th>Status To Date</th>
</tr>
</thead>
</table>
| PBSC      | Filgrastim-mobilized peripheral blood stem cells for allogeneic transplantation with unrelated donors | • Opened to accrual Apr 1996  
• More than 22,200 URDs enrolled  
• Will close to accrual upon FDA license; another protocol will open for all unlicensed product |
| 10-CBA    | A multi-center access and distribution protocol for unlicensed cryopreserved cord blood units for transplantation in pediatric and adult patients with hematologic malignancies and other indications | • Opened to accrual Oct 2010  
• 2,131 enrolled  
• Open indefinitely to allow distribution and access to unlicensed cord units |
| rHuG-CSF  | Long-term follow-up study evaluating hematologic and non-hematologic cancers, thrombotic events, and autoimmune disorders in unrelated donors undergoing bone marrow harvest versus peripheral blood stem cell mobilization with recombinant human granulocyte colony-stimulating factor | • Opened to accrual Oct 2010  
• More than 19,200 donors of 21,932 targeted enrollment |
| 10 CMS-MDS-1 | Assessment of allogeneic HCT in Medicare beneficiaries with MDS and related disorders | • Opened to accrual Dec 2010  
• 913 patients enrolled |
| KIR-DS    | A multi-center study looking at the selection of a favorable KIR donor | • Opened to accrual Jun 2011  
• URD sample management  
• 1,451 of 1,800 samples requested  
• 382 of 600 targeted patient enrollment |
| Statin    | Impact of donor statin use on graft-versus-host disease after unrelated donor HCT; URD data collection | • Opened to accrual Oct 2011  
• 4,176 of 7,000 targeted donors enrolled |
| Ancestry  | Optimizing ancestry self-reporting for the Be The Match Registry | • Collaboration with NMDP / Be The Match Bioinformatics  
• 2,497 enrolled  
• Analysis in process |
| 09-PLEX   | A phase II study evaluating the safety and efficacy of intravenous plerixafor for the mobilization and transplantation of HLA-matched sibling donor hematopoietic stem cells in recipients with hematological malignancies | • Opened to accrual May 2013  
• 62 donor / recipient pairs of 64 targeted enrollment |
| Astellas  | Unrelated donor sample collection for donors whose recipient is enrolled in a randomized, double-blind, placebo-controlled, Phase III trial to evaluate the protective efficacy and safety of a therapeutic vaccine, ASP0113, in cytomegalovirus-seropositive recipients undergoing allogeneic hematopoietic cell transplant | • Donor sample collection only  
• Opened to accrual Apr 2014  
• Two donors enrolled |
<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Title</th>
<th>Status To Date</th>
</tr>
</thead>
</table>
| BMT CTN 1102-QOL| A study comparing reduced intensity allogeneic hematopoietic cell transplant to hypomethylating therapy or best supportive care in patients aged 50-75 with intermediate-2 and high risk myelodysplastic syndrome | • Survey Research Group performing QOL assessments  
• Total of 39 baseline assessments completed |
| 13-SCP          | A randomized study to evaluate the impact of survivorship care planning on cancer survivors self-management and adherence to care recommendations and utilization of follow-up care | • In collaboration with Health Services Research Program  
• Protocol released to sites Sep 2014 |
| 13-TLEC         | Prospective non-therapeutic study, assessing the long-term toxicity of HCT for childhood leukemia | • Protocol released to sites Sep 2014 |
| 12-MOXE         | Study of the anti-CD22 recombinant immunotoxin moxetumomab pasudotox (CAT-8015, HA 22) in children with B-lineage acute lymphoblastic leukemia and minimal residual disease prior to allogeneic hematopoietic cell transplantation | • IND accepted Nov 2014  
• Expect to release protocol to sites by Jan 2015 |
| BMT CTN 1102-Ancillary CEA study | A cost effectiveness ancillary study to the parent study 1102 above | • Collaborating with Fred Hutchinson Cancer Research center to perform Cost Effectiveness Analysis (CEA) study  
• Survey Research Group to perform CEA survey collection  
• Logistical processes being developed |
## APPENDIX L: GLOSSARY

<table>
<thead>
<tr>
<th>Abbreviation/ Acronym</th>
<th>Meaning</th>
</tr>
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<tbody>
<tr>
<td>AA</td>
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<tr>
<td>ABiL</td>
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<td>AGNIS</td>
<td>A Growable Network Information System</td>
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<td>AL</td>
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<td>alloHCT</td>
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<td>AMI</td>
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<tr>
<td>AML</td>
<td>acute myeloid (myelogenous) leukemia</td>
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<td>APL</td>
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<td>ASBMT</td>
<td>American Society of Blood and Marrow Transplantation</td>
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<tr>
<td>ASH</td>
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<td>AT</td>
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<td>AVN</td>
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<td>AYAs</td>
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<tr>
<td>BEAM</td>
<td>Rituximab/Carmustine, Etoposide, Cytarabine, Melphalan</td>
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<tr>
<td>BM</td>
<td>bone marrow</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
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<td>BMT CTN</td>
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<td>BRIDG</td>
<td>Biomedical Research Integrated Domain Group</td>
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<td>Bu</td>
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<tr>
<td>BuCy</td>
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<td>caDSR</td>
<td>Cancer Data Standards Registry and Repository</td>
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<td>chitinase-3-like-1</td>
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<td>CI</td>
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<td>CIBMTR</td>
<td>Center for International Blood and Marrow Transplant Research</td>
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<tr>
<td>Abbreviation/ Acronym</td>
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<td>CMS</td>
<td>Centers for Medicare and Medicaid Services</td>
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<td>CMV</td>
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<td>CPSS</td>
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<td>CR</td>
<td>complete remission</td>
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<tr>
<td>CR1</td>
<td>first complete remission</td>
</tr>
<tr>
<td>CR2</td>
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<td>CRC</td>
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<td>DISCO</td>
<td>Data and Information for Statistical Center Operations</td>
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<td>DLBCL</td>
<td>diffuse large B-cell lymphoma</td>
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<td>donor lymphocyte infusion</td>
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<td>DRI</td>
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<td>DSRCTP</td>
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<td>Meaning</td>
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<td>GVL</td>
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<td>HRQoL</td>
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<td>icNK</td>
<td>immuno-competent natural killer</td>
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<td>Institutional Review Board</td>
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<td>liter</td>
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<td>LIG4</td>
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<td>LOS</td>
<td>length of (hospital) stay</td>
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<td>LRF</td>
<td>late rituximab failure</td>
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<td>Abbreviation/Acronym</td>
<td>Meaning</td>
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<td>LTL</td>
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<tr>
<td>M</td>
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<td>MAC</td>
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<td>MCW</td>
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<td>MDS</td>
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<td>myeloid derived suppressor cells</td>
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<td>MED-A, MED-B</td>
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<td>melphalan</td>
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<td>MF/SS</td>
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<td>MFD</td>
<td>matched family donor</td>
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<tr>
<td>MLII</td>
<td>mucolipidosis type II, also known as I-cell disease</td>
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<tr>
<td>MM</td>
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<td>MMF</td>
<td>mycophenolate</td>
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<td>MMUD</td>
<td>mismatched unrelated donor</td>
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<tr>
<td>MNC</td>
<td>mononuclear cells</td>
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<tr>
<td>MPD</td>
<td>myeloproliferative disorder</td>
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<td>MRD</td>
<td>matched related donor OR minimal residual disease</td>
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<td>magnetic resonance imaging</td>
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<td>MSD</td>
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<td>methotrexate</td>
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<td>MUD</td>
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<td>neurologic functional score</td>
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<td>natural killer (cell)</td>
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<td>NMA</td>
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<td>NMC</td>
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<td>mismatched unrelated donor</td>
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<td>NMDP</td>
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<td>NRM</td>
<td>non-relapse mortality</td>
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<td>non-myeloablative stem cell transplantation</td>
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<td>NW</td>
<td>normal weight</td>
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<td>obese</td>
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<td>OHIC</td>
<td>other high income countries (not the United States or Canada)</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>overall survival</td>
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<tr>
<td>Abbreviation/ Acronym</td>
<td>Meaning</td>
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<td>overweight</td>
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<td>peripheral blood</td>
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<td>Pediatric Blood and Marrow Transplant Consortium</td>
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<td>peripheral blood progenitor cells</td>
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<td>pneumocystis jiroveci pneumonia</td>
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<td>progression-free survival</td>
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<td>PGF</td>
<td>primary graft failure</td>
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<td>Ph+</td>
<td>Philadelphia chromosome positive</td>
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<tr>
<td>Ph+ALL</td>
<td>Philadelphia chromosome positive acute lymphoblastic leukemia</td>
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<td>Philadelphia chromosome negative</td>
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<td>quality of life</td>
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<td>Resource for Clinical Investigations in Blood and Marrow Transplant</td>
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<td>risk group</td>
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<td>RIT</td>
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<td>risk of overweight</td>
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<tr>
<td>RR</td>
<td>relative risk OR relapse rate</td>
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<td>radiation therapy</td>
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<td>HLA-identical siblings</td>
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<td>single nucleotide polymorphism</td>
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<td>Southwestern Oncology Group</td>
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<tr>
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<tr>
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<td>T cell epitope</td>
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<td>tyrosine-kinase inhibitor</td>
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<td>total lymphoid irradiation</td>
</tr>
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<td>TLR</td>
<td>toll-like receptors</td>
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<tr>
<td>TNC</td>
<td>total neutrophil count OR total nucleated cell</td>
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<tr>
<td>TRM</td>
<td>transplant-related mortality / treatment-related mortality</td>
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<td>umbilical cord blood</td>
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<td>UMIC</td>
<td>upper middle income countries</td>
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<td>unrelated donor</td>
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<td>United States</td>
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<td>United States and Canada</td>
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<td>VGPR</td>
<td>very good partial response</td>
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<td>versus</td>
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<td>white blood cell</td>
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The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement 5U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID).

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

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