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PROGRESS REPORT
JANUARY-DECEMBER
2006

RESEARCH SCIENCE INNOVATION

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CIBMTR Progress Report January – December 2006

List of Abbreviations

Acronym	Definition
AGNIS	A Growable Network Information System
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myelogenous Leukemia
ASBMT	American Society for Blood & Marrow Transplantation
ATG	Anti-Thymocyte Globulin
BMI	Body Mass Index
BMT	Blood and Marrow Transplant
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
CHS	Chediak-Higashi Syndrome
CIBMTR	Center for International Blood and Marrow Transplant Research
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogeneous Leukemia
CMV	Cytomegalovirus
COG	Children's Oncology Group
CR	Complete Remission
Cy	Cyclophosphomide
DLI	Donor Leukocyte or Lymphocyte Infusion
EBMT	European Group for Bone & Marrow Transplantation
FOCIS	Federation of Clinical Immunology Societies
G-CSF	Granulocyte-Colony Stimulataing Factor
GVHD	Graft versus Host Disease
HCT	Hematopoietic Stem Cell Transplant
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HRSA	Health Resources and Services Administration
IATO	Interim Authority to Operate
IBMTR	International Blood and Marrow Transplant Registry
IRB	Institutional Review Board
IRC	Institutional Review Committee
IV	Intravenous
KIR	Killer Immunoglobulin-like Receptor
LOS	Loss of Sex Chromosome
mHAg	Human Minor Histocompatibility Antigen

NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NHLBI	National Heart, Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMA	Non-inherited Maternal Antigens
NIST	National Institute of Standards and Technology
NK	Natural Killer
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PHA	Public Health Authority
QOL	Quality of Life
RCI BMT	Resource for Clinical Investigators in Blood & Marrown Transplantation
RR	Relative Risk
SCID	Severe Combined Immune Deficiency
SCTOD	Stem Cell Therapeutic Outcomes Database
SNP	Single Nucleotide Polymorphism
TBI	Total Body Irradiation
TED	Transplant Essential Data
TED F/U	Transplant Essential Data Follow Up
TGF-B1	Transforming Growth Factor Beta 1
UCB	Umbilical Cord Blood
URD	Unrelated Donor
VOD	Veno-Occlusive Disease

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

1.0 INTRODUCTION

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a clinical research program dedicated to addressing important issues in the field of (HCT). It offers a unique resource of data and statistical expertise to the medical and scientific community. The CIBMTR is comprised of a network of more than 400 transplant centers that share data on outcomes of HCand a Statistical Center that maintains a clinical database with information on more than 200,000 transplant recipients. These data and analytic support available through the CIBMTR Statistical Center have led to successful completion of hundreds of studies. This Progress Report describes CIBMTR research activities for the period January 1 through December 31, 2006.

1.1. History

The CIBMTR was formed in July 2004 through an affiliation of the International Bone Marrow Transplant Registry (IBMTR) of the Medical College of Wisconsin and the research arm of the National Marrow Donor Program (NMDP-Research). Both the IBMTR and NMDP-Research have broad research expertise in HCT, including observational research and clinical trials. The IBMTR is a voluntary organization involving more than 400 transplant centers in 47 countries (Appendix 1) that have collaborated to share patient data and conduct scientific studies since 1972. The NMDP was established in 1987 to provide unrelated donors for patients in need of HCT; NMDP-Research analyzes data from these transplants to assess and improve results. The NMDP also has established a repository of donor-recipient biologic samples for a large subset of these transplants. The NMDP Network includes 164 transplant centers (Appendix 1), 80 donor centers, 101 collection centers, 89 apheresis centers and 17 cord blood banks.

Now in its third year, the CIBMTR brings together the research efforts of both organizations, each with complementary strengths. **This affiliation represents a continued commitment of the two organizations to coordinate their efforts and resources and to provide a single point of focus for development and support of transplant-related clinical research.**

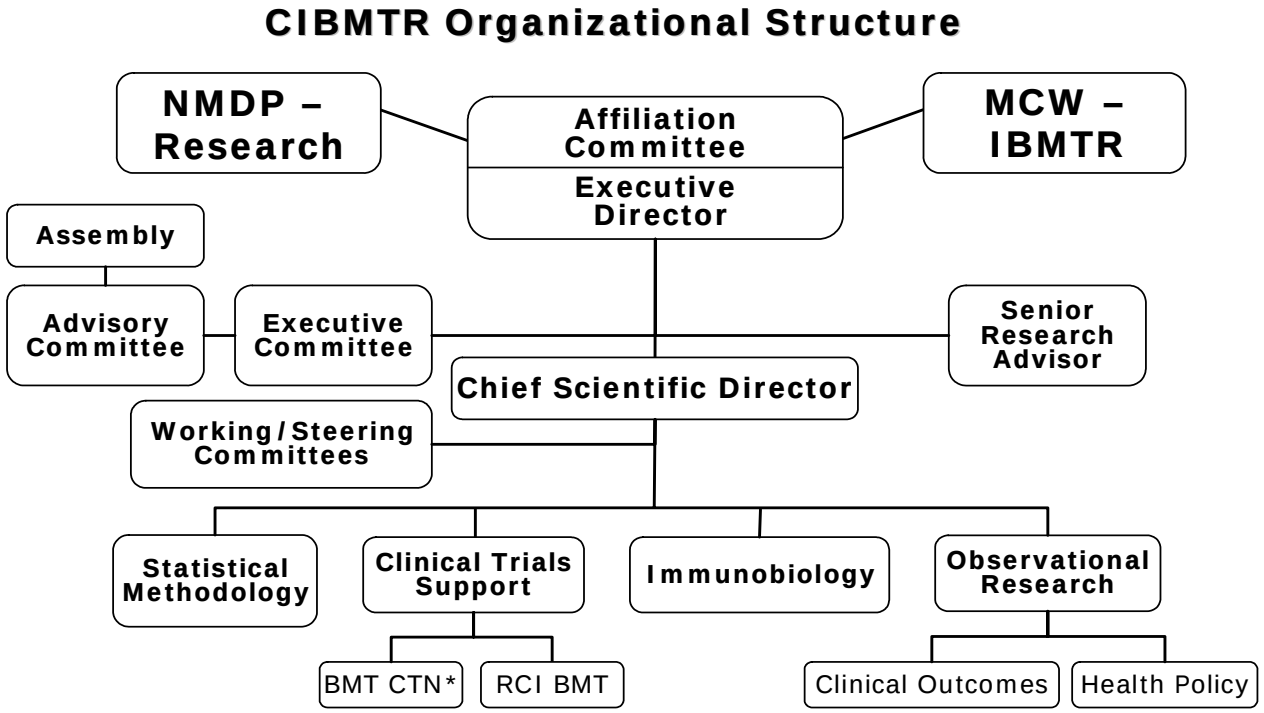
1.2. Organizational Structure

CIBMTR activities are funded in large part by a U. S. National Institutes of Health (NIH) cooperative agreement jointly sponsored by the National Cancer Institute (NCI), the National Heart Lung and Blood Institute (NHLBI) and the National Institute for Allergy and Infectious Disease (NIAID), U24-CA76518. U24-CA76518 provides support to the CIBMTR Statistical Center to establish a resource of data and statistical expertise for clinical research in blood and marrow transplantation. CIBMTR Scientific, Executive and Advisory (Appendix 2 and 3) Committees provide policy and scientific oversight for this work. This Progress Report deals primarily with CIBMTR activities funded by U24-CA76518.
The organizational structure of the CIBMTR is shown in Figures 1 and 2. The Chief Scientific Director has primary responsibility for administrative and scientific operations. The CIBMTR Statistical Director

has responsibility for the statistical quality of all CIBMTR studies. The Center has four major areas or programs of research activity:

- Observational Research
- Clinical Trials
- Immunobiology
- Statistical Methodology

U24-CA76518 provides funding for some aspects of all of these programs but does not directly support the conduct of clinical trials.



*The Data and Coordinating Center of the BMT Clinical Trials Network is a collaboration of the CIBMTR, the NMDP and the EMMES Corporation

Figure 1

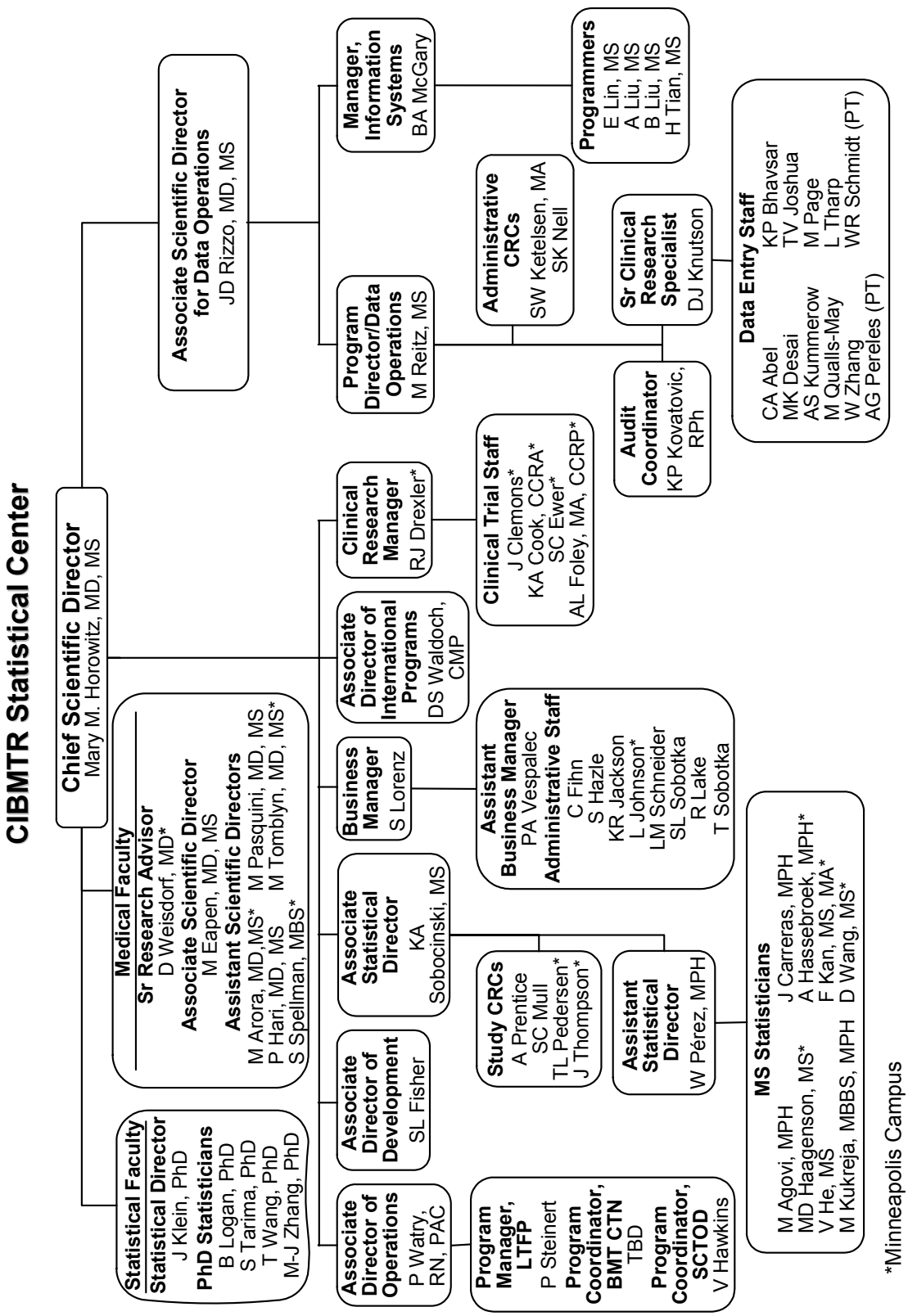

CIBMTR Statistical Center
Chief Scientific Director
Mary M. Horowitz, MD, MS
Medical Faculty
Sr Research Advisor
D Weisdorf, MD*
Associate Scientific Director
M Eapen, MD, MS
Assistant Scientific Directors
M Arora, MD,MS* M Pasquini, MD, MS
P Hari, MD, MS M Tomblyn, MD, MS*
S Spellman, MBS*
Statistical Faculty
Statistical Director
J Klein, PhD
PhD Statisticians
B Logan, PhD
S Tarima, PhD
T Wang, PhD
M-J Zhang, PhD
Associate Scientific Director for Data Operations
JD Rizzo, MD, MS
Manager, Information Systems
BA McGary
Programmers
E Lin, MS
A Liu, MS
B Liu, MS
H Tian, MS
Program Director/Data Operations
M Reitz, MS
Administrative CRCs
SW Ketelsen, MA
SK Nell
Sr Clinical Research Specialist
DJ Knutson
Audit Coordinator
KP Kovatovic, RPh
Data Entry Staff
CA Abel
MK Desai
AS Kummerow
M Qualls-May
W Zhang
AG Pereles (PT)
KP Bhavsar
TV Joshua
M Page
L Tharp
WR Schmidt (PT)
Clinical Research Manager
RJ Drexler*
Clinical Trial Staff
J Clemons*
KA Cook, CCRA*
SC Ewer*
AL Foley, MA, CCRP*
Associate Director of International Programs
DS Waldoch, CMP
Business Manager
S Lorenz
Assistant Business Manager
PA Vespalec
Administrative Staff
C Fihn
S Hazle
KR Jackson
L Johnson*
LM Schneider
SL Sobotka
R Lake
T Sobotka
Associate Statistical Director
KA Sobocinski, MS
Associate Director of Development
SL Fisher
Associate Director of Operations
P Watry, RN, PAC
Study CRCs
A Prentice
SC Mull
TL Pedersen*
J Thompson*
Assistant Statistical Director
W Pérez, MPH
Program Manager, LTFP
P Steinert
Program Coordinator, BMT CTN
TBD
Program Coordinator, SCTOD
V Hawkins
MS Statisticians
M Agovi, MPH
MD Haagenson, MS*
V He, MS
M Kukreja, MBBS, MPH
J Carreras, MPH
A Hassebroek, MPH*
F Kan, MS, MA*
D Wang, MS*
*Minneapolis Campus
CRC= Clinical Research Coordinator; LTFP=long-term follow-up program; BMT CTN= Blood and Marrow Transplant Clinical Trials Network; SCTOD=Stem Cell Therapeutic Outcomes Database

Figure 2

1.2.3. Committee Responsibilities

The CIBMTR Committee structure is designed to ensure that the activities of the CIBMTR (and the use of resources made available through the Statistical Center) are consistent with the priorities of the scientific and medical community it serves and that the CIBMTR operates with broad input from members of the HCT community.

Working Committees develop and execute the CIBMTR's scientific agenda. Working Committee responsibilities include:

- designing and conducting studies relevant to their subject area and involving CIBMTR data, statistical resources, networks and/or centers;
- considering proposals to use CIBMTR data for studies pertinent to their subject area;
- periodically assessing and revising relevant sections of CIBMTR data collection forms; and
- planning and conducting workshops at CIBMTR meetings.

Working Committees have responsibility for setting priorities for CIBMTR observational studies that use the large clinical databases of the IBMTR and NMDP. These observational studies are a core activity of the CIBMTR. There are 17 Working Committees (Appendix 4):

- **Acute Leukemia**: cellular therapy for acute leukemias, preleukemia and myelodysplastic disorders
- **Chronic Leukemia**: cellular therapy for chronic leukemias and myeloproliferative disorders
- **Lymphoma**: cellular therapy for Hodgkin and non-Hodgkin disease
- **Plasma Cell Disorders**: cellular therapy for multiple myeloma and other plasma cell disorders
- **Solid Tumors**: cellular therapy for solid tumors
- **Pediatric Cancer**: cellular therapy for childhood malignancies and other issues related to use of cellular therapy in children
- **Non-Malignant Marrow Disorders**: cellular therapy for aplastic anemia, congenital disorders of hematopoiesis and other non-malignant hematopoietic disorders
- **Immune Deficiencies/Inborn Errors**: cellular therapy for congenital and acquired immune deficiencies and inborn errors of metabolism
- **Autoimmune Diseases**: cellular therapy for autoimmune disorders
- **Graft Sources/Manipulation**: issues related to graft procurement, quality and manipulation
- **Graft versus Host Disease** (GVHD): biology, prevention and treatment of GVHD and its complications
- **Late Effects and Quality of Lif**e (QOL): issues related to long-term survivors of cellular therapy, including clinical and psychosocial effects of transplantation
- **Immunobiology**: histocompatibility and other genetic and immunologic issues related to cellular therapy
- **Infection/Immune Reconstitution**: prevention and treatment of posttransplant infections and issues related to recovery of immune function
- **Regimen-Related Toxicity and Supportive Care**: preparative regimens, prevention and treatment of early non-GVHD toxicities and supportive care in the early posttransplant period
- **Health Services and Psychosocial Issues**: access to cellular therapy including social and economic barriers to care and influence of psychosocial factors on HCT outcome
- **Donor Health and Safety**: donor safety and outcomes

Each Working Committee is headed by 2-4 chairs appointed by the Advisory Committee to non-renewable five-year terms. Chairs must be members of a CIBMTR Research Center (see Section 2.0) and are selected for expertise in their topic area and to ensure adequate expertise with both autologous and allogeneic transplantation (where relevant) and adequate experience with IBMTR and NMDP activities. Working Committees are allocated specific CIBMTR resources, including statistician time, determined by the Chief Scientific Director in consultation with the Statistical Director.

Membership on CIBMTR Working Committees is open to any individual willing to take an active role in development of studies using CIBMTR data and/or resources. Proposals for CIBMTR observational studies are submitted to the appropriate Working Committee and evaluated by the Committee membership. The Working Committees are also encouraged to develop studies in important areas in Where no relevant or appropriate proposals addressing those areas are submitted.

Two CIBMTR **Steering Committees** provide an additional level of oversight for use of certain resources. These are the Immunobiology Steering Committee and the Clinical Trials Advisory Committee. The NMDP Histocompatibility Committee serves as the Immunobiology Committee (Appendix 5) for the CIBMTR, reviewing and approving use of donor-recipient specimens from the NMDP Repository for conducting CIBMTR studies approved by the Immunobiology Working Committee. These are studies that link outcome data with biologic and genetic factors derived from analyses of these biologic materials. Although U24-CA76518 does not directly fund clinical trials, CIBMTR data, data collection forms and networks are valuable resouces for individuals or groups planning such trials and providing those resources is an important feature of the program that this cooperative agreement funds. This past year, a Clinical Trials Advisory Committee (CTAC, Appendix 6) was formed to more formally review requests for CIBMTR resources to assist in planning and implementing clinical trials and a program established (the Resource for Clinical Investigations in Blood and Marrow Transplantation, RCI BMT) to make these resources more accessible to the scientific community. In some instances, the CIBMTR has partnered with individuals and groups to seek separate funding for such trials. [Of note, the CIBMTR Statistical Center, together with NMDP and the EMMES Corporation, also functions as the Data and Coordinating Center of the U.S. Blood and Marrow Transplant Clinical Trials Network (BMT CTN), a separately funded (U01-HL069294) clinical trials network with its own oversight and governing mechanism. A Progress Report covering BMT CTN activities funded by U01-HL069294 is available from the CIBMTR Statistical Center upon request.]

The CIBMTR **Assembly** is the voting membership. It is comprised of a single representative from each CIBMTR Research Center. CIBMTR **Advisory Committee** (Appendix 2) members and officers are elected by the CIBMTR Assembly. The CIBMTR Advisory Committee also includes appointed members representing donor centers (n=1), collection centers (n=1), patients (n=2) and individuals with expertise in business (n=1), ethics (n=1) and information systems (n=1), as well as representatives from the NCI, NHLBI, NIAID and the U.S. Health Resources and Services Administration (HRSA). The CIBMTR Advisory Committee meets biannually to review scientific and other activities of the CIBMTR.

The CIBMTR **Executive Committee** (Appendix 3) is a subcommittee of the Advisory Committee that provides ongoing advice and counsel to the CIBMTR Statistical Center between meetings of the Advisory Committee. It includes the Chair, Chair-elect or Immediate Past Chair, four Vice-Chairs (each representing a geographic region), and the appointed donor center, collection center and patient representatives of the Advisory Committee. Additionally, the CIBMTR Senior Research Advisor, Chief Scientific Director, Statistical Director, Senior Research Advisor and Program Leaders serve as ex officio members with voting privileges. The Executive Committee is responsible for ensuring that the organization carries out its mission and fulfills the requirements of CIBMTR policies and procedures. In this capacity it:

- provides direction to the Chief Scientific Director and Statistical Center for scientific activities and

policy decisions;
- finalizes priorities for scientific studies after obtaining input from the Working Committees;
- reviews results of audits and recommends measures to correct deficiencies;
- appoints a CIBMTR Program Chair for the annual meeting.

The Executive Committee meets at least annually at the Tandem/BMT Meetings and by conference call three additional times per year.

Establishment of two standing subcommittees of the Advisory Committee was approved in 2005: the Consumer Advocacy Committee (CAC) and the International Studies Committee.

Consumer Advocacy Committee (CAC):

The CAC was established to help provide the patient and donor perspective in developing the CIBMTR's research agenda and to help in communicating important information from CIBMTR studies to the non-medical community. A charter for this committee was approved in February 2006 followed by a formal call for nominations. An interview and approval process was completed in September. There are now nine members including two co-chairs (Appendix 7). This committee meets in person annually at the BMT Tandem meetings and by periodic conference calls.

International Studies Committee:

This committee's major charge is to facilitate communication between non-U.S. centers and the CIBMTR leadership (as well as other national, regional and international organizations) and to design, develop and conduct studies dealing with questions specific to geographic regions. A first in person meeting occurred during the February 2006 Tandem sessions (attended by 35 international representatives) at which discussion focused on how to structure this new group. This process is in progress. The committee is scheduled to re-convene in February 2007.

The **Nominating Committee** (Appendix 8) includes 5 members elected by the CIBMTR Assembly. It is responsible for preparing a slate of candidates for the Advisory, Nominating and Clinical Trials Advisory Committees. It seeks input from the CIBMTR Assembly, Advisory Committee and Working Committee chairs in preparing its slate through a mailed request for nominees distributed in Spring of each year. The slate of candidates is distributed by e-mailed ballot in the Fall of each year.

1.2.4. Statistical Center

Milwaukee Campus

Since 1972, the IBMTR Statistical Center at the Medical College of Wisconsin in Milwaukee (now the CIBMTR Statistical Center/Milwaukee Campus) has been central to IBMTR activities, coordinating data collection and management and providing statistical and administrative support for studies using registry data (see current personnel in Figure 2); it continues to play an important coordinating role for the CIBMTR. The CIBMTR Milwaukee Campus is an academic division of the Medical College of Wisconsin. The Medical College provides administrative support for the CIBMTR in grants and account management, personnel issues and development activities.

Mary M. Horowitz, MD, MS is Chief Scientific Director of the CIBMTR and John P. Klein, PhD is Statistical Director. Dr. Horowitz is the Robert A. Uihlein Professor of Hematologic Research at the Medical College of Wisconsin and is an attending physician in the Medical College's HCT program. She also holds an MS in Biostatistics. Dr. Horowitz also serves as Principal Investigator for the Data

and Coordinating Center of the BMT CTN. Dr. Klein is a Professor and Chief of the Division of Biostatistics at the Medical College of Wisconsin and an internationally recognized expert in survival analysis.

The CIBMTR Milwaukee Campus has two Associate Scientific Directors (Drs J. Douglas Rizzo and, Mary Eapen) and two Assistant Scientific Directors (Drs. Hari Parameswaran and Marcelo Pasquini) who provide scientific leadership for CIBMTR activities. Dr. Rizzo is an adult hematologist /oncologist who completed a Robert Wood Johnson fellowship in epidemiology and cost-effectiveness research at the Johns Hopkins University. He also holds an MD degree in Epidemiology from the Medical College of Wisconsin. As Program Leader for the CIBMTR's Observational Research Program (see Figure 1.1) Dr. Rizzo supervises data operations at the Milwaukee campus. Additionally, he provides medical oversight for the Regimen Related Toxicity/Supportive Care, Late Effects/Quality of Life and the Health Policy/Psychosocial Issues Working Committees. Dr. Rizzo also serves as an attending physician in the Medical College of Wisconsin adult HCT unit.

Dr. Eapen is a pediatric hematologist/oncologist who received her clinical HCT training and an MS in Clinical Research at the University of Minnesota. She provides medical oversight and biostatistical support to the Pediatric Cancer, Non-malignant Marrow Disorders, Immune Deficiencies/Inborn Errors and Graft Sources and Manipulation Working Committees. She also serves as a Protocol Officer for the BMT CTN.

Dr. Parameswaran Hari completed his Hematology/Oncology fellowship at the Medical College of Wisconsin after serving as a Specialist Registrar in Haematology at Leicester University Teaching Hospitals in the United Kingdom. He is board certified in Medical Oncology, Clinical and Laboratory Haematology and Internal Medicine and also holds an MS in epidemiology from the Medical College of Wisconsin. He has been an Assistant Professor since July, 2004. He serves as Scientific Director of the Lymphoma and Plasma Cell Disorders Working Committees. Dr. Marcelo Pasquini did his residency in Internal Medicine at the University of Miami/Jackson Memorial Hospital, completed a Hematology-Oncology fellowship at the University of Utah and a one-year fellowship in HCT at the Medical College of Wisconsin. He also holds an MS in epidemiology from the Medical College. He has been an Assistant Professor at the Medical College of Wisconsin since July, 2005. He is the Scientific Director of the Autoimmune Disease Working Committee and serves as a Protocol Officer for the BMT CTN.

The CIBMTR Milwaukee Campus has four PhD Biostatisticians in addition to Dr. Klein, the Statistical Director. Mei-Jie Zhang has worked with the Statistical Center since 1991; he provides expertise in Cox regression analyses and other multivariable techniques. Brent Logan joined the Statistical Center in July 2001; he brings expertise in clinical trial design and analysis of multiple endpoints. Sergey Tarima joined the Statistical Center in 2005; his area of expertise is in estimation of missing and censored survival data. Tao Wang joined the Statistical Center in January 2002 and has special interest in genetic immunobiology. Other PhD members of the Medical College of Wisconsin, Division of Biostatistics, also participate in selected CIBMTR studies. Additionally, there are six MS biostatisticians contributing to CIBMTR research activities on the Milwaukee Campus: Kathleen Sobocinski (the Associate Statistical Director and who has worked with the Statistical Center since 1973), Waleska Perez (the Assistant Statistical Director, who has worked with the Statistical Center since 1998) and Jeanette Carreras, Manisha Kukreja, Manza Agovi and Vincent He. Paula Watry joined the CIBMTR organization in October 2004 as Associate Director of Operations; previously she had 10 years clinical experience as a Physician's Assistant in the Medical College of Wisconsin HCT program. Ms. Watry has as a major responsibility serving as liaison between the Milwaukee and Minneapolis campuses (see below). Thirty-six other research and administrative staff also work at the Milwaukee campus (Figure 2).

Minneapolis Campus

The Minneapolis campus of the CIBMTR (previously NMDP-Research, Inc.) is located at the NMDP Coordinating Center and also provides significant scientific and statistical support for CIBMTR research activities. Dr. Daniel Weisdorf serves as Senior Research Advisor to the CIBMTR and as Scientific Director of the Acute Leukemia Working Committee. Dr. Weisdorf is Professor of Medicine and Director of the Adult Blood and Marrow Transplant (BMT) Program at the University of Minnesota. He has served as NMDP Scientific Director since 2002 and previously as chair of the IBMTR Acute Leukemia Working Committee, as a member of the IBMTR Executive Committee and as Chair of the BMT CTN Steering Committee. Dr. Mukta Arora is an Assistant Professor in the Division of Hematology, Oncology and Transplantation, at the University of Minnesota. She has an MS degree in Clinical Research from the University of Minnesota. She serves as Scientific Director of the CIBMTR Chronic Leukemia, GVHD and Solid Tumor Working Committees. Dr. Marcie Tomblyn is also an Assistant Professor in the Division of Hematology, Oncology and Transplantation at the University of Minnesota. Dr. Tomblyn completed her Hematology/Oncology Fellowship at Northwestern University in 2003 and then did a year as a fellow in HCT. She obtained an MS degree in Clinical Investigation at Northwestern University in 2004. She serves as Scientific Director of the CIBMTR Infection and Immune Reconstitution Working Committee and as a Protocol Officer for the BMT CTN. Both Drs. Weisdorf and Tomblyn are actively involved in the new CIBMTR clinical trials support program, the RCI BMT. Stephen Spellman, Manager of NMDP Scientific Services with oversight for the donor-recipient research sample repository, also serves as Scientific Director of the Immunobiology Working Committee. He received his MBS. degree from the University of Minnesota in Immunobiology and Molecular Biology. There are also four MS level statisticians at the CIBMTR Minneapolis Campus: Michael Haagenson (Senior Statistician, who has worked in NMDP's Research Operations since 2000), Fiona Kan, Dan Wang and Anna Hassebroek.

Rebecca Drexler B.S. A.A.S serves as Clinical Research Manager of the CIBMTR Minneapolis campus. Ms. Drexler has more than 20 years experience in Medical Research and Product Development of which seven were in the area of Clinical and Regulatory Affairs. She is a member of the Association of Clinical Research Professionals. She supervises a staff of nine administrative and research personnel at the Minneapolis campus.

1.3. C.W. Bill Young Stem Cell Transplantation Program

A U.S. Health Resources and Services Administration (HRSA) Contract (#HHSH234200637015C) was awarded on September 27, 2006 to the CIBMTR to administer the Stem Cell Therapeutic Outcomes Database (SCTOD) for the U.S. C.W. Bill Young Cell Transplantation Program. The Outcomes Database is charged with collecting data on all allogeneic (related and unrelated) HCTs done in the U.S. and all HCTs done with products procured through the C.W. Bill Young Program but performed outside the U.S. The Database will contain information critical for evaluation of the Program's operations and the status of transplant recipients. The goal is to make blood and marrow transplants available to all who need them and to increase their safety and effectiveness.

The infrastructure and expertise for data collection, management and analysis established through the U24-CA76518 allowed the CIBMTR to propose an approach to managing the Outcomes Database and its responsibilities that will be efficient for the government and for the transplant programs who must participate. However, the activities funded by this contract are largely separate from those funded by U24-CA76518. The emphasis of the Outcomes Database contract is collection of a basic set of data that will enable analyses of Program use, center-specific outcomes, donor registry and cord blood inventory size and patient access to HCT. This is a much more restricted data set (in terms of data fields captured) than the Research data set funded by U24-CA76518 (see Figure 3); the SCTOD will not capture data on most allogeneic transplants done in non-U.S. CIBMTR centers or on autologous

transplants. Additionally, the research scope of the Outcomes Database contract is narrowly specified and does not include the breadth of studies made possible by U24-CA76518. Additional information on the C.W. Bill Young Cell Transplantation Program and the SCTOD is included in Appendix 9.

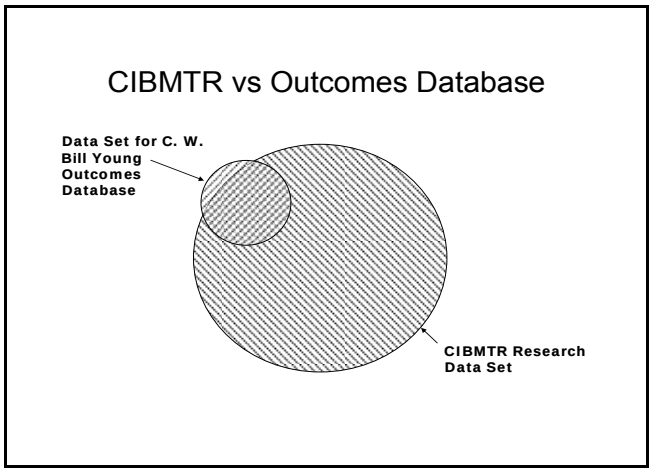


Figure 3

1.4. Selected CIBMTR Accomplishments in 2006:

- 406 Centers in 41 countries submitted data to the CIBMTR Statistical Center (Figure 4)
- A record 196 active studies are in progress within the 17 Working Committees
- A record 93 proposals for new studies were received prior to the 2006 annual meeting with a record 54 approved for initiation
- 10 presentations were made at the 2006 American Society of Hematology (2 posters, 8 oral)
- 48 scientific papers were submitted to, or accepted in or published in peer-reviewed journals
- The CIBMTR was approved as a Member Society of the Federation of Clinical Immunology Societies (FOCIS)
- 6503 samples were distributed by the NMDP Repository to Principal Investigators for Immunobiology Working Committee studies
- 6331 samples were distributed by the NMDP Repository for an ongoing NMDP retrospective high resolution HLA typing program that generates data for CIBMTR studies

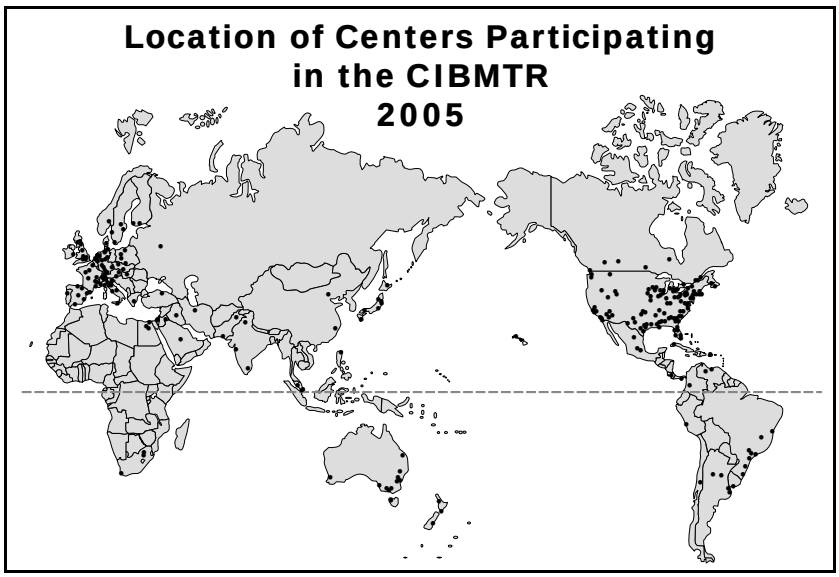


Figure 4

2.0 ACCRUAL

The CIBMTR collects data on large numbers of transplant recipients annually, including information on new patients and follow-up information on previously reported patients. Data come from two sources: CIBMTR centers, who must register consecutive transplant recipients, and NMDP transplant centers who must provide outcome data on all transplants facilitated by NMDP.

Figure 5 shows cumulative accession of allogeneic transplants since IBMTR data collection began in 1991, cumulative accession of autologous transplants since 1990 (when data collection for autotransplants was initiated) and cumulative accession of unrelated donor transplants through NMDP since 1987 *Table 2.1* shows the distribution of diseases for which transplants reported to CIBMTR were performed; the data include allogeneic transplants done since 1970 and autologous transplants since 1989. *Table 2.2* shows similar information for transplants reported to NMDP.

Until 1990, the IBMTR collected *comprehensive* clinical data on all patients transplanted in participating centers. Increasing numbers of patients and increasing demands on clinical research associates and data managers in participating centers then made such an approach impractical. In 1990, when initiating data collection for autotransplants, the IBMTR used a system whereby basic data (*Transplant Essential Data or Registration Forms)* were *registered* for all cases and comprehensive data *(Report Forms)* provided for a subset of these (see below). In 1995, the IBMTR expanded this dual level reporting to include allotransplants as well as autotransplants. Registration and Report Forms may be viewed on the CIBMTR website, www.cibmtr.org. NMDP requires a comprehensive report form on all transplants it facilitates.

The dramatic increase in Report Form submission to the IBMTR in the early 1990's reflected initiatives in use of peripheral blood stem cell allografts, cord blood transplants and autotransplants for solid tumors as well as continuing enthusiasm for the CIBMTR research program in the transplant community. It was also problematic since funds for reimbursing Report Forms are not unlimited. Steps were taken to limit the number of Report Forms submitted by allowing some centers to become *Registration Centers* (see Appendix 1). *Registration Centers* submit only the initial Transplant Essential Data (TED) form at 100 days posttransplant and the follow-up TED form yearly. The TED form was developed in collaboration with the European Group for Blood and Marrow Transplantation (EBMT), to minimize work for centers participating in both organizations (about 30% of CIBMTR centers) and to allow better collaboration and coordination between the two organizations. *Registration Centers* do not receive reimbursement for these data but do receive all CIBMTR publications and communications. Individuals at *Registration Centers* may serve on Working Committees but may not be officers and may not serve on the Executive Committee. Additionally, for the past several years we have exempted selected cases in *Research Centers* from comprehensive reporting requirements as described below.

The potential dangers in limiting collection of comprehensive data are twofold: the *Research database* may not be representative of the larger target population and some studies may lack adequate numbers of cases for analysis. To minimize these problems, we implemented a Preregistration system for *Research Centers* (those committed to providing complete Report Forms). The Preregistration system uses data from the TED form plus a few additional data fields to allow rational selection of patients for comprehensive data reporting. Research centers submit the TED form early in the course of the transplant procedure. Information is entered in a randomization program that weights cases for selection to provide adequate numbers of cases for current and future studies and to ensure adequate representation of all transplant types and indications. Centers receive notification of whether a full Report Form will be required within two business days, allowing prospective data collection for

designated patients. Detailed procedures for Registration and Pre-registration are found in the Instruction Manual which, along with the required forms, are available on the CIBMTR website (www.cibmtr.org).

Appendix 1 lists institutions currently reporting data to the CIBMTR and the NMDP. We estimate that the CIBMTR collects data on about 65% of allogeneic HCTs done in North and South America, about 30% of allogeneic transplants done elsewhere and about 60% of autologous HCTs done in North and South America. Legislation passed by the U.S. Congress in December 2005 requiring all U.S. transplant centers to submit allogeneic transplant outcomes data to a single national outcomes database will have impact on the volume of data received from within the U.S. (see section 1.3 above).

Significant efforts were made throughout 2006 to continue harmonization of all previous IBMTR and NMDP comprehensive data collection forms. This project, was completed in late December 2006 and involved key staff members from both the Milwaukee and Minneapolis campuses. A select group of transplant center data managers was given the opportunity to review the drafts and made valuable suggestions which were incorporated into the final forms. The release date for the major common forms with accompanying manuals has been delayed to synchronize with anticipated release of a new system to submit these data electronically, FormsNet2.0™ which is being developed in collaboration with NMDP's Information Services department. Several instructional sessions focused on these forms were held during the 2006 BMT Tandem meetings and additional training sessions are planned for the 2007 BMT Tandem meetings to orient data management personnel in participating centers.

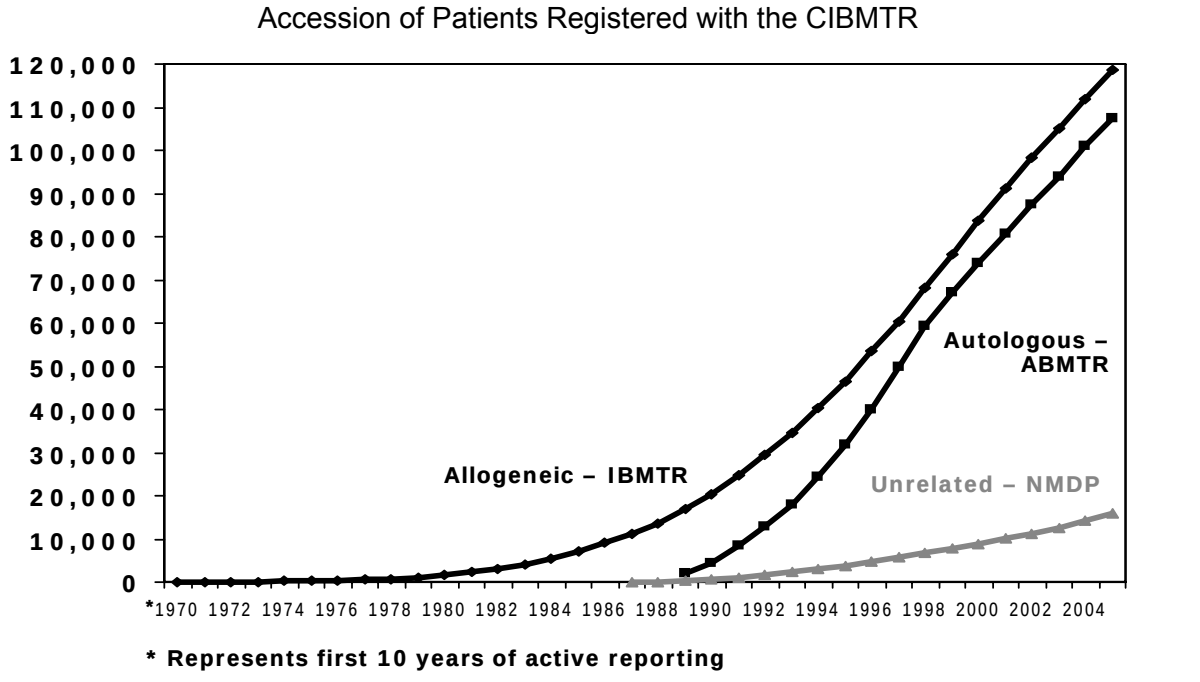


Figure 5

Table 2.1 Distribution of diseases in CIBMTR database submitted by IBMTR centers

	Allogeneic Transplants		Autologous Transplants	
Disease	Registration Data	Comprehen-sive Data	Registration Data	Comprehen-sive Data
Acute lymphoblastic leukemia	21115	9878	1419	426
Acute myelogenous leukemia	31736	13625	6507	1851
Chronic myelogenous leukemia	23915	11452	694	271
Chronic lymphocytic leukemia	1949	664	561	114
Hodgkin disease	957	341	12247	2151
Non-Hodgkin lymphoma	8063	2941	29752	6166
Plasma cell disorders	2765	1097	23791	4614
Breast cancer	162	89	23045	7692
Neuroblastoma	169	88	2669	759
Ovarian cancer	21	8	1666	692
Melanoma	45	15	58	2
Lung cancer	9	2	221	124
Sarcoma (soft tissue, bone and other)	54	14	789	248
Ewing sarcoma	59	24	716	236
Wilm tumor	6	2	247	45
Myelodysplastic syndromes	9002	3508	266	77
Other leukemia	1414	590	138	34
Medulloblastoma	4	3	535	119
Germ cell tumor	7	3	517	64
Brain tumors	5	3	1026	238
Testicular cancer	9	4	1180	485
Other malignancies[b]	493	209	789	248
Autoimmune diseases[c]	48	17	307	63
Severe aplastic anemia	8226	4969	—	—
Inherited erythrocyte abnormalities	4361	2826	—	—
SCID and other immunodeficiencies	3034	1418	—	—
Inherited disorders of metabolism	1516	779	—	—
Histiocytic disorders	522	236	—	—
Other non-malignancies	327	62	—	—
TOTAL	119993	54867	109140	26719

[a] Registration began in 1991 and comprehensive data collection in 1992; data for 1989-90 were collected retrospectively.

[b] Includes retinoblastoma, head and neck tumors, mediastinal neoplasms, GI tract tumors, pancreatic cancer, hepatobiliary, kidney and urinary tract tumors, prostate cancer, cervical, uterine cancer, vaginal cancer and thymoma.

[c] Includes multiple sclerosis (n=104), systemic sclerosis (n=46), systemic lupus erythematosis (n=57), rheumatoid arthritis (n=7), Idiopathic Thrombocytopenia Purpura. (N=8), Crohn's disease (n=11), other (n=72).

SCID= Severe Combine immune defieiency

Table 2.2 Distribution of diseases in NMDP database, 1987-2006 (comprehensive data available for all patients).

Disease	Total
Acute myelogenous leukemia	4453
Acute lymphoblastic leukemia	3109
Other leukemia	667
Chronic myelogenous leukemia	3522
Myelodysplastic.disorder	1699
Non-hodgkin lymphoma	939
Hodgkin lymphoma	60
Plasma cell disorder	130
Other Malignancies	47
Breast cancer	4
Severe aplastic anemia	786
Inherited erythrocyte abnormalities	34
SCID & other immune system disorders	288
Inherited platelet disorders	19
Inherited metabolism disorders	303
Histiocytic disorders	151
Other	17
Total	16228

3.0 CIBMTR STUDIES

The following section summarizes CIBMTR research activities over the past year and planned for the coming year. Publications include papers published, accepted for publication or submitted for publication, January through December 2006. Preliminary Results sections describe selected studies in final or near final stages of analysis or areas with other significant study-related activities over the preceding year. Abstracts are provided for selected studies; abstracts for other studies and reprints of published papers are available from the Statistical Center upon request. Planned studies are those in early stages of execution or planned to begin in the next year.

3.1 Acute Leukemia Working Committee.

Co-Chair: Armand Keating, MD, University of Toronto, Toronto, Ontario, Canada
Co-Chair: Martin S. Tallman, MD, Northwestern University, Chicago, IL
Co-Chair: Jorge Sierra, MD, Hospital Sant Pau, Barcelona, Spain
Statisticians: Waleska S. Pérez, MPH
Mei-Jie Zhang, PhD
Scientific Director: Daniel J. Weisdorf, MD

3.1.1 Publications

LK98-07/D96-66: Lazarus HM, Pérez WS, Klein JP, Kollman C, Bate-Boyle B, Bredeson CN, Gale RP, Geller RB, Keating A, Litzow MR, Marks DI, Miller CB, Rizzo JD, Spitzer TR, Weisdorf DJ, Zhang M-J, Horowitz MM. **Autotransplantation versus HLA-matched unrelated donor transplantation for acute myeloid leukemia (AML): a retrospective analysis from the Center for International Blood and Marrow Transplant Research.** *Br J Haematol. 132:755-769, 2006*. Most patients with AML lack HLA-identical sibling donors for transplantation. Autotransplants and unrelated donor transplants are therapeutic options. To compare autologous versus unrelated donor transplantation for AML in first (CR1) or second complete remission (CR2), we compared the outcomes of 668 autotransplants with outcomes of 476 unrelated donor transplants reported to the CIBMTR. Proportional hazards regression adjusted for differences in prognostic variables. In multivariate analyses treatment-related mortality was significantly higher and relapse lower with unrelated donor transplantation. Adjusted three-year survival probabilities (95% confidence intervals [CI]) were: in CR1 57 (53-61)% with autotransplants and 44 (37-51)% with unrelated donors (p=0.002); in CR2, 46 (39-53)% and 33 (28-38)%, respectively (p=0.006). Adjusted three-year leukemia-free survival probabilities were in CR1, 53 (48-57)% with autotransplants and 43 (36-50)% with unrelated donor (p=0.021); CR2 39 (32-46)% and 33 (27-38)%, respectively (p=0.169). We concluded that both autologous and unrelated donor transplantation produce prolonged leukemia-free survival. High treatment-related mortality offsets the superior anti-leukemia effect of unrelated donor transplantation three-year survival for AML patients in CR1 and CR2. Cytogenetics, however, were known in only two-thirds of patients and an influence of selection bias on results cannot be excluded.

LK98-10: Tallman MS, Pérez WS, Lazarus HM, Gale RP, Maziarz RT, Rowe JM, Marks DI, Cahn J-Y, Bashey A, Bishop MR, Christiansen N, Frankel SR, García JJ, Ilhan O, Laughlin MJ, Liesveld J, Linker C, Litzow MR, Luger S, McCarthy PL, Milone GA, Pavlovsky S, Phillips GL, Russell JA, Saez RA, Schiller G, Sierra J, Weiner RS, Zander AR, Zhang M-J, Keating A, Weisdorf DJ, Horowitz MM. **Pretransplantation consolidation chemotherapy decreases leukemia relapse after autologous blood and bone marrow transplants for acute myelogenous leukemia in first remission.** *Biol Blood Marrow Transplant. 12:204-216, 2006.* There is controversy about whether pretransplant

consolidation chemotherapy affects outcome of subsequent autotransplantation for AML. To determine the association between prior consolidation and outcome of autotransplantation for AML in first remission, we compared posttransplant outcomes of 146 patients receiving no consolidation versus outcomes of 244 patients receiving standard-dose (<1 gm/m^2) and 249 receiving high-dose (1-3 gm/m^2) cytarabine prior to autotransplantation. We used proportional hazards regression to adjust for differences in pretransplant prognostic variables. One-year treatment-related mortality was similar among the cohorts. Five-year relapse rates were 49 (39-58)% with no consolidation versus 35 (29-42)% with standard-dose cytarabine versus 40 (33-48)% with high-dose cytarabine (p=0.07). Five-year leukemia-free survival rates were: 39 (30-47)% with no consolidation, 53 (46-60)% with standard-dose cytarabine and 48 (40-56)% with high-dose cytarabine (p=0.03). Similarly, five-year overall survival was better among patients receiving consolidation: 42 (34-51)% with no consolidation, 59 (52-65)% with standard-dose cytarabine and 54 (46-61)% with high-dose cytarabine (p=0.01). Most patients received one or two cycles of consolidation, there was no detectable effect of the number of consolidation courses on transplant outcome. In multivariate analyses, risks of relapse and treatment failure were lower in patients receiving consolidation, especially among patients receiving blood cell grafts. Outcomes were similar with standard-dose and high-dose cytarabine. We conclude that patients with AML in CR1 remission should receive consolidation before autotransplantation.

LK00-01: Marks DI, Forman SJ, Blume KG, Pérez WS, Weisdorf DJ, Keating A, Gale RP, Cairo MS, Copelan EA, Horan JT, Lazarus HM, Litzow MR, McCarthy PL, Schultz KR, Smith DD, Trigg ME, Zhang M-J, Horowitz MM. **A comparison of cyclophosphamide and total body irradiation with etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografts for acute lymphoblastic leukemia in first or second complete remission**. *Biol Blood Marrow Transplant. 12:438-453, 2006.* We compared outcomes of 298 patients with acute lymphoblastic leukemia (ALL) in CR1 or CR2 receiving HLA-matched sibling allografts after cyclophosphamide and total body irradiation (Cy-TBI) conditioning with 204 patients receiving etoposide and TBI (etposide-TBI). Four groups were compared: Cy-TBI<13 Gy (n=217), Cy-TBI≥13 Gy (n=81), etoposide-TBI<13 Gy (n=53) and etoposide-TBI≥13 Gy TBI (n=151). Analyses of relapse, leukemia-free survival and survival were done separately for CR1 and CR2 transplants. Treatment-related mortality did not differ by conditioning regimen. In CR1, there were also no significant differences in relapse, leukemia-free survival or survival by conditioning regimen. In CR2, outcomes differed among conditioning groups. In comparison with Cy-TBI<13 Gy, risks of relapse, treatment failure (inverse of leukemia-free survival) and mortality tended to be lower with etoposide (regardless of TBI dose) or with TBI doses ≥13 Gy. For both CR1 and CR2 transplants, causes of death were similar among the groups; disease recurrence accounted for 47% of deaths. We conclude that for HLA-identical sibling allografts for ALL in CR2, there is an advantage in substituting etoposide for Cy or, when using Cy, to increasing TBI doses to ≥13 Gy.

D00-52: Tallman MS, Dewald GW, Gandham S, Logan BR, Keating A, Lazarus HM, Litzow MR, Mehta J, Pedersen T, Pérez WS, Rowe JM, Wetzler M, Weisdorf, DJ. **Impact of cytogenetics on outcome of matched unrelated donor HCT for acute myeloid leukemia in first or second complete remission**. *Blood, In Press.* We compared treatment-related mortality, relapse rate, disease-free survival and overall survival by cytogenetic risk group in 263 patients with AML in CR1and 300 patients in CR2 undergoing matched unrelated donor HCT. Among patients in CR1, disease-free survival rates at 5 years were similar for patients with favorable, intermediate and unfavorable cytogenetics: 29 (8-56)%, 30 (22-38)%, 27 (19-39)% and 29 (8-56)%, respectively. Among patients in CR2, disease-free survival rates at 5 years were 42 (33-52)%, 35 (28-43)% and 38 (23-54)% with favorable, intermediate and unfavorable cytogenetics. We conclude that cytogenetics have little association with overall outcome of unrelated donor HCT for patients in CR1. Among those in CR2, outcome is modestly, but not significantly, better for patients with favorable cytogenetics. The graft-versus-leukemia effect

appears effective, even in patients with unfavorable cytogenetics. Matched unrelated donor HCT should be considered for patients with unfavorable cytogenetics who lack an HLA-matched sibling donor.

R02-28: Bishop MR, Logan BR, Gandham S, Bolwell BJ, Cahn J-Y, Lazarus HM, Litzow MR, Marks DI, Wiernik PH, McCarthy PL, Russell JA, Miller CB, Sierra J, Milone G, Keating A, Loberiza FR, Giralt S, Horowitz MM, Weisdorf DJ. **Hematopoietic stem cell transplantation for adults with acute lymphoblastic leukemia: Comparative analysis of autologous and unrelated donor bone marrow transplantation following a myeloablative conditioning regimen.** *Submitted.* For adults with high risk or recurrent ALL, who lack a suitable sibling donor, the decision between autologous and unrelated donor HCT is difficult due to variability in relapse and treatment-related mortality. An analysis was performed on data from two transplant registries to determine outcomes between autologous and unrelated donor HCT for 260 adult ALL patients in CR1 or CR2. All patients received a myeloablative conditioning regimen. Treatment-related mortality at one year post-transplant was higher with unrelated donor HCT ($p < 0.001$); however, there was minimal difference in treatment-related mortality according to disease status (unrelated donor HCT: CR1 = 45% vs. CR2 = 41%; Autologous HCT: CR1 = 5% vs. CR2 = 6%). Relapse at 3 years post-transplant was higher with autologous HCT and increased in patients transplanted in CR2 (CR1/autlogouso = 45% vs. CR1/unrelated donor = 15%, $p < 0.0001$; CR2/autologous = 81% vs. CR2/unrelated donor = 24%, $p <0.0001$). Five year leukemia-free (29% vs. 33%) and overall survival (29% vs. 34%) rates were similar for autologous vs. unrelated donor HCT, respectively; these results were not significantly affected by disease status at transplant. These data suggest either autologous or unrelated donor HCT can result in long-term survival for adult ALL patients, but the optimal time (CR1 vs. CR2) to perform HCT remains an important question. Efforts to decrease TRM in unrelated donor HCT and relapse rates in autologous HCT are necessary to improve the efficacy of these two options for adult ALL patients.

LK03-02: Schlenk RF, Pasquini MC, Pérez WS, Zhang M-J, Krauter J, Antin JH, Bashey A, Bolwell BJ, Büchner T, Cahn J-Y, Cairo MS, Copelan EA, Cutler C, Döhner H, Gale RP, Ilhan O, Lazarus HM, Liesveld JL, Litzow MR, Marks DI, Maziarz RT, McCarthy PL, Nimer SD, Sierra J, Tallman MS, Weisdorf DJ, Horowitz, MM, Ganser A. **HLA-identical sibling allogeneic transplants versus chemotherapy in acute myelogenous leukemia with t(8;21) in first complete remission: Collaborative study between the German AML Intergroup and CIBMTR**. *Submitted*. We studied the role of HLA-matched sibling HCT in treating t(8;21) AML in first remission by comparing outcomes of 118 patients receiving HCT with 132 similar patients receiving chemotherapy. Characteristics of the cohorts were similar except that chemotherapy recipients were significantly older. To adjust for time to treatment bias, outcomes were compared using left-truncated Cox regression models. Transplants were associated with higher treatment-related mortality [relative risk (RR) 6.76, 95% confidence interval (CI) 2.95-15.45, $p<0.001$], lower relapse (RR 0.47, 95% CI 0.25-0.85, $p=0.01$) and similar relapse-free survival ($p=0.2$). Loss of sex chromosomes (LOS) in addition to t(8;21) significantly affected overall survival. Patients without LOS experienced shorter survival after HCT (RR 3.05, $p=0.02$), whereas patients with LOS had similar survival regardless of postremission therapy. In both cohorts, white blood cell count (WBC) at diagnosis > 25 $x10^9$/L was associated with a higher relapse risk (RR=2.09, $p=0.03$), lower relapse-free (RR=1.9, $p=0.008$) and overall survival (RR=1.91, $p=0.01$). In this cohort of patients with t(8;21) AML , HCT did not improve overall survival, since reduction of relapse was offset by high transplant-related mortality, These results suggest that HCT should be reserved for patients with t(8;21) AML who fail postremission therapy.

3.1.3 Planned Studies

LK01-02: Treatment of relapsed and refractory AML: Outcomes of HCT versus salvage chemotherapy. *(Study Chair: M de Lima, MD Anderson Cancer Center, Houston, TX; Study Statistician: WS Pérez).*

LK02-02: Allogeneic HCT for treatment of therapy-related myelodysplastic syndrome and AML. *(Study Chair: MR Litzow, Mayo Clinic, Rochester, MN; Study Statistician: WS Pérez).*

R02-05: Unrelated donor HCT for AML and ALL relapsing after autologous transplantation. *(Study Chairs: J Foran, University of Alabama, Birmingham, AL; S Pavletic, NIH Bethesda, MD; Study Statistician: WS Pérez).*

R02-09: Evaluation of donor leukocyte infusions to treat relapsed hematologic malignancies after related and unrelated donor myeloablative HCT. *(Study Chairs: A Loren, University of Pennsylvania, Philadelphia, PA; D Porter, University of Pennsylvania, Philadelphia, PA; J Leis, Oregon Health and Sciences University, Portland, OR; Study Statistician: WS Pérez).*

R02-14/LK04-02/GV01-01: Comparison of conventional versus reduced intensity conditioning for allogeneic HCT in patients with AML or myelodysplasia. (*Chairs: SM Luger, University of Pennsylvania, Philadelphia, PA; M Pulsipher, University of Utah School of Medicine, Salt Lake City, UT; O Ringdén, Huddinge University Hospital, Huddinge, Sweden; B Bolwell, Cleveland Clinic Foundation, Cleveland, OH; Study Statistician: WS Pérez).*

LK03-03: Outcome of HCT in patients with active leukemia at the time of transplantation. *(Study Chair: M Duval, Service d'Hemato-Oncologie, Hôpital Sainte-Justine, Montreal, QC, Canada; Study Statistician: V He).*

R03-50: Outcome and prognostic factors for unrelated donor transplantation for adult Philadelphia negative ALL in CR1. *(Study Chair: D Marks, Bristol Children's Hospital, Bristol, UK; Study Statistician: V He).*

LK04-01: Comparison of autologous and allogeneic HCT for acute promyelocytic leukemia in CR2. *(Study Chairs: M Rubinger, CancerCare Manitoba, Winnipeg, Manitoba, Canada; A Grigg, Royal Melbourne Hospital, Melbourne, Victoria, Australia; J Szer Royal, Melbourne Hospital, Melbourne, Victoria, Australia; M Tallman, Northwestern University, Chicago, IL; Study Statistician: WS Pérez).*

LK04-03: Comparison of autologous and HLA-identical sibling HCT for AML in CR1. *(Study Chairs: A Keating, Princess Margaret Hospital, Toronto, Ontario, Canada; V Gupta, Princess Margaret Hospital, Toronto, Ontario, Canada; C Cutler, Dana Farber Cancer Institute, Boston, MA; Study Statistician: M Kukreja).*

LK05-01: Outcome of allogeneic HCT in AML with adverse-risk karyotype in CR1 using HLA-matched related versus alternative donors. *(Study Chairs: V Gupta, Princess Margaret Hospital, Toronto, Ontario, Canada; M Tallman, Northwestern University, Chicago, IL; Study Statistician: WS Pérez).*

LK05-02: Analysis of second unrelated donor HCT for relapsed leukemia: Comparison of transplantation using the same versus a different donor. *(Study Chairs: A Toor, Loyola University Medical Center, Maywood, IL; P Stiff, Loyola University Medical Center, Maywood, IL; D Weisdorf, University of Minnesota, Minneapolis, MN; Study Statistician: WS Pérez).*

LK05-03: Extramedullary relapse following allogeneic HCT for AML. *(Study Chairs: B Savani, NIH, Bethesda, MD; J Barrett, NIH, Bethesta, MD; Study Statistician: WS Pérez).*

LK06-01: Comparison of allogeneic HCT transplantation versus conventional chemotherapy for AML in CR1 in patients age 60 years and older. *(Study Chairs: S Farag, Indiana University Cancer Center, Indianapolis, IN; Study Statistician: M-J Zhang).*

3.2 Chronic Leukemia Working Committee.

Co-Chair: Sergio Giralt, MD, MD Anderson Cancer Center, Houston, TX
Co-Chair: Jeffrey Szer, MD, Royal Melbourne Hospital, Parkville, Australia
Co-Chair: Ann Woolfrey, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Statisticians: Manisha Kukreja MBBS, MPH
Sergey Tarima, PhD
Scientific Director: Mukta Arora, MD, MS

3.2.1 Publications

CK02-02: Giralt SA, Arora M, Goldman JM, Lee SJ, Maziarz RT, McCarthy PL, Sobocinski KA, Horowitz MM for the Chronic Leukemia Working Committee of the CIBMTR. **Effect of introduction of imatinib on use of HCT for chronic myelogenous leukemia (CML).** S*ubmitted.* The discovery and approval of imatinib drastically changed the therapeutic algorithm for CML. Imatinib is now considered the therapy of choice for patients with newly diagnosed CML, including those previously considered candidates for allogeneic HCT. We compared numbers and types of allogeneic HCTs performed for CML in North America before and after the introduction of imatinib, and publication of the International Randomized Trial of Interferon and STI571 (IRIS) using transplants reported to the CIBMTR. The number of HCTs for CML registered with the CIBMTR in 1998 was 617; 62% were done in first chronic phase. Only 1% of patients had received imatinib prior to transplantation. In 2003, the number of HCTs reported was 223. 44% were done in first chronic phase and 77% of patients had received imatinib prior to transplantation. The introduction of imatinib therapy has had a profound impact on the use of allogeneic transplantation for CML with a marked decrease in the number of transplants for CML and an accompanying decrease in the proportion done in early chronic phase. Most patients now receive a trial of imatinib before proceeding to HCT.

3.2.2 Preliminary Results

CK98-02: Long-term follow-up of HCT for chronic lymphocytic leukemia (CLL). (*Study Chair: E Montserrat, Institute of Hematology & Oncology, Barcelona, Spain; Study Statistician: K Sobocinski*) *Analyses in progress.* In 1996, we reported on 54 patients receiving allotransplants for CLL in 1984-92. Transplant-related mortality was high but about 40% of patients achieved long-term survival. Since then, numbers of persons receiving allogeneic and autologous transplants for CLL have increased. We studied 242 patients receiving allografts and 83 patients receiving autografts for CLL in 1990-99. Median age was 47 years for allograft recipients and 50 years for autograft recipients. 211 had received two or more prior treatment regimens; 186 received fludarabine for at least one of these regimens. The median interval between diagnosis and transplantation was 46 months (range, 2-214 months). Allografts tended to be done in patients with more advanced, resistant disease. At time of transplantation, 37% of allograft recipients and 70% of autograft recipients were in clinical CR or had Rai stage 1 disease. 78% of allografts were from HLA-identical siblings, 10% from other relatives and 12% from unrelated donors; 14% were T-cell depleted. Peripheral blood was the graft source for 25% of allografts and 71% of autografts. 72% of autografts were treated to remove CLL cells. The most common conditioning regimens were CyTBI (42%) and CyTBI plus other drug(s) (33%) for allografts

and CyTBI (80%) for autografts. 100-day mortality was 18% with HLA-identical sibling transplants, 30% with alternative donor transplants, and 1% with autotransplants. Three-year survival probabilities were 49 (41-57)%, 41 (27-55)%, and 87 (81-96)%, respectively. In preliminary analyses, survival after allografts was better in patients with less advanced disease and good performance status. These data indicate that HCT was increasingly used as salvage therapy for CLL in the 1990s with encouraging rates of long-term survival. Data on long-term (>5 year) outcomes were collected during the past year and are being analyzed.

CK00-02: Outcome of allogeneic transplantation for myelofibrosis. *(Study Chairs: K Ballen, Massachusetts General Hospital, Boston, MA; S Giralt, MD Anderson Cancer Center, Houston, TX; Study Statistician: K Sobocinski) Manuscript in preparation.* Myelofibrosis is a myeloproliferative disorder characterized by splenomegaly, bone marrow fibrosis and immature white and red blood cells. Allogeneic transplantation is the only curative therapy. In this study, we analyzed the outcomes of 320 patients receiving allogeneic HCT for myelofibrosis between 1989 and 2002. This is the largest report of HCT for myelofibrosis. Patients received a variety of conditioning and GVHD prophylaxis regimens. Most received ablative conditioning with either TBI (n=117) or busulfan (n=150) and Cy. Bone marrow was the graft source in 208 patients. 170 transplants were from an HLA-identical sibling donor, 117 from an unrelated donor, and 33 from an alternative related donor. Median ages at transplant were 45 (<1-73), 47 (1-69) and 40 (<1-65) years, respectively. Median follow up times for survivors were 41 (3-136), 48 (4-124) and 32 (7-118) months, respectively. Both early and long-term survival rates were highest after HLA-identical sibling transplantation. 100-day mortality was 22% after sibling transplants, 42% after unrelated donor transplants, and 27% after alternative family donor transplants. Corresponding five-year overall survival rates were 39%, 31% and 31%. In multivariate analysis of 215 adult recipients of myeloablative transplants, having an HLA-identical sibling donor, Karnofsky performance score greater than or equal to 90% at time of HCT younger age, more recent date of transplantation, and absence of blasts in peripheral blood prior to HCT correlated with better survival. Among 18 patients with all of these favorable factors, the five-year probability of survival was 81%. In conclusion, 1) allogeneic HCT cures approximately 1/3 of patients with myelofibrosis; 2) young patients with HLA-matched sibling donors have superior survival; 3) results have improved over the last decade. Future research directions will focus on the use of reduced intensity conditioning regimens to reduced treatment-related mortality.

CK00-05: Identical-twin transplants for B-cell CLL. *(Study Chair: S Pavletic, National Cancer Institute, Bethesda, MD; Study Statistician: K Sobocinski). Manuscript in preparation.* Studies of genetically identical-twin transplants are a novel opportunity to study how transplants work because: (1) there is no allogeneic graft versus leukemia effect; (2) there are no leukemia cells in the graft; and (3) there is no graft exposure to chemotherapy. We conducted an international study that identified 19 subjects who received syngeneic bone marrow (N=11) or blood cell (N=8) transplants after myeloablative conditioning. Eleven were males; median age was 51 years (range, 37-68 years). Eighteen received TBI. None had Richter transformation. Interval from diagnosis to HCT was 27 months (5-171 months). At transplant, 8 had Rai stage 3/4 disease, 5 had >50x10^9/L lymphocytes, 10 had received >3 prior therapies, 8 had received prior fludarabine, and 5 had a prior CR. Eighteen engrafted and 13 achieved posttransplant CR; the median time to CR was 3 months (1-5 months). The probability of survival at 100 days was 89 (72-99)%. 10 subjects are alive (8 disease-free) at a median follow-up of 63 months range, (9-116 months). Ten subjects either never achieved CR (N=6) or relapsed posttransplant (N=4). The five-year cumulative incidence of relapse was 52 (27-77)%. Estimated five-year overall and leukemia-free survival probabilities were 59 (34-81)% and 43 (20-67)%, respectively. Causes of death were interstitial pneumonitis (N=1) and leukemia (N=8). The five-year cumulative incidence of treatment-related mortality was 5 (0-20)%. We used a highly sensitive PCR method to examine post transplant blood (2 patients) or bone marrow (2 patients) samples for the tumor specific IgH gene (CDR III) to assess minimal residual disease. IgH CDR III was polymerase

chain reaction amplified in pretransplant B-CLL samples from 4 patients to obtain the sequence to design tumor-specific primer probes for minimal residual disease. No evidence of residual disease was detected in two patients at 12 and 21 months posttransplant. A very weak clonal signal was identified in one patient at 64 months. All three of these patients were in continuous clinical CR at 12, 60, and 66 mo, respectively. In one patient, who relapsed with B-CLL 6 years after transplant, molecular studies at 10 years post transplant demonstrated a very strong molecular signal but of a different clone. Additional investigation identified familial CLL where the donor was also diagnosed with B-CLL soon after marrow donation. Molecular analysis of the donor B-CLL showed a clone identical to the recipient's post-transplant relapse, strongly indicating B-CLL transmission at the time of HCT. This study demonstrates that identical twin transplants can be performed in advanced B-CLL with low treatment-related mortality and with a high-rate of durable clinical and molecular remissions. The five-year leukemia relapse rate of 52% is higher than that in studies of similar subjects receiving allotransplants but lower than after autotransplants. We also report B-CLL transfer from a twin donor demonstrating the need for careful evaluation of allogeneic donors prior to graft collection.

CK02-03: Matched pairs analysis of intravenous (IV) versus oral busulfan as a conditioning agent prior to transplantation. *(Study Chair: M Horowitz, CIBMTR, Milwaukee, WI; Study Statistician: K Sobocinski). Manuscript in preparation.* Using CIBMTR data on outcome of transplants performed using oral busulfan as part of the pretransplant conditioning regimen, a matched pairs analysis was conducted comparing these data against clinical data obtained from patients receiving IV busulfan in four Phase II clinical studies and two clinical amendments. The primary objective of the analysis was to compare two clinically important outcomes in patients receiving IV versus oral busulfan, i.e., overall survival to day 100, and the incidence of either hepatic veno-occlusive disease (VOD) or mortality through post-transplant day +28 (VOD28). Primary matching criteria included disease, disease stage/status, stem cell source, and performance score at time of transplant; a goal of three oral busulfan matches per each IV busulfan recipient was sought. A total of 216 patients (161 allotransplant recipients, 55 autotransplant recipients) were identified in the CIBMTR database that matched criteria for 101 of the 138 IV busulfan patients. No matches could be found for 37 IV busulfan patients. Of the 101 IV busulfan patients (70 allo, 31 auto), 47 had three, 21 had two, and 33 had one CIBMTR oral busulfan match(es). There were no graft failures among the patients receiving IV busulfan; six (2.9%) oral busulfan patients failed to engraft (p=0.19). Overall incidence of VOD28 was 4.6% (4/83) with IV and 20.3% (38/149) with oral busulfan (p<0.001). Among autotransplant recipients, 100-day mortality was 0% for those receiving IV and 9.3% for those receiving oral busulfan (p=0.16). Among allotransplant recipients, 100-day mortality was 8.7% with IV and 22.5% with oral busulfan (p=0.015). Logistic regression analysis showed that only the mode of busulfan administration was a significant factor for the risk of VOD28, with IV busulfan associated with a greatly reduced risk (p=0.004) compared to oral busulfan. Bayesian analyses provided the same conclusion, and indicated that there was a >99% probability that IV busulfan was superior to oral busulfan with regard to the probability of VOD28 and 100-day mortality. Logistic regression analyses by treatment group indicated that IV busulfan was associated with a lower probability of 100-day mortality compared to oral busulfan for all patients combined (p=0.005) and for allogeneic transplant recipients only (p=0.021), but not for autotransplant recipients. In conclusion, based on this matched pair analysis, there appears to be a beneficial effect of using IV rather than oral busulfan on the outcome of HCT, with lower early mortality associated with IV administration.

CK03-02: Late relapse in long-term CML survivors. *(Study Chairs: J Douglas Rizzo, CIBMTR, Medical College of Wisconsin, Milwaukee, WI and J Goldman, Hammersmith, London, UK; Study Statistician: K Sobocinski). Manuscript in preparation.* We studied 6548 recipients of allogeneic HCTs performed between 1978 and 1997 to determine long-term rates of overall survival, disease-free survival and relapse. As of December 2002, 2710 of the 6548 had survived for >5 yr, 1926 for >7 yr, 1044 for >10 yr, 212 for >15 yr and 7 for >20 yr. 2234 patients were alive and in continuing remission

five or more years post-HCT. Of these, the median age at HCT was 34 years, 60% had received TBI as part of their conditioning; 67% had received cyclosporine and methotrexate for GVHD prophylaxis. Among patients alive and in remission five years after HCT, the cumulative incidences of subsequent relapse at 15 years post-HCT were 17%, 15%, 12% and 7% for recipients of sibling transplants in first chronic phase, recipients of sibling transplants not in first chronic phase, recipients of alternative donor transplants in first chornic phase and recipients of alternative donor transplants not in first chronic phase, respectively. The latest relapse occurred 16 years post-HCT. Corresponding survival rates at 15 years were 85%, 83%, 80% and 75%. 174 of the 2234 patients surviving in remission at five years post HCT subsequently died; the causes of death were CML (2% of five-year survivors), GVHD (1%), second cancer (<1%), infection (1.4%), organ failure (<1%) and other (1%). We conclude that remissions after allogeneic HCT are generally durable. However, after a high-risk period early post-HCT, there is a low but constant risk of relapse. Rescue strategies in patients with late relapse may include donor cell infusions or imatinib, though few data exist regarding the efficacy of these approaches in this patient group.

3.2.3 Planned Studies

CK02-01: Busulfan versus TBI for conditioning prior to allogeneic transplantation. *(Study Chair: E Copelan, Ohio State University, Columbus, OH; Study Statistician: M Kukreja)*.

R02-25: Impact of HLA genetic disposition on clinical outcome of unrelated HCT for CML. *(Study Chair: E Petersdorf, Fred Hutchinson Cancer Center, Seattle, Washington; Study Statistician: M Haagenson)*.

CK03-01: Impact of imatinib on HCT outcome. *(Study Chairs: S Lee, Dana Farber Cancer Institute, Boston, MA; R Maziarz, Oregon Health Sciences University, Portland, OR; Study Statistician: M Kukreja).*

CK04-01: Comparison of outcome of allogeneic HCT and imatinib mesylate therapy in patients with chronic phase CML. *(Study Chairs: F Ravandi, R. Champlin, MD Anderson, Houston TX; Study Statistician: M Kukreja).*

CK06-03: Reduced intensity conditioning prior to allogeneic HCT for CLL/small cell lymphocytic lymphoma. *(Study Chairs: J Leis, R. Maiziarz, R. Sobeck, Oregon Health & Science University, Portland, Oregon; Study Statistician: M Kukreja).*

3.3 Lymphoma Working Committee.

Co-Chair: Hillard M. Lazarus, MD, Case Western Reserve University, Cleveland, OH
Co-Chair: Julie M. Vose, MD, University of Nebraska, Omaha, NE
Co-Chair: Koen van Besien, MD, University of Illinois, Chicago, IL
Statisticians: Jeanette Carreras, MPH
Mei-Jie Zhang, PhD
Scientific Director: Parameswaran Hari, MD, MS

3.3.1 Publications

LY01-02: Navarro WH, Loberiza, Jr FR, Bajorunaite R, Armitage JO, Ballen K, Bashey A, Bredeson CN, Carreras J, Freytes CO, Gibson J, Hale GA, Horowitz MM, Lazarus HM, LeMaistre CF, Lister J, Marks D, Martino R, Maziarz RT, Pavlovsky S, Schiller G, Schouten HC, Stadtmauer E, van Besien K, Vose JM, Rizzo JD**. Impact of body mass index on mortality of patients with lymphoma**

undergoing autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant 12:541-551, 2006.* High-dose therapy with autologous HCT is frequently used to improve outcomes in lymphoma. However, small studies suggest a survival disadvantage among obese patients. Using a retrospective cohort analysis, we studied the outcomes of 4,681 patients undergoing autologous HCT for Hodgkin or non-Hodgkin lymphoma between 1990 and 2000 according to body mass index (BMI). Four groups categorized by BMI were compared using Cox proportional hazards regression to adjust for other prognostic factors. 1,909 patients were categorized as normal weight (BMI=18-25), 121 underweight (BMI<18), 1,725 overweight (BMI>25-30), and 926 obese (BMI>30) at time of HCT. Outcomes evaluated include overall survival, relapse, treatment-related mortality, and lymphoma-free survival. Treatment-related mortality was similar among the normal, overweight and obese groups; the underweight group had a higher risk of treatment-related mortality (RR 2.46, 95% CI 1.59-3.82, p<0.0001] compared to the normal BMI group. No differences in relapse were noted. Overall mortality was higher in the underweight group (RR 1.48, 95% CI 1.17-1.88, p=0.001) and lower in the overweight (RR 0.87, CI 0.79-0.96; p=0.004) and obese (RR 0.76, 95% CI 0.67-0.86, p<0.0001) groups compared to the normal BMI group. In the light of our inability to find differences in survival among overweight, obese and normal weight patients, obesity alone should not be viewed as a contraindication to proceeding with autologous HCT for lymphoma when otherwise indicated.

LY02-01: Hari P, Carreras J, Zhang MJ, Rizzo JD, Gale RP, Armitage JO, Bashey A, Bolwell BJ, Bredeson CN, Bujan-Boza WA, Burns LJ, Cairo MS, Freytes CO, Gibson J, Goldstein SC, Hale GA, Herzig RH, Inwards DJ, Keating A, LeMaistre CF, Maharaj D, Marks DI, Mason JR, Maziarz RT, McCarthy PL, Miller AM, Shouten HC, Slavin S, Urbano-Ispizua A, Wiernik PH, Vose JM, Lazarus HM, Van Besien K**. Reduced-intensity versus myeloablative conditioning prior to HLA-matched sibling HCT for follicular lymphoma.** *Submitted.* We compared outcomes of HLA-identical sibling transplants for follicular lymphoma in 224 recipients reported to the CIBMTR between 1997 and 2002. Conditioning regimens were categorized as myeloablative (N=127) or reduced-intensity (N=97). Reduced intensity transplants increased from <10% of transplants in 1997 to about 80% in 2002. Median follow-up of survivors was 37 mo (4-82 mo) for reduced intensity versus 49 mo (4-96 mo) for myeloablative transplants (p=0.001). At 3 years, overall survival rates for the reduced intensity and myeloablative cohorts were 62 (52-72)% and 70 (62-78)%, respectively (p=NS). Corresponding progression free survival rates were 53 (43-63)% and 66 (58-74)% (p=NS). In multivariate analysis, there were no differences in treatment-related mortality, progression-free or overall survival between the cohorts. A lower Karnofsky performance score and resistance to chemotherapy pretransplant were associated with higher treatment-related mortality and lower progression-free and overall survival. Intensity of the conditioning regimen did not correlate with any of these outcomes. An increased risk of lymphoma-progression after reduced intensity transplants was not statistically significant (RR=1.93, 95% CI 0.92-4.07, p=0.08). We found no significant benefits for reduced intensity compared to conventional conditioning. Further study with a larger dataset and longer follow-up is needed to assess the risk of relapse following reduced intensity conditioning.

3.3.2 Preliminary Results

LY01-01: Outcome of autologous HCT for Non-Hodgkin lymphoma (NHL) in patients age 55 years or older. *(Study Chair: H Lazarus, Case Western Reserve University, Cleveland, OH; Study Statistician: J Carreras). Manuscript in preparation.* The goal of this study was to compare the clinical outcomes of elderly (age $\geq$ 55 years) versus younger (< 55 years) patients receiving autotransplant for NHL while adjusting for patient-, disease-, and treatment-related variables. We studied autotransplant outcomes in 1,004 NHL patients age $\geq$ 55 years and 2,331 NHL patients<55 years during the years 1990-2000. Younger patients were more likely to have follicular lymphoma, B symptoms at diagnosis, primary refractory disease, to receive marrow rather than blood as the graft source, and to receive a TBI-containing preparative regimen. In multivariate analysis, older patients were more likely than

younger patients to experience treatment-related mortality. Relapse risk was higher in older patients who received hematopoietic growth factors. Among patients with chemosensitve disease, the risks of treatment failure and death were higher in older than in younger patients; no differences in outcome by age were observed for patients with chemo-resistant disease. Autotransplant in elderly NHL patients is feasible but disease-related outcomes and treatment-related mortality are statistically inferior to younger patients. Studies to improve supportive approached in older patients are needed.

LY04-02: Autologous versus HLA-identical sibling transplantation for diffuse large cell lymphoma. *(Study Chair: B Hayes-Lattin, Oregon Health Science University, Portland, OR; Study Statistician: J Carreras). Manuscript in preparation. Poster presentation at American Society of Hematology meeting, December 2006*. No randomized trials have compared autologous HCT to allogeneic HCT for diffuse large B-Cell lymphoma. We analyzed the outcomes of 916 patients, 837 receiving autotransplants and 79 receiving HLA-identical sibling transplants, ages 18-60 years, between 1995 and 2003. Patients receiving T-cell depleted allografts or reduced-intensity conditioning were excluded. There were significant baseline differences between the groups in disease stage, B symptoms, extranodal disease and marrow involvement. Allotransplant recipients were significantly more likely to have $\geq$3 chemotherapy regimens prior to HCT (53% versus 40%), and to have chemo-resistant lymphoma (39% versus 16%). At one year, treatment-related mortality was higher after allotransplantation (41 [30-52]%) than after autotransplantation (11[9-14]%, p<0.001), but risks of relapse/progression were similar (30 [21-41]% and 33 [29-36]%, respectively, p=0.69). Outcomes are summarized in the table below. In multivariate analysis, allogeneic and autologous HCT had differential early and late effects on outcomes. In the first 12 months after transplant, allogeneic HCT was associated with higher treatment-related mortality (RR 4.76, 95% CI 3.14-7.22, p<0.001), treatment failure (RR 2.08, 95% CI 1.56-2.77, p<0.001) and mortality (RR 2.78, 95% CI 2.06-3.77, p<0.001) but similar risk of progression (RR 1.14, 95% CI 0.75-1.74, p=0.54) compared to autologous HCT. Among patients surviving 12 mo post-transplant, no significant difference was observed in subsequent outcomes. Covariates that increased the risks of treatment-related and overall mortality were older age (51-60 years), Karnofsky performance score <90%, chemoresistance at transplant, and earlier transplant year (before 2001 versus later). Older age and chemoresistance were also associated with lower progression-free survival. There were no significant interactions between graft type and other prognostic variables; in particular, relative risks of outcomes with allogeneic versus autologous HCT were similar for patients with chemosensitive and chemoresistant disease. In summary, myeloablative allogeneic HCT increased risks of early treatment-related mortality and mortality without a beneficial effect on progression compared to autologous HCT.

Outcomes	AutoHCT (95%CI)	AlloHCT (95%CI)
Acute GVHD @ day100	N/A	42 (31-53)
Chronic GVHD @ 5years	N/A	27 (18-38)
Treatment-related mortality @ 5years	18 (15-20)	45 (34-57)
Relapse/progression @ 5years	39 (36-43)	33 (23-44)
Progression-free survival @ 5years	43 (40-46)	26 (18-37)
Overall survival @ 5years	49 (46-53)	27 (18-37)

LY05-02: Clinical outcome of a second autologous HCT for NHL and Hodgkin disease relapsing after a first autologous HCT. *(Study Chair: S Smith, University of Chicago, Chicago, IL; Study Statistician: J Carreras). Manuscript in preparation. Poster presentation at American Society of*

Hematology meeting, December 2006. Autologous HCT salvages many patients with relapsed lymphomas but few patients relapsing after autologous HCT are cured. We determined feasibility of stem cell collection, engraftment kinetics, treatment-related mortality, progression free survival and overall survival for a second autologous HCT (HCT2) for lymphoma relapsing after prior autologous HCT (HCT1). We studied 35 patients, 20 with Hodgkin disease and 15 with diffuse or follicular large cell and immunoblastic NHL, receiving HCT2 for relapse between 1986 and 2003. Median (range) age at HCT2 was 36 years (16-61); 61% had a performance score less than 90. HCT2 was performed >1 year after HCT1 in 80%. Median (range) time from diagnosis to HCT1 was 20 mo (4-162 mo), from HCT1 to relapse, 17 mo (3-68 mo), and from relapse to HCT2, 5 mo (1-40 mo). 83% underwent a 2nd stem cell / marrow harvest prior to HCT2. Median time to an absolute neutrophil count >0.5 x 10^9/L was 11 days. The best response to HCT2 was complete remission in 22 patients and partial remission in 5; 8 patients had either no response or progressive disease. At a median follow up of 92 mo (32-124 mo) after HCT2, 26 patients (74%) have died with 17 (65%) dying of relapsed lymphoma. Two (6%) patients developed therapy-related myelodysplasia. The probability of treatment-related mortality at day 100 was 12 (3-25)%. The one, three and five-year probabilities of progression-free survival were 45 (29-62)%, 33 (18-50)% and 30 (15-46)%, respectively. The one, three and five-year probabilities of overall survival were 63 (46-78)%, 34 (12-50)% and 31 (17-47)%, respectively. There were no differences in outcomes between Hodgkin disease or NHL. Patients relapsing more than six months after HCT1 appeared to have better overall survival. In summary, HCT2 is feasible in patients with lymphoma after relapsing an HCT1. Stem cells harvested prior to HCT2 resulted in rapid engraftment with a day 100 treatment-related mortality (12%) lower than that reported for allogeneic HCT in this setting. Relapse is the primary reason for failure, but approximately one-third of patients enjoy long-term disease free survival. HCT2 should be considered for young patients with relapsed Hodgkin disease or NHL post-HCT1 without alternative transplant options.

	HCT1 (%)	HCT2 (%)
Sensitive disease status pre-HCT	26 (79)	24 (75)
Stem cell source: Bone marrow	15 (43)	10 (29)
Blood	13 (37)	21 (60)
Both	7 (20)	4 (11)
Median days to platelet recovery $\geq$ 20 x 10^9/L	17 (7-376)	20 (1-101)
Stem cell harvest between HCT1 and HCT2		29 (83)
Different conditioning regimen for HCT2		25 (74)
Outcomes		
Treatment-related mortality @ 1 yr		21 (9-37)
Progression-free survival @ 5years		30 (15-46)
Overall survival @ 5 years		31 (17-47)

LY05-03: Allogeneic HCT with non-myeloablative or reduced intensity conditioning for relapsed and refractory Hodgkin disease. *(Study Chair: M Devetten, University of Nebraska Medical Center, Omaha, NE; Study Statistician: J Carreras). Manuscript in preparation. Oral presentation at American Society of Hematology meeting, December 2006*. Myeloablative allogeneic HCT salvages some patients with relapsed and refractory Hodgkin disease but has high treatment-related mortality. Reduced intensity conditioning regimens attempt to lower treatment-related mortality, in particular after previous autotransplants. We studied the outcomes of 143 patients after unrelated donor HCT using reduced intensity conditioning for relapsed and refractory Hodkgin disease between 1999 and 2004. Reduced intensity was defined following established CIBMTR criteria as TBI<500 cGy, busulfan<9 mg/kg, melphalan<150 mg/m2 or fludarabine without busulfan/melphalan. Median (range) age was 30 years (13-53), 68% had a Karnofsky score $\geq$ 90%, 95% patients had $\geq$ 3 chemotherapy regimens prior to HCT and 89% had undergone prior autotransplant. At transplant 62 (44%) had chemosensitive disease and 67 (47%) were chemoresistant. At a median follow-up of 25 months (range, 3-64 months), the

probability of day 100 mortality was 18 (12-25)%, acute GVHD grade 2-4 was 60 (51-69)%, chronic GVHD at two years was 68 (60-76)% and treatment-related mortality at two years was 33 (25-41)%. Probabilities of progression free survival were was 30% at one year and 20% at two years. Probabilities of overall survival were 56% at one year and 37% at two years. Relapse/progression was rare after two years. Presence of extranodal disease (RR 2.36, 95% CI 1.26-4.41, p=0.007) and Karnofsky performance score <90% (RR 3.05, 95% CI 1.58-5.87, p<0.001) predicted treatment-related mortality. Extranodal disease (RR 2.11, 95% CI 1.34-3.31, p<0.001), elevated serum LDH at transplant (RR 1.86, 95% CI 1.18-2.93, p=0.001) and Karnofsky performance score <90% (RR 2.33, 95% CI 1.45-3.75, p<0.001) were associated with increased risk of death. The major cause of death (44%) was progressive Hodgkin disease. A comparison group of 38 patients reciving myeloablative unrelated donor HCT between 1996 and 2004 was also analyzed. The myeloablative HCT group did not differ in age, performance score or extranodal disease, but differed in GVHD prophylaxis, previous autologous HCT (74% versus 89% in the reduced intensity group, p=0.02) and stem cell source (peripheral blood 45% versus 73%, p<0.001). More myeloablative HCT recipients (63%) were transplanted before 2003 and a yearly increase in proportion of reduced intensity transplants was seen. Use of donor lymphocyte infusions was similar (13% of myeloablative versus 14% of reduced intensity recipients). There was a lower risk of treatment-related mortality with reduced intensity compared to myeloablative HCT that did not reach statistical significance. However, the available sample size meant that this comparison had low statistical power. We conclude that unrelated donor HCT using reduced intensity conditioning is associated with acceptable early treatment-related mortality and can salvage some heavily pretreated patients with relapsed and refractory Hodgkin disease.

3.3.3 Planned Studies

D98-10: Unrelated donor HCT for NHL *(Study Chair: P Bierman, University of Nebraska Medical Center, Omaha, NE; Study Statistician: G Nelson).*

LY03-01: Effects of pre-transplant in-vivo rituximab on the outcomes of autologous HCT in patients with NHL. (*Study Chair: J Vose, University of Nebraska Medical Center, Omaha, NE; Study Statistician: J Carreras).*

LY04-01: Alternative donor HCT for children with NHL. *(Study Chair: G Hale, St. Jude Children's Research Hospital, Memphis, TN; Study Statistician: J Carreras).*

LY04-03: Outcomes of autologous versus allogeneic HCT for patients with NHL with pre-existing central nervous system involvement. *(Study Chair: R Maziarz, Oregon Health & Science University, Portland, OR; Study Statistician: J Carreras).*

LY05-01: Effectiveness of donor leukocyte infusion in the management of relapsed NHL after allogeneic HCT. *(Study Chair: M Tomblyn, University of Minnesota, Minneapolis, MN; Study Statistician: J Carreras).*

LY06-01: Effects of pre-transplant rituximab therapy on the outcomes of allogeneic HCT for NHL. *(Study Chair: H Khoury, Washington University School of Medicine, St. Louis, MO; Study Statistician: J Carreras).*

LY06-02: Nonmyeloablative HCT in patients who experience relapse after autologous stem cell transplantation for lymphoma. *(Study Chair: C Freytes, University of Texas Health Science Center, San Antonio, TX; Study Statistician: J Carreras).*

LY06-03: HLA identical sibling HCT versus HLA matched unrelated donor HCT in patients with follicular lymphoma. *(Study Chair: A Sureda, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; Study Statistician: J Carreras).*

LY06-05: Comparison of autologous versus allogeneic HCT for T-cell NHL. *(Study Chair: S Smith, University of Chicago, Chicago, IL; Study Statistician: J Carreras).* .

LY06-06: A prognostic model for prolonged event-free survivalafter autologous or allogeneic HCT for relapsed and refractory Hodgkin's disease. *(Study Chair: P McCarthy, Roswell Park Cancer Institute, Buffalo, NY; Study Statistician: J Carreras).*

3.4 Plasma Cell Disorders Working Committee.

Co-Chair: Donna Reece, MD, Princess Margaret Hospital, Toronto, Ontario, Canada
Co-Chair: David H. Vesole, MD, St. Vincent's Comprehensive Cancer Center, New York, NY
Co-Chair: Gustavo Milone, MD, Angelica Ocampo-Fundaleu, Buenos Aires, Argentina
Statisticians: Waleska S. Pérez, MPH
Mei-Zie Zhang, PhD
Scientific Director: Parameswaran Hari, MD, MS

3.4.1 Publications

MM00-01: Vesole DH, Pérez WS, Akasheh M, Boudreau C, Reece DE, Bredeson CN for the Plasma Cell Disorders Working Committee of the Center for International Blood and Marrow Transplant Research. **High dose therapy and autologous HCT for patients with primary systemic amyloidosis: A CIBMTR study**. *Mayo Clin Proc. 81:880-888, 2006*. The purpose of this study was to determine the outcome of high dose therapy with autologous HCT in patients with primary systemic amyloidosis. 107 eligible patients from 48 transplant centers were reported to the CIBMTR between 1995 and 2001. Hematologic and organ responses were assessed at 100 days and one year. Treatment-related mortality was assessed at day +30 post-HCT. A multivariate analysis assessed factors influencing overall survival. Improvement at day + 100 was seen in $\geq$ 1 amyloid-affected site (bone marrow, kidney, liver, heart) in 28 of 77 patients (36%); the one year responses included complete response (16%), partial response (16%), stable disease (31%) and disease progression (10%). With a median follow up of 30 months, the 1 and 3-year survival rates were 66 (56-75)% and 56 (45-66)%, respectively. Day + 30 treatment-related mortality was 18 (11-26)%. In multivariate analysis, only the year of transplant (those patients most recently transplanted) was associated with post-HCT survival (p=0.024). In this multi-institutional CIBMTR study, the 3-year survival was comparable to single center results with more recently transplanted patients faring better. Of note, treatment-related mortality was higher than that reported by single centers which may reflect differences in patient selection and/or experience in treating this challenging disease. Better understanding of recently recognized prognostic factors and more stringent patient selection will hopefully result in lower treatment-related mortality and improved survival.

MM01-01: Anagnostopoulos A, Hari PN, Pérez WS, Ballen K, Bashey A, Bredeson CN, Freytes CO, Gale RP, Gertz MA, Gibson J, Goldschmidt H, Lazarus HM, McCarthy PL, Reece DE, Vesole DH, Giralt SA. **Autologous or allogeneic stem cell transplantation in patients with waldenstrom's macroglobulinemia**. *Biol Blood Marrow Transplant. 12:845-854, 2006*. The role of HCT in Waldenstrom's macroglobulinemia has not been extensively studied. To determined the potential for long term disease control using HCT, we performed a retrospective review of 36 patients with Waldenstom's who received autologous (N=10) or allogeneic (N=26) HCT 1986 and 2002. The following outcomes were described: non-relapse mortality, relapse, progression-free survival and

overall survival. Median age at the time of HCT was 51 (range, 30-76) years and median time from initial treatment to HCT was 29 (range, 2-198) months. Seventy-eight percent of the patients had ≥2 prior chemotherapy regimens and 52% had resistant disease to salvage chemotherapy. Fifty-eight percent of patients in the allogeneic HCT group received myeloablative conditioning regimens containing TBI, 19% of all allograft recipients received a non-myeloablative/reduced intensity conditioning. After a median follow-up of 65 months, 15/36 (42%) patients are alive. Primary disease accounted for 29% and 25% of the deaths in the allogeneic and autologous HCT groups respectively. Relapse rate at three years was 29 (14-48)% and 24 (4-54)% for the allogeneic and autologous HCT group respectively. Progression-free survival at three years was 31 (14-50)% and 65 (32-91)% and overall survival was 46 (27-65)% and 70 (40-93)% respectively for the allogeneic and autologous HCT group. Non relapse mortality at three years was 40 (23-59)% and 11 (0-36)% respectively for the allogeneic and autologous HCT groups. Autologous HCT is a safe and feasible treatment option for patients with Waldenstrom's especially for those who present with adverse prognostic factors. Allogeneic HCT carries a much higher (40%) non-relapse-mortality risk and should not be considered outside the context of a clinical trial.

3.4.2 Preliminary Results

MM00-02: Outcomes following syngeneic HCT for multiple myeloma: A matched comparison to autologous transplantation. *(Study Chair: A Bashey, Blood and Marrow Transplant Group of Georgia, Atlanta, GA; Study Statistician: WS Pérez). Manuscript in preparation. Oral presentation at the American Society of Hematology meeting in December 2006.* Relapse is the main cause of treatment failure following autologous HCT for multiple myeloma. Syngeneic HCT offers the advantage of a myeloma-free-graft. However, a potential disadvantage is the lack of a graft versus myeloma effect. We compared the probabilities of treatment-related mortality, disease progression, progression-free survival and overall survival after syngeneic versus autologous HCT for myeloma done between 1988 and 2003. Median follow up was >70 months in both groups. 43 syngeneic HCT recipients were matched to 170 autologous HCT recipients using a propensity score. The propensity score was calculated using the variables of age, Durie-Salmon stage at diagnosis, sensitivity to pretransplant therapy, time from diagnosis to HCT and year of HCT; scores ranged from 0.004-0.286. Syngeneic HCT recipients (cases) were matched in random order to autologous transplant (control) recipients with similar propensity scores. Patients who underwent tandem transplants were excluded. Median age (range) was 53 and 52 years in cases and controls. Most patients in both groups (60% of cases, 66% of controls) were transplanted within 12 months of diagnosis. Except for a higher proportion of patients with IgG myeloma (58% versus 41%, p<0.01) and peripheral blood grafts (92% versus 56%, p<0.01) in the control group there were no statistically significant differences in baseline characteristics between the two groups. Five-year outcomes are summarized in the table.

5-year outcome, probability (95% CI)	Syngeneic	Autologous
Treatment-related mortality	14 (6-26)	9 (5-13)
Disease progression	43 (28-59)	71 (64-78)
Progression-free survival	42 (27-58)	20 (14-27)
Overall survival	60 (44-75)	40 (32-48)
Median follow up survivors, months	88 (23-161)	85 (3-151)

In multivariate analysis, risks of progression and treatment failure were significantly lower after syngeneic than autologous HCT [RR of progression=0.49,95%CI 0.28-0.86, p=0.011); RR of treatment failure=0.64, 95%CI 0.40-1.05, p=0.08)]. Treatment-related mortality at one year was 14 (6-26)% in the syngeneic group and 9 (5-13)% in controls (p=0.31). The five-year risk of mortality was lower in the syngeneic group but the difference was not statistically significant (RR= 0.68, 95%CI 0.40-1.16, p=0.15). Disease recurrence accounted for 80% of deaths in the autologous and 55% in the syngeneic

cohort. We conclude that syngeneic HCT for multiple myeloma results in superior progression-free survival and lower progression rates compared to autologous HCT, confirming previous smaller analyses and emphasizing the importance of a disease-free graft. Interestingly, these data suggest that relapse rates similar to those observed after nonmyeloablative allogeneic transplantation - another source of tumor free grafts - can occur in the absence of clinical GVHD.

3.4.3 Planned Studies

MM02-01/D01-117: Comparison of second autologous transplant versus related or unrelated non-myeloablative allogeneic HCT in patients with multiple myeloma who relapse after autologous transplantation. *(Study Chairs: C Freytes, University of Texas Health Science Center, San Antonio, TX; D Vesole, St. Vincent's Comprehensive Cancer Center, NY, NY; Study Statistician: WS Pérez)*.

MM02-02: Outcomes of non-secretory versus secretory multiple myeloma after autologous transplantation. *(Study Chairs: S Kumar, Mayo Clinic, Rochester, MN; M. Lacey, Mayo Clinic Rochester, MN; Study Statistician: WS Pérez)*.

MM02-03/MM03-01: The graft-versus-myeloma effect in patients receiving non-myeloablative conditioning. *(Study Chair: O Ringdén, Huddinge University Hospital, Huddinge, Sweden; Study Statistician: WS Pérez)*.

MM04-01: Comparison of Durie-Salmon and International Prognostic Index staging systems as predictors of outcomes in patients with multiple myeloma undergoing HCT. *(Study Chair: P Hari, CIBMTR, Milwaukee, WI; Study Statistician: WS Pérez).*

MM05-01: Clinical outcome of patients with IgD and IgM multiple myeloma undergoing autologous HCT. *(Study Chair: D Reece, Princess Margaret Hospital, Toronto, Ontario, Canada; Study Statistician: WS Pérez).*

MM05-02: Effect of obesity on outcome in patients with multiple myeloma undergoing autologous HCT. *(Study Chair: D Vogl, University of Pennsylvania, Philadelphia, PA; Study Statistician: WS Pérez).*

MM06-01: Outcomes of autologous stem cell transplantation after initial treatment with a thalidomide-containing or non-thalidomide-containing induction regimen for multiple myeloma. *(Study Chair: V Roy, Mayo Clinic, Jacksonville, FL; Study Statistician: WS Pérez).*

MM06-02: Clinical outcome of high-dose chemotherapy and autologous HCT in elderly patients with multiple myeloma. *(Study Chairs: A Chanan-Khan, Roswell Park Cancer Institute, Buffalo, NY; S Kumar, Mayo Clinic, Rochester, MN; Study Statistician: WS Pérez).*

MM06-03/HS06-01: Comparison of outcomes of autologous HCT for multiple myeloma between the African-American and Caucasian-American populations. *(Study Chairs: P Mehta, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR; P Hari, CIBMTR, Milwaukee, WI; Study Statistician: A Hassebroek).*

MM06-04: Comparison of outcomes of patients undergoing autologous transplantation after achieving less than a partial response to initial chemotherapy compared with those receiving additional salvage chemotherapy prior to undergoing autologous transplantation. *(Study Chairs: R Vij, Washington University, St. Louis, MO; Study Statistician: WS Pérez)*.

3.5 Solid Tumors Working Committee.

Co-Chair: Patrick J. Stiff, MD, Loyola University Medical Center, Maywood, IL
Co-Chair: Richard Childs, MD, National Heart, Lung and Blood Institute, Bethesda, MD
Co-Chair: Didier Blaise, MD, Institut Paoli Calmettes, Marseille, France
Statistician: Kathleen A. Sobocinski, MS
Sergey Tarima, PhD
Scientific Director: Mukta Arora, MD MS

3.5.1 Publications

BC99-01: Ueno NT, Rizzo JD, Demirer T, Cheng YC, Hegenbart U, Zhang MJ, Bregni M, Carella A, Blaise D, Bashey A, Bitran JD, Bolwell BJ, Elfenbein GJ, Fields KK, Freytes CO, Gale RP, Lazarus HM, Champlin RE, Stiff PJ, Niederwieser D. **Allogeneic HCT for metastatic breast cancer.** *Submitted.* To determine the feasibility and efficacy of allogeneic HCT for metastatic breast cancer, we reviewed data from 18 CIBMTR/EBMT centers for 76 women who underwent allogeneic HCT between 1992 and 2000. Median age at transplantation was 41 years (range, 25-60 years) and median follow-up for the survivors was 25 months. At time of transplantation, 28 patients (37%) had responsive disease (20 partial responses), 22 (29%) had stable disease, and 18 (24%) had progressive disease. Of the 76 patients, 66 (87%) received stem cells from an HLA-matched sibling and 2 (3%) from an unrelated donor. Sixty-eight patients (90%) received peripheral blood stem cells and 6 (11%) received bone marrow. Acute GVHD occurred in 39 patients (51%) and was grade III-IV in 14 patients (36%). Chronic GVHD occurred in 19 patients (25%). Treatment-related mortality at day 100 was 22%. Overall survival at two years was 22%. Median survival time and median time to progression were both 8 months; 15% remained free of progression at two years. Progression-free survival at two years was 9%, with median progression-free survival of 4 months. Univariate analysis revealed that the presence of any GVHD (acute or chronic) was associated with longer time to progression (11 versus 3 months, P=0.03), but GVHD had no effect on overall or progression-free survival.

ST99-01: Lazarus HM, Stiff PJ, Carreras J, Logan BR, Akard L, Bolwell BJ, Childs RW, Gale RP, Klein JP, Lill MC, Pérez WS, Stadmauer EA, Rizzo JD. **Utility of single versus tandem autotransplants for advanced testes/germ cell cancer.** *Submitted.* Tandem autotransplants are used to treat advanced testis cancer but their value compared to a single autotransplant is unknown. To evaluate the results of autotransplant in relapsed testicular/germ cell cancer, we analyzed data from 300 patients undergoing autotransplants in 1989-2002. We compared results for those patients intended to undergo tandem autotransplant procedures (N=102) versus patients in whom a second autotransplant was not planned (N=198). Five-year survival probability was 35 (25-46)% in the planned tandem transplant cohort compared to 42 (35-49)% in the group not planned to have a second transplant (p=0.29). Probability of progression-free survival at 5 years for these cohorts was 34 (25-44)% and 38 (31-45)%, respectively (p=0.50). The planned tandem autotransplant cohort had significantly more advanced disease at diagnosis and greater likelihood of cisplatin-resistance. Patients intended to receive tandem transplants had lower treatment-related mortality at one year (3% versus 10%, p=0.02). Using propensity scores to adjust for differences in other potential prognostic factors, the planned tandem autotransplant cohort had significantly lower treatment-related mortality (p=0.044) but no difference in the risk of relapse (p=0.541) compared to the planned single transplant cohort. These results indicate that tandem autotransplants for testicular cancer may have lower treatment-related mortality risks than single transplants with no differences in disease-related outcomes or overall survival at 3 years. Patient selection bias for either transplant approach, however, may affect the results of this observational study; a randomized trial is needed to determine which approach, if either, is better.

3.5.2 Preliminary Results

PC99-02: Autologous blood or marrow stem cell transplantation for Ewing sarcoma. *(Study Chair: S Gardner, The Hassenfeld Children's Center, New York, NY; Study Statistician: J Carreras). Manuscript in preparation.* Despite initial responses to standard dose chemotherapy and irradiation, most patients with high risk or recurrent Ewing sarcoma ultimately succumb to their disease. The aim of this study was to determine progression-free and overall survival of patients with Ewing sarcoma treated with autotransplantation and to examine factors associated with post-HCT survival. We studied 136 patients; two-thirds received HCT as part of their initial treatment and one-third were treated after developing recurrent disease. The three-year progression-free and overall survival rates for the entire cohort were 31 (23-39)% and 36 (28-45)%, respectively. Factors associated with poor survival following HCT included poor performance status, metastatic disease and relapse prior to intensive therapy. Patients with localized tumors treated with HCT as part of their initial therapy had three-year progression and overall survival rates of 52% and 62%, respectively. Patients with metastatic disease at diagnosis treated with HCT prior to relapse had three-year progression-free and overall survival rates of 34% and 39%, respectively. There were no survivors amongst the 9 patients receiving HCT for relapsed metastatic disease. At the present time, there does not appear to be a role for autotransplantation in patients with recurrent Ewing sarcoma who had metastatic disease at diagnosis. Patients with localized disease with high risk features and a subset of patients with metastatic disease may have improved survival with the use of autotransplantatiaon as part of their initial treatment.

3.5.3 Planned Studies

ST99-03: High dose chemotherapy with autologous blood or marrow transplantation for soft tissue sarcoma. *(Study Chair: P Stiff, Loyola University Medical Center, Maywood, IL; Study Statistician: M Agovi).*

ST00-02: Allografts for renal cell cancer. *(Study Chair: A John Barrett, NHLBI/NIH, Bethesda, MD; Study Statistician: K Sobocinski).*

ST02-02: Allografts for colorectal cancer. *(Study Chair: A John Barrett, NHLBI/NIH, Bethesda, MD, O Ringden, Huddinge University Hospital, Huddinge, Sweden; Study Statistician: K Sobocinski*).

ST06-01: Autografts for desmoplastic tumors. *(Study Chair: E Staudtmauer, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Study Statistician: K Sobocinski).*

ST06-02: Allografts for ovarian cancer. *(Study Chair: JO Bay, Centre Jaen Perrin, Clermont-Ferrand, France, D. Blaise, Institut Paoli Calmettes, Marseille, France; Study Statistician, K Sobocinski)*

3.6 Pediatric Cancers Working Committee.

Co-Chair: Bruce M. Camitta, MD, Midwest Children's Cancer Center, Medical College of Wisconsin, Milwaukee, WI
Co-Chair: Stephan Grupp, MD, Children's Hospital of Philadelphia, Abramson Pediatric Research Center, Philadelphia, PA
Co-Chair: Stella Davies, MD, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH
Statisticians: Dan Wang, MS
Mei-Jie Zhang, PhD
Scientific Director: Mary Eapen MD, MS

3.6.1 Publications

PC03-02: Eapen M, Raetz E, Zhang M-J, Muehlenbein C, Devidas M, Abshire T, Billett A, Homans A, Camitta B, Carroll W and Davies SM. **Outcomes after HLA-matched sibling transplantation or chemotherapy in children with B-precursor acute lymphoblastic leukemia in a second remission: a collaborative study of the Children's Oncology Group and the Center for International Blood and Marrow Transplant Research.** *Blood 107:4961-4967, 2006.* The best treatment approach for children with B-precursor ALL in CR2 after a marrow relapse is controversial. To address this question, we compared outcomes in 196 patients enrolled on chemotherapy trials and 186 HLA-matched sibling transplants, treated between 1991 and 1997. Groups were similar except that chemotherapy recipients were younger (5 versus 8 years) and less likely to have combined marrow and extra-medullary relapse (12% versus 30%). To adjust for time-to-transplant bias, treatment outcomes were compared using left-truncated Cox regression models. The relative efficacy of chemotherapy and transplantation depended on time from diagnosis to first relapse and the transplant conditioning regimen used. For children with early first relapse (<36 months), risk of a second relapse was significantly lower with HCT with a TBI containing conditioning regimen (RR 0.50, 95% CI 0.34-0.73, p=0.0004) than with chemotherapy regimens. For children with a late relapse, risks of second relapse were similar after HCT with a TBI-containing regimen and chemotherapy but significantly higher after HCT with non-TBI containing conditioning regimens (RR 2.51, 95%CI 1.23-5.16, p=0.01). These data support HLA-matched sibling donor transplantation using a TBI-containing regimen in CR2 for children with ALL and early relapse.

PC03-03: Eapen M, Rubinstein P, Zhang M-J, Camitta BM, Stevens C, Cairo MS, Davies SM, Doyle JJ, Kurtzberg J, Pulsipher MA, Ortega JJ, Scaradavou A, Horowitz MM, Wagner JE. **Comparable long-term survival after unrelated and HLA-matched sibling donor hematopoietic stem cell transplantations for acute leukemia in children younger than 18 months.** *J Clin Oncol 24:145-151, 2006.* Outcomes in children younger than 18 months at diagnosis of acute leukemia undergoing HLA-matched sibling donor transplantation with bone marrow grafts (n=101) and unrelated donor transplantation with bone marrow (n=85) or cord blood grafts (n=81) were compared using Cox proportional hazards models. Unrelated donor transplant recipients were younger, more likely to have MLL gene rearrangement, to have advanced disease, and to have received irradiation prior to transplant. Treatment-related mortality rates were 6%, 15% and 31% after HLA-matched sibling, unrelated donor bone marrow and unrelated donor cord blood transplantation, respectively. Risks of relapse, overall and leukemia-free survival were significantly associated with disease status at transplantation, with worse outcome in infants with advanced leukemia. Though unrelated donor transplantation done in CR1 was associated with the lowest disease recurrence, overall and leukemia-free survival rates were similar after HLA-matched sibling and unrelated donor transplantation after adjustment for disease status. Relapse, survival and leukemia-free survival after unrelated donor transplants did not differ by graft type; three-year probabilities were 49% and 54% after HLA-matched sibling and unrelated donor transplantation in CR1, respectively. Corresponding rates for those with advanced disease were 20% and 30%. We conclude that unrelated donor transplantation should be considered for infants with acute leukemia in CR1 using the same eligibility criteria as is currently used for those with HLA-matched sibling donors.

PC03-05: Eapen M, Zhang MJ, Devidas M, Raetz E, Barredo JC, Ritchey AK, Godder K, Grupp S, Lewis VA, Malloy K, Carroll WL, Davies SM, Camitta BM. **Outcomes after HLA-matched sibling transplantation or chemotherapy in children with acute lymphoblastic leukemia in a second remission after an isolated central nervous system relapse: A collaborative study of the Children's Oncology Group and the Center for International Blood and Marrow Transplant Research.** *Submitted. Oral presentation at the American Society of Hematology meetings in December 2006.* The optimal treatment for children with ALL in second remission after an isolated central nervous system relapse is unknown. To address this question, we compared outcomes in 149

patients enrolled on Pediatric Oncology Group chemotherapy trials 9061 (n=79) and 9412 (n=70) and HLA-matched sibling transplant recipients (n=60) reported to the CIBMTR. Patients received treatment between 1990 and 2000. Median follow-up was 8 years and 9 years after chemotherapy and transplantation, respectively. Groups were similar with respect to sex and leukocyte count at diagnosis. Chemotherapy recipients were younger at diagnosis (5 versus 7 years) and more likely to have had a longer duration of first remission (duration of first remission $\geq$18 months: 70% versus 48%). All transplant recipients received bone marrow grafts and 83% received a TBI-containing preparatory regimen. The median time to transplantation after achieving a second remission was 2.5 months (range, <1 – 8). To adjust for time-to transplant bias, we used left-truncated Cox regression models to examine treatment outcomes. Risks of a subsequent leukemia relapse were similar in both treatment groups. As expected, risks of a subsequent leukemia relapse were significantly higher in older patients (11-17 years; RR 2.63, p-0.004) and those with a short duration of first remission ($\leq$18 months; RR 4.22, p<0.001) regardless of type of treatment. Relative to chemotherapy recipients, risks of treatment-related mortality (RR 4.29, p=0.001), treatment failure (RR 2.37, p=0.003) and overall mortality (RR 2.68, p=0.002) in the first two years after achieving a second remission were significantly higher in recipients of HLA-matched sibling transplants. Among chidlren who survived the first two years after achieving second remission, subsequent mortality and treatment failure risks did not differ by treatment group. In both treatment groups, recurrent leukemia was the commonest cause of death (60% and 56% after chemotherapy and transplantation, respectively). The 8-year probabilities of leukemia-free survival (adjusted for age and duration of first remission) were 66% and 58% after chemotherapy and transplantation, respectively. These data support use of chemotherapy alone for patients with ALL and isolated central nervous system relapse who achieve a second remission regardless of duration of first remission.

3.6.2 Preliminary Results

D01-59: Unrelated donor bone marrow transplants for AML in children. *(Study Chair: N Bunin, Children's Hospital of Philadelphia, Philadelphia, PA; Study Statistician: D Wang). Manuscript in preparation.* We analyzed patients who received unrelated donor bone marrow transplants for AML in patients <18 years and transplanted in 1990–2003 in the U.S. Recipients of peripheral blood or umbilical cord blood grafts and those who reduced intensity conditioning regimens were excluded. Nine-five percent of 337 eligible surviving cases were followed for a minimum of 12 months after transplantation. Primary outcomes studied were neutrophil recovery, grades 2 – 4 acute and chronic GVHD, treatment-related mortality, relapse, leukemia-free survival and overall survival. Cumulative incidence rates were calculated for neutrophil recovery, grades 2 – 4 acute GVHD, chronic GVHD, treatment-related mortality and relapse. Probabilities of leukemia-free and overall survival were calculated using the Kaplan-Meier estimator. Risks of grades 2-4 acute GVHD were higher in recipients of T-replete bone marrow grafts, those with poor performance score at transplantation and those who received their grafts from female donors. Risks of chronic GVHD were higher in older transplant recipients (>10 years). Treatment-related mortality was higher in older transplant recipients (>10 years). Leukemia relapse was significantly higher in recipients transplanted after primary induction failure or in relapse at transplantation. There were no significant differences in risks of relapse between those transplanted in CR1 and CR2. Treatment failure (relapse or death; inverse of leukemia-free survival)was significantly higher in older recipients, those transplanted after primary induction failure or in relapse and poor risk cytogenetics. There were no significant differences in risks of treatment failure between those transplanted in CR1 and CR2. Overall mortality was significantly higher in older recipients, those transplanted after primary induction failure or in relapse and those with intermediate or poor risk cytogenetics. There were no significant differences in risks of overall mortality between those transplanted in CR1 and CR2. Recurrent leukemia was the most common cause of mortality.

3.6.3 Planned Studies

D98-071: Analysis of engraftment and outcome of unrelated donor transplantation for pediatric myelodysplastic syndrome. *(Study Chair: P Woodard, St. Jude Children's Research Center, Memphis, TN, J Perentesis, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Study Statistician: D Wang).*

D01-59: Outcomes after unrelated donor HCT for children with AML. *(Study Chair: N Bunin, Children's Hospital of Philadelphia, Philadelphia, PA; Study Statistician: D Wang).*

R02-34: Outcomes after unrelated donor HCT in children with Philadelphia chromosome positive ALL. *(Study Chair: H Frangoul, Vanderbilt University Medical Center, Nashville, TN; Study Statistician: D Wang*).

PC05-01: Outcomes after HCT for children with NHL. *(Study Chair: G Hale, St. Jude Children's Research Hospital, Memphis, TN, T. Gross, Children's Hospital of Columbus, Columbus, OH; Study Statistician: D Wang).*

PC05-02: Outcomes after unrelated HCT for children with advanced ALL in third clinical remission. *(Study Chair: E Nemecek, Oregon Health & Science University; Study Statistician: D Wang).*

3.7 Non-Malignant Marrow Disorders Working Committee.

Co-Chair: Judith C.W. Marsh, MD, St. George's Hospital Medical School, London, UK
Co-Chair: Ricardo Pasquini, MD, Hospital de Clinicas, Curitiba, Brazil; Co-Chair Mark Walters, MD, Children's Hospital-Oakland, Oakland, CA
Statisticians: Jeanette Carreras, MPH
Sergey Tarima, PhD
Scientific Director: Mary Eapen, MD, MS

3.7.1 Publications

AA98-02: Passweg JR, Pérez WS, Eapen M, Camitta CM, Gluckman E, Hinterberger W, Hows JM, Marsh JC, Pasquini R, Schrezenmeier H, Socié G, Zhang M-J, Bredeson CN. **Bone marrow transplants from mismatched related and unrelated and HLA-mismatch related donors for severe aplastic anemia.** *Bone Marrow Transplant 37:641-649, 2006.* For patients with acquired severe aplastic anemia without an HLA-matched sibling donor and not responding to immunosuppressive treatment, HCT from a suitable alternative donor is often attempted. We examined risks of graft failure, GVHD and overall survival after 318 alternative donor transplants between 1988 and 1998. Sixty-six patients received allografts from 1- antigen and 20 from >1-antigen HLA-mismatched related donors; 181 from matched and 51 from mismatched unrelated donors. Most patients were young, had had multiple red blood cell transfusions and poor performance score at transplantation. We did not observe differences in risks of graft failure and overall mortality by donor type. The probabilities of graft failure at 100 days after 1 antigen mismatched related donor, >1 antigen mismatched related donor, matched unrelated donor and mismatched unrelated donor transplants were 21%, 25%, 15% and 18%, respectively. Corresponding probabilities of overall survival at 5 years were 49%, 30%, 39% and 36%, respectively. Though alternative donor transplantation results in long-term survival, treatment-related mortality rates were high and were adversely affected by poor performance score and older age at transplantation. Therefore, early referral for transplantation should be encouraged for patients who fail immunosuppressive therapy and

have a suitable alternative donor.

AA01-01: Panepinto JA, Walters MC, Carreras J, Marsh J, Bredeson CN, Gale RP, Hale GA, Horan J, Hows JM, Klein JP, Pasquini R, Roberts I, Sullivan K, Eapen M, Ferster A. **Matched related donor transplantation for sickle cell disease: Report from the Center for International Blood and Marrow Transplant Research.** *Submitted.* Allogeneic HCT is the only known therapy to cure sickle cell disease though few patients receive this therapy. We port outcomes after HLA-matched sibling HCT in 68 patients with sickle cell disease, transplanted in 1989 to 2002. Of these, 33 (49%) were transplanted between 1999 and 2002. Median age at transplantation was 10 (range 2-30 years). Hemoglobin SS was the predominanat genotype. Indications for HCT were predominanatly stroke (n-24) and recurrent vaso-occlusive crises (n=24); others included acute chest syndrome, increasing transfusion requirements, progressive iron overload and recurrent priapism. Forty-four patients (66%) received ≥ 10 red blood cell transfusions prior to HCT. Twenty patients (26%) had poor performance scores prior to transplantation. Busulfan and Cy was the most frequently used conditioning regimen (n=63, 92%). Fifty-five patients (81%) received bone marrow allografts, 9 patients (13%) received mobilized peripheral blood, 3 patients (4%) received umbilical cord blood, and 1 patient received umbilical cord blood and bone marrow from the same donor. All patients achieved neutrophil recovery and the probability of platelet recovery ≥ 20,000/ul at day 100 was 93 (86-98)%. The probabilities of grades 2-4 acute GVHD at day 100 and chronic GVHD at 5 years were 10 (4-19)% and 22 (12-33)%, respectively. Sixty-five of the 68 patients are alive after HCT with a median follow up of 5 years. The five-year probabilities of overall and disease-free survival were 97 (88-100)% and 84 (75-95)%, respectively. We defined treatment failure (inverse of disease-free survival) as death from any cause or disease recurrence defined as having a hemoglobin S >50%. Recurrent disease was the prefominant cause of treatment failure (n=10). Of the 10 patients with treatment failure, 8 had return of clinical symptoms while the remaining 2 were symptom-free. Three patients died: all deaths occurred more than 100 days after HCT. Causes of death were hemorrhage (n=1), multi-organ failure (n=1) and unknown (n=1). Of the 10 patients with stroke that had magnetic resonance imaging of the brain pre- and post-transplant, 8 showed stable disease post transplant, one showed improvement and one had a worsening scan. We conclude that overall survival after HCT for sickle cell disease is excellent; however recurrent disease and chronic GVHD remain a concern. Future studies should focus on strategies aimed at reducing disease recurrence.

D01-04: Wagner JE, Eapen M, MacMillan ML, Harris RE, Pasquini R, Boulad F. Zhang MJ, Auerbach AD. **Unrelated donor bone marrow transplantation for the treatment of Fanconi anemia.** *Blood 1st Ed, prepublished online 10/12/06; DOI 10.1182/blood-2006-07-036657.* While allogeneic HCT is the only approach that can correct hematological complications of Fanconi Anemia, unrelated donor transplantation for this disorder is severely limited by graft rejection and regimen-related toxicity with resultant poor survival. To identify those patients most likely to benefit from this procedure, we evaluated the impact of potential prognostic factors on hematopoietic recovery, GVHD and overall survival in 98 patients with Fanconi Anemia receiving unrelated donor transplants from 1990 to 2003. Median age at transplantation was 12 years (range 0.8–33). Of the 67 patients with known complementation group, 35 were in group A, 12 in group C and 7 in other groups. Forty-five of 98 (46%) had diepoxybutane (DEB) T cell mosaicism. Sixty-nine percent had aplastic anemia prior to transplantation; 56% received prior androgen therapy and 24% received > 20 blood product transfusions. Fifty-four percent received Cy and irradiation and, 46%, fludarabine-containing preparative regimens. All patients received bone marrow grafts. Seventy-eight percent were matched at HLA A, B, (low resolution) and DRB1; 22% were mismatched at a single locus. Seventy-one percent of grafts were T-cell depleted. In order to adjust for differences in follow up between recipients treated with and without fludarabine-containing preparative regimens (median 21 versus 135 months since fludarabine was used exclusively after 1998), all patients were censored at 12 months for transplant-outcomes. Neutrophil recovery (>500/ul) was significantly less likely with non-fludarabine preparative

regimens in patients with DEB mosaicism (cumulative incidence 52%, p<0.0001) than in those without DEB mosaicism (89%); however, neutrophil recovery was not influenced by DEB mosaicism in patients who received fludarabine-containing preparatory regimens (94% and 93%). Platelet recovery was also less likely with non-fludarabine containing preparatory regimens (19% versus 76%, p<0.0001). Favorable prognostic factors were absence of myelodysplasia/leukemia and fewer than 20 blood product transfusions prior to transplantation. Acute and chronic GVHD were significantly lower in recipients of T-cell depleted grafts (17% and 18%, respectively) than in recipients of non T cell depleted grafts (62% and 47%, respectively). Mortality was significantly higher with non-fludarabine containing preparative regimens (RR 3.24, 95% CI 1.86–5.66, p<0.0001) than with fludaraine containing preparative regimens; corresponding probabilities of overall survival were 17% and 57%. Mortality was also significantly higher in patients who had received > 20 blood product transfusions (RR 2.10, 95% CI 1.16–3.76, p=0.01). Age, disease status at transplantation, HLA disparity, complementation group, DEB mosaicism or DEB sensitivity, and donor-recipient CMV status were not associated with mortality. Based on these results, significant practice changes in application of unrelated donor HCT for Fanconi Anemia should be considered: use of fludarabine in the preparatory regimen and transplantation prior to > 20 blood product transfusions.

AA98-03: Champlin RE, Pérez WS, Passweb JR, Klein JP, Camitta BM, Gluckman E, Bredeson CN, Eapen M, Horowitz MM. **Bone marrow transplantation for severe aplastic anemia: a randomized controlled study of conditioning regimens.** *Submitted.* The addition of antithymocyte globulin (ATG) to a regimen of high dose cyclophosphamide has been advocated to enhance engraftment after allogeneic bone marrow transplant (BMT) for severe aplastic anemia (SAA). In a prospective clinical trial, 134 patients were randomized to receive cyclophosphamide alone or in combination with ATG. All patients received T-cell-replete bone marrow from an HLA-matched sibling. With a median follow-up of 6 years, the 5-year probabilities of survival were 74% for the cyclophosphamide alone group and 80% for the cyclophosphamide plus ATG group (p=0.44). Graft failure and GVHD rates were similar in both groups. With the survival rates achieved, this study is not adequately powered to detect significant differences between the two treatment groups. In conclusion, the results of allogeneic BMT for SAA have improved over time related to advances in supportive care. The addition of ATG to the preparative regimen did not significantly improve the outcome.

3.7.2 Preliminary Results

AA00-01: Comparison of allogeneic bone marrow and peripheral blood HCT for aplastic anemia: Collaborative study of the CIBMTR and EBMT. *(Study Chair: H Schrezenmeier, University of Berlin, Germany; Study Statistician: M Eapen). Manuscript in preparation.* We obtained long-term follow-up on 134 peripheral blood stem cell (PBSC) and 558 bone marrow (BM) recipients of HLA-matched sibling donor transplants. Rates of hematopoietic recovery and grade 2-4 acute graft-versus-host disease (GVHD) were similar after PBSC and BM transplants. Chronic GVHD (relative risk [RR] 2.64, p=0.004) and overall mortality (RR 2.20, p=0.012) were higher after transplantation of PBSC than after BM in younger patients (≤20 years); the 5-year probabilities of chronic GVHD were 27% and 12% after PBSC and BM transplants, respectively. Corresponding probabilities of overall survival were 73% and 85%. In older patients, rates of chronic GVHD and overall mortality were similar after PBSC and BM transplants. The current report is based on data reported to two Registries. Nevertheless, the data shown warrant cautious use of PBSC grafts and emphasize the need for randomized trials to evaluate graft types other than BM in transplantation.

AA00-03: Comparison of outcome following HLA-Identical sibling bone marrow transplantation for Fanconi Anemia with radiation versus non-radiation conditioning regimens. *(Study Chair: R Pasquini, Hospital de Clinicas-Federal University, Of Parana-Brazil, Curitiba, Brazil; Study Statistician: J Carreras). Manuscript in preparation.* Preparatory regimen related toxicities remain a major obstacle

for patients with Fanconi Anemia undergoing HCT. Attempts to decrease such adverse events included modified radiation conditioning and lower doses of chemotherapeutic agents. This study compares HLA-matched sibling bone marrow transplantation outcomes in patients with Fanconi Anemia who received preparatory regimens with and without radiation. One hundred forty-eight patients were analyzed. The median follow up was 96 months and 58 months for patient who received radiation and non-radiation regimens, respectively. No significant differences in neutrophil recovery, 100-day mortality, acute and chronic GVHD and overall survival were evident between the two regimen groups. Factors associated with poorer survival were age >10, use of androgen therapy prior to HCT and donor or recipient CMV seropositivity. In summary, non-radiation and radiation-containing conditioning regimens appear to produce equivalent outcomes in patients receiving HLA-identical sibling bone marrow transplants for Fanconi anemia.

D00-03: Outcome of unrelated donor HCT for children with severe aplastic anemia. *(Study Chair: N Kamani, Children's National Medical Center, Washington, DC; Study Statistician: M Eapen). Manuscript in preparation.* We studied 195 U.S. unrelated donor bone marrow transplantations for children with severe aplastic anemia from 1989-2003. Patients with Fanconi Anemia and other congenital causes of aplastic anemia are excluded. Most recipients achieved neutrophil recovery after transplantation (178 of 195). Of the seventeen patients who did not achieve neutrophil recovery, 6 received a second infusion and 1 achieved neutrophil recovery. Fifteen of 178 patients subsequently lost their graft; the median time to graft loss was 1.4 months. Risks of acute GVHD were higher in patients with poor performance scores ($<$90%) and in those who received T-replete bone marrow grafts. Risks of mortality were higher in patients with poor performance scores ($<$90%), those who were transplanted later in the course of their disease ($>$24 months after diagnosis), those who received grafts from donors older than 30 years and those who received grafts mismatched at $\geq$ 1 HLA loci.

3.7.3 Planned Studies

AA02-03: Allogeneic transplants with fludarabine-based conditioning regimens for paroxysmal nocturnal hemoglobinuria. *(Study Chair*: *D Elebutei, St. George's Hospital Medical School, Cranmer Terrace, London; Study Statistician: J Carreras).*

AA03-01: Second HLA matched related transplants for severe aplastic anemia. *(Study Chair: J Horan, University of Rochester, Rochester, NY; Study Statistician: J Carreras).*

AA03-02: HLA-identical sibling HCT sibling for thalassemia. *(Study Chair: M Sabloff, Ottawa Hospital, Ottawa, Ontario, Canada; Study Statistician: J Carreras).*

AA04-01: Allogeneic HCT for congenital amegakaryocytic thrombocytopenia. *(Study Chair: G Hale, St. Jude's Children's Research Hospital, Memphis, TN; Study Statistician: J Carreras).*

AA05-01: Late graft failure after HLA-identical sibling transplants for severe aplastic anemia. *(Study Chair: R Pasquini, Hospital de Clinicas-Federal University, Of Parana-Brazil, Curitiba, Brazil; Study Statistician: J Carreras).*

AA06-01: Myeloablative versus reduced-intensity conditioning for unrelated donor transplantation for aplastic anemia. *(Study Chair: P Anderlini, MD Anderson Cancer Center, Houston TX; Study Statistician: J Carreras)*

3.8 Immune Deficiencies/Inborn Errors Working Committee.

Co-Chair: Alexandria Filipovich MD, Children's Hospital Medical Center; Cincinnati, OH
Co-Chair: Mitchell Horwitz MD, Medicine/Cellular Therapeutics, Duke University Medical Center,Durham, NC
Co-Chair: Carmem Maria Sales-Bonfim MD, Federal University of Parana, Rua General Carneiro, Curitiba, Brazil
Statisticians: Anna Hassebroeck MS, MA
Sergey Tarima, PhD
Scientific Director: Mary Eapen MD, MS

3.8.1 Publications

ID98-03: Eapen M, DeLaat CA, Baker KS, Cairo MS, Cowan MJ, Kurtzberg J, Steward CG, Veys PA, Filipovich AH. **Hematopoietic cell transplantation for Chediak-Higashi Syndrome.** *Bone Marrow Transplant, In Press.* Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder; characterized by oculocutaneous albinism, recurrent infections, microscopic finding of large granules in hematopoietic and other cells, bleeding diathesis, and neurologic abnormalities. We reviewed outcomes after allogeneic HCT in 35 children with CHS. Twenty-two patients had a history of the life-threatening accelerated phase of CHS prior to HCT and 11 were in accelerated phase at transplantation. Thirteen patients received their allograft from an HLA-matched sibling, 10 from an alternative related donor and 12 from an unrelated donor. Eleven recipients of HLA-matched sibling donor, 3 recipients of alternative related donor and 8 recipients of unrelated donor HCT are alive. With a median follow up of 6.5 years, the five-year probability of overall survival was 62%. Mortality was highest in those with accelerated phase disease at transplantation and after alternative related donor HCT. Only 4 of 11 patients with active disease at transplantation are alive. Seven recipients of alternative related donor HCT had active disease at transplantation and this may have influenced the poor outcome in this group. Although numbers are limited, HCT appears to be effective therapy for correcting and preventing hematologic and immunologic complications of CHS, and an unrelated donor may be a suitable alternative for patients without an HLA-matched sibling. Early referral and transplantation in remission after accelerated phase disease may improve disease-free survival.

3.8.2 Preliminary Results

ID98-05/D99-54: HCT for infantile osteopetrosis. *(Study Chair: A Fasth, Queen Silvia Children's Hospital, Goeteberg, PJ Orchard, University of Minnesota, Minneapolis, MN.; Study Statistician: M Eapen). Manuscript in preparation.* Infantile osteopetrosis is a rare lethal disorder; children are severely affected within months after birth and, if left untreated, only about 30% survive to 6 years of age. Some small studies show HCT to be effective in reconstituting osteoclast function thus offering the possibility of cure. We studied 94 children receiving HCT for osteopetrosis between 1978 -1999. Median age at HCT was 6 (range, 1-132) months. Median interval from diagnosis to HCT was 4 (range, 1-119) months. 48% of allografts were from HLA-identical siblings, 22% from alternative related donors and 30% from unrelated donors. Twelve children received umbilical cord blood grafts, one, a peripheral blood graft and the remainder, bone marrow. Busulfan and Cy (77%) was the most frequently used preparative regimen; 18% received TBI. 14% of grafts were T-cell depleted. Post-HCT, 44 children were alive with a median follow-up of 49 (range, 4-266) months. 3-year probabilities of overall survival among recipients of HLA-identical sibling, alternative related and unrelated donors were 50 (35-64)%, 57 (34-75)% and 38 (20-55)%, respectively. This analysis is the largest yet conducted on the outcome of HCT for osteopetrosis and confirms the effectiveness of HCT as therapy for this disorder.

ID99-02: The role of HCT in Langerhans Cell Histiocytosis. *(Study Chair: RM Egeler, Leiden University Medical Center, Leiden, The Netherlands; Study Statistician: M Eapen). Manuscript in preparation.* Langerhans cell histiocytosis is a poorly understood and occasionally aggressive disorder that features lesional cells akin to Langerhans cells. We studied the results of HCT for Langerhas Cell Histiocytosis through the collaborative use of three large observational databases. The study included 22 allogeneic transplant recipients (HLA-identical and non-identical related as unrelated donors) reported to the CIBMTR, the EBMT and the Japanese Registry. Twenty of the 22 patients (91%) in this cohort were younger than two years of age at transplantation. All patients received front-line therapy but failed to achieve remission. All patients had multi-organ involvement and 20 of 22 (91%) had bone marrow involvement prior to or at transplantation. All but one patient had at least one poor prognosis organ involvement (bone marrow, liver or lung). Six patients had stable disease at transplantation and 16, progressive disease. With a median follow up of more than 4 years, 8 of 22 patients are alive. The one and two year probabilities of overall survival were 45 (25-66)% and 35 (16-56)%, respectively. Causes of mortality included: recurrent/progressive disease (n=2), veno-occlusive disease (n=2), infections (n=7) and diffuse alveolar hemorrhage (n=1). We conclude that while HCT is feasible for patients who fail conventional therapy for Langerhans Cell Histiocytosis, treatment-related mortality is high. It is uncertain whether newer approaches in transplantation such as reduced-intensity conditioning regimens may lower treatment-related mortality and improve results.

ID05-01: Unrelated donor HCT for life-threatening hemophagocytic disorders. *(Study Chair: KS Baker, University of Minnesota, Minneapolis, MN, Study Statistician: M Eapen). Oral presentation at American Soceity of Hematology meetings, December 2006.* HLH is a rare immunoregulatory disorder characterized by widespread infiltration of histiocytes and T cells into organs, including the central nervous system (CNS), and is fatal in most cases without HCT. HLH can be inherited in an autosomal recessive pattern with unaffected sibling donors available for fewer than 20% of patients thus necessitating alternative donor HCT in the majority of cases. Data on 91 patients who underwent unrelated donor HCT and reported to the Center for International Blood and Marrow Transplant Research between 1989-2005 were analyzed. Fifty-one percent of patients were $<$1 yr at HCT and 29% had a Lansky performance score $\leq$80%. In a subset of patients (n=51) additional disease specific characteristics were available: 8 had a family history of HLH, of patients tested, 19 were confirmed to have either a perforin or MUNC-13 gene mutation; CNS disease was present at diagnosis in 21 patients and remained active in 4 at HCT; and 5 patients had active systemic disease at HCT. Most patients (80%) were conditioned with busulfan (BU), cyclophosphamide (CY), and etoposide (VP16) with or without anti-thymocyte globulin. Graft sources were bone marrow (86%), peripheral blood stem cells (4%) and cord blood (10%). Graft vs. host disease (GVHD) prophylaxis was cyclosporine or tacrolimus based in 89% of patients and T-cell depletion in 11%. Fifty-nine percent of grafts were matched at HLA A, B and DRB1, 34%, mismatched at 1-locus and 7%, mismatched at 2-loci. Neutrophil recovery was achieved by day 42 in 91% of patients. The probabilities of grades 2-4 acute at day-100 and chronic GVHD at 3-years were 41% and 23%, respectively. In multivariate analysis, the risk of overall mortality was 2-fold higher in patients who did not receive BU/CY/VP16 as their conditioning regimen (RR 1.99, p=0.03). In the sub-set of patients from whom disease-specific characteristics were available, overall mortality was higher in those with active systemic disease at HCT (RR 3.11, p=0.04). Early mortality was high, 35% at day-100 after HCT. Causes of early mortality included GVHD (n=5), infections (n=8), interstitial pneumonitis (n=8), organ failure (n=6), hemorrhage (n=3) and persistent disease (n=2). With a median follow-up of 49 months (range, 5-145) the 1- and 3-year probabilities of overall survival were 52% and 47%, respectively. For 46 patients with documented systemic remission at HCT, the 1- and 3-year probabilities of overall survival were 56% and 49%, respectively. These data represent the largest experience with unrelated donor HCT for HLH and demonstrate that a BU/CY/VP16 conditioning regimen provides cure in over 50% of patients. Outcome of HCT for patients with active systemic disease was poor with only 1 of 5 such patients surviving, demonstrating a need for novel therapies in patients who fail to respond to standard pre-transplant

treatment. Unrelated donor HCT for HLH was associated with high early mortality and future studies should explore strategies to decrease early HCT-related mortality.

3.8.3 Planned Studies

ID98-02/D00-111: HCT for severe combined immunodeficiency syndrome. *(Study Chair: A Filipovich, Children's Hospital Medical Center, Cincinnati, OH; Study Statistician: A Hassebroek).*

ID00-01: Analysis of incidence and risk factors for development of cancer in patients with immunodeficiencies after allogeneic transplantation *(Study Chair: N Kamani, , Stem Cell Transplant & Immunology Children's National Medical Center, Washington, DC; Study Statistician: A Hassebroek).*

ID02-02: Descriptive study of outcomes after HCT for leukocyte adhesion deficiency. *(Study Chair: N Farinha, Portugal, Study Statistician: A Hassebroek).*

ID04-02: Unrelated HCT for severe combined immunodeficiency syndrome and Wiskott-Aldrich syndrome: analysis of outcome by graft-type. *(Study Chair: A Filipovich, Children's Hospital Medical Center, Cincinnati, OH; Study Statistician: A Hassebroek).*

ID06-01: A comparison of outcome of allogeneic HCT for congenital immunodeficiencies and malignant disorders. *(Study Chair: M Horowitz, Duke University, Chapel Hill, North Carolina; Study Statistician: A Hassebroek).*

ID06-02: A comparison of outcomes of allogeneic HCT for inborn errors of metabolism and malignant disorders. *(Study Chair: M Horowitz, Duke University, Chapel Hill, North Carolina; Study Statistician: A Hassebroek).*

ID 06-03: Survival/toxicity in patients with Hurlers syndrome undergoing HCT. *(Study Co-Chair, M Hansen, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Study Co-Chair, P Orchard, University of Minnesota, Minneapolis, MN; Study Statistician: A Hassebroek).*

3.9 Autoimmune Disorders Working Committee.

Co-Chair: Richard Nash, MD, Dept. of Transplantation Biology, Fred Hutchinson Cancer Research Center, Seattle, WA
Co-Chair: Harold Atkins, MD, Ottawa General Hospital, Ottawa, Ontario, Canada
Statisticians: Manza Agovi, MPH
Brent Logan, PhD
Scientific Director: Marcelo Pasquini, MD, MS

This Working Committee has undergone several recent changes in leadership and staffing. The current chairs assumed their roles in January, 2005 and conducted their first meeting at the BMT Tandem Meetings in February 2005. In August, 2005, the Scientific Director of this committee left the CIBMTR; Dr. Marcelo Pasquini assumed this role in fall of 2005. Manza Agovi became the MS statistician for the committee in fall 2006. These changes in statistician and scientific director position have created some delays in implementing projects but teleconferences of the Committee chairs, statisticians and scientific director are now conducted on a regular basis and a much faster rate of progress is anticipated over the next year.

3.9.1 Preliminary Results/Planned Studies

AI05-02: The effect of allogeneic HCT on the activity and progression of Multiple Sclerosis: A cross-sectional study. (*Study Chair: R Nash Fred Hutchinson Cancer Research Center, Seattle, WA; Study Statistician: M Agovi). Data collection in progress.* This study was approved at the Autoimmune Disease Working Committee in February, 2005. Thirteen patients who had had allogeneic HCT for a hematological malignancy and in addition had a concomitant diagnosis of MS before HCT were identified through the CIBMTR database and Dr. Nash's personal communication with transplant physicians in the US and Canada. Ten patients were contacted by the transplant program at which they had been treated and all 10 patients agreed to participate in the study. The three other patients could not be contacted and were excluded. Eight of the study participants agreed to have a neurological assessment in Seattle at the University of Washington and two were assessed by local neurologists. The evaluations included a complete history and physical examination, magnetic resonance imaging MRI of the brain and lumbar puncture (n=8). A summary of this evaluation was presented by Dr. Nash at the Autoimmune Working Committee meeting in February 2006. The final evaluation required for this group of 10 patients was completed in March, 2006. Self-assessment questionnaires were completed to determine the pretransplant and current Extended Disability Status Score (EDSS). One of the 10 patients who was early after HCT died from leukemia relapse. Data on the early pretransplant MS status is still being collected. Issues were identified in the evaluations of MS patients which included incomplete or lack of scheduled assessments of MS before and early after HCT as well as difficulty in getting historical data to fully assess the early course of disease. Four other patients have now been identified who are early after HCT one of whom has agreed to participate in the study. Four surviving patients were identified in Europe who are eligible for follow-up on this study as well as another patient who died one year after HCT. The European transplant programs caring for these patients have agreed to participate in this cross-sectional study.

AI06-01: HCT for autoimmune cytopenias. (*Study Chairs: H Atkins, Ottawa Hospital, Ottawa, Ontario, Canada; M Pasquini, Medical College of Wisconsin, Milwaukee, WI; Study Statistician: M Agovi) Data file in preparation*. For this study, the eligibility criteria included patients with diagnoses of Idiopathic Thrombocytopenic Purpura, Autoimmune Hemolytic Anemia, Evan's Syndrome or other autoimmune cytopenias who underwent either an autologous or allogeneic HCT and were reported to the CIBMTR during a 10 year period from 1996 to 2005. Eleven patients were identified as having received an allogeneic HCT with a pretransplant diagnosis of one of these diseases. Six patients were identified as having received an autologous HCT for idiopathic thrombocytopenic purpura. Descriptive tables will be prepared of patient, disease, transplant, and outcome related information. Categorical and continuous variables will be summarized as percent and median with range, respectively. The Kaplan-Meier product limit method will be used to calculate the median and range of follow up. We are also further investigating the database for patients transplanted before 1996 to identify other eligible cases.

AI06-02: Effect of HCT on rheumatoid arthritis and systemic lupus erythematous when present as coexisting disease at time of transplant *(Study Chair: R Nash Fred Hutchinson Cancer Research Center, Seattle, WA; Study Statistician: M Agovi)*. *Data file preparation.* For this study, patients were selected from the database if they had undergone allogeneic or autologous HCT between 1995 and 2004 and had the presence of a coexisting autoimmune disease other than multiple sclerosis at time of transplant. From the CIBMTR database, 260 and 226 patients were identified who had had co-existing autoimmune diseases before allogeneic or autologous HCT, respectively. The diseases most frequently represented were rheumatoid arthritis (n=85, allogeneic; n=99, autologous), psoriasis (n=77, allogeneic; n=45, autologous) and systemic lupus erythematosus (SLE; n=28, allogeneic; n=27, autologous). There are sufficient numbers of cases so that an analysis of outcomes could be done for each of the major disease categories. The status of the autoimmune disease, overall survival and

treatment-related mortality will be evaluated. If necessary, strategies to further enhance the database on autoimmune disease outcomes will be established.

AI06-03: Overview of HCT for autoimmune diseases performed in North and South America *(Study Chairs: P. McSweeney, Rocky Mountain Cancer Centers, Denver, Colorado; H. Atkins, Ottawa Hospital, Ottawa, Ontario, Canada; Study Statistician: M. Kukreja) Analyses in progress. Accepted for Poster Presenatation the BMT Tandem meetings in February 2007.* The numbers and types of cases of allogeneic HCT and high-dose immunosuppressive therapy with autologous stem cell support reported to CIBMTR between 1994 and 2005 were quantified. There were 139 cases identified of which 111 had autologous and 28 had allogeneic HCT. The diseases most frequently represented were multiple sclerosis (MS) (n=51), systemic sclerosis (n=36) and SLE (n=17). We will report on the characteristics of the transplant and the recipient including type of high-dose immunosuppressive therapy, graft type and any manipulation of the grafts. We will also report on overall survival. Outcomes of the autoimmune disease will not be reported. Comparisons will be made to the available published cases of transplantation for autoimmune diseases performed in the Americas but not reported to the CIBMTR and to the European experience to summarize the activity of HCT for this indication and to determine if there are regional differences in the experience.

3.10 GVHD Working Committee.

Co-Chair: A. John Barrett, MD, National Heart, Lung and Blood Institute, Bethesda, MD
Co-Chair: Olle Ringden, MD, PhD, Huddinge University, Huddinge, Sweden
Co-Chair: Claudio Anasetti, MD, H. Lee Moffitt Cancer Center and Research Institute, Moffitt Cancer Center, Tampa, FL
Co-Chair: Steve Pavletic, MD, National Cancer Institute, Bethesda, MD
Statistician: Dan Wang, MS
Tao Wang, PhD
Scientific Director: Mukta Arora, MD, MS

3.10.1 Publications

GV02-01: Khoury HJ, Loberiza FR, Ringden O, Barrett J, Bolwell BJ Cahn J-Y, Champlin RE, Gale RP, Hale GA, Urbano-Ispizua A, Martino R, McCarthy PL, Tiberghien P, Verdonck LF, Horowitz MM. **Impact of post transplant G-CSF on outcomes of allogeneic jematopoietic stem cell transplantation.** *Blood 2006; 107:1712-1716.* Granulocyte-colony-stimulating factor (G-CSF) is often administered after HCT to accelerate neutrophil recovery, but it is unclear whether it affects long-term transplant outcomes. We analyzed the impact of giving post-transplant G-CSF on the outcomes of allogeneic HCT for AML and CML in 2,719 patients transplanted between 1995 and 2000. These included 1,435 recipients of HLA-identical sibling bone marrow, 609 recipients of HLA-identical peripheral blood grafts, and 675 recipients of unrelated donor bone marrow. Outcomes were compared between patients receiving or not receiving G-CSF within 7 days of HCT according to graft type. Median follow-up was >30 (range, 2-87) months. G-CSF shortened the post-transplant neutropenic period, but did not affect treatment-related mortality at day +30 or day +100. Probabilities of acute and chronic GVHD, leukemia-free and overall survival were similar whether or not G-CSF was given. Multivariate analyses confirmed that giving G-CSF did not affect the risk of GVHD, treatment-related mortality, leukemia-free survival, or overall survival. In conclusion, results of this study found no long-term benefit or disadvantage of giving G-CSF post-transplant to promote hematopoietic recovery.

3.10.2 Preliminary Results

GV99-03: Donor leukocyte infusions (DLI) to treat hematologic malignancy relapse following allogeneic HCT in a pediatric population. *(Study Chair: J Levine, University of Michigan, Ann Arbor, MI; Study Statistician: M-J Zhang). Manuscript in preparation.* The effectiveness of DLI in prolonging

survival following post-allogeneic HCT relapse depends, at least in part, on the disease being treated. Because most of the research involving DLI has been conducted in adults, it is uncertain how well children respond to DLI strategies. This study examined the outcomes following DLI in a relatively large series of children relapsing after allogeneic HCT and compared these to outcomes of similar children who did not receive DLI. The DLI cohort include 49 children <18 years who received DLI for a post-transplant relapse between July 1991 and December 1999. Forty seven patients had bone marrow relapse, in 39 cases based on morphology and in eight based on cytogenetic analysis alone. In one case, a cytogenetic relapse in the bone marrow was also associated with central nervous system involvement. Six of the cytogenetic only relapses occurred in children with CML. Two patients had isolated extramedullary relapse, one testicular and one central nervous system. The median time from HCT to relapse was 7 (range, 1-116) months. The median time from relapse to DLI was 45 (range, 6-683) days. Patients received mean and median cell doses of 1.9×10^8 CD3+ cells/kg and 1×10^8 CD3+ cells/kg. One of 17 children with ALL, 4 of 17 with AML, 4 of 8 with CML and 1 of 6 with myelodysplasia have had durable responses and remain alive and in remission at time of last follow-up. The survival of the children who received DLI was not significantly different from the survival of 1229 children who received non-DLI treatment for relapse, though the statistical power of this comparison was low. The findings in this study are not inconsistent with the anecdotal evidence of durable remissions in children with post transplant relapse.

GV00-02: Risk factors for acute GVHD after HLA-matched related HCT for leukemia. *(Study Chair: T Hahn, Roswell Park Cancer Institute, Buffalo, NY; PL McCarthy, Roswell Park Cancer Institute, Buffalo, NY; Study Statistician: M-J Zhang). Manuscript in preparation*. HLA-matched related donor HCT is a curative therapy for leukemia and other hematologic malignancies and disorders. However, acute GVHD remains a significant cause of morbidity and mortality that limits its success. We retrospectively analyzed risk factors for acute GVHD after HLA-identical sibling HCT in 2416 patients treated for AML (n=934), ALL (n=542), or CML (n=940) from 1995-2002 in 226 centers, worldwide. All patients received cyclosporine and methotrexate with (15%) or without (85%) other agents for GVHD prophylaxis. 746 (31%) patients developed grade II-IV acute GVHD on or before day +100 post-HCT. The study population was divided into 2 cohorts: Early (1995-1998) and Late (1999-2002). Patient characteristics that significantly changed over time were: age of the recipient (p=0.0197), performance status (p=0.028), and recipient-donor CMV status (p<0.0001). The cumulative incidence of acute GVHD did not change over time. Risk factors for acute GVHD in the Early cohort were: race (RR=1.51 for White/Black versus Asian/Hispanic, p=0.0014), age (RR=1.21 for ≥ 40 years versus < 40 years, p=0.04), disease (RR=1.49 for CML versus AML/ALL, p<0.0001), disease status (RR=1.5 for advanced versus early/intermediate, p=0.003), conditioning regimen (RR=1.31 for CyTBI+/-other versus Busulfan andCy+/-other, p=0.0033) and donor pregnancy (RR=1.35 for donor ever pregnant versus no/male donor, p=0.004). These risk factors were tested in the Late cohort, but only age (RR=2.15 for ≥ 40 years p<0.0001 and RR=1.55 for 20-39 years p=0.018 versus age<20 years) and conditioning regimen (RR=1.6 for CyTBI+/-other versus Busulfan and Cy+/-other, p=0.0002) remained significant predictors of acute GVHD. Although the incidence of overall grade II-IV aGVHD has not changed over time, the risk factors for this outcome have. Determination of pre-transplant risk factors for acute GVHD may allow the identification of high-risk patients who may benefit from more intensive immunosuppression.

3.10.3 Planned Studies

D96-01: Determination of whether risk factors for acute and chronic GVHD in Children receiving unrelated donor marrow transplants differ by diagnosis. *(Study Chair: S Davies, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Study Statistician: D Wang).*

D01-91: Effect of rituximab on HCT outcome. *(Study Chair: V Ratanatharathorn, Karmanos Cancer Institute, Detroit, MI; Study Statistician: D Wang).*

D01-92: Risk factors for development of acute GVHD in adults receiving unrelated donor HCT. *(Study Chair, N Chao, Duke University, Durham, NC; Study Statistician: D Wang).*

GV04-02/R04-82: Factors determining leukemia relapse in patients with chronic GVHD. *(Study Chair: S. Pavletic, NIH, Bethesda, MD; Study Statistician: D. Wang).*

GV05-01: Effect of grade and duration of acute GVHD on relapse rates. *(Study Chair: S Mineishi, University of Michigan, Ann Arbor, MI; Study Statistician: D Wang).*

GV05-02: Study of risk factors and impact of age on outcome of GVHD after allogeneic HCT for hematologic malignancies. *(Study Chair: M Jagasia, Vanderbilt University Medical Center, Nashville, TN; Study Statistician: D Wang).*

GV05-03: Risk factors for mortality in pediatric chronic GVHD. *(Study Chair: D Jacobsohn, Children's Memorial Hospital, Chicago, IL; Study Statistician: D Wang).*

GV05-04: The graft-versus-leukemia effect after unrelated donor HCT. *(Study Chair: O Ringden, Karolinska University Hospital Huddinge, Sweden; Study Statistician: M Arora).*

GV05-05: DLI after reduced intensity HCT. *(Study Chair: R Sobecks, Cleveland Clinic Foundation, Cleveland, OH; Study Statistician: D Wang).*

GV06-01: A case-control analysis of methotrexate and non-methotrexate containing GVHD prophylaxis regimens in matched related and matched unrelated donor transplantation. *(Study Chairs: C Cutler, Dana-Farber Cancer Institute, Boston, MA, J Antin, Dana-Farber Cancer Institute, Boston, MA; Study Statistician: D Wang).*

GV06-02: GVHD after non T-cell depleted reduced intensity hematopoietic stem cell transplants. *(Study Chair: DR Couriel, University of Texas MD Anderson Cancer Center, Houston, TX; RM Saliba, University of Texas MD Anderson Cancer Center, Houston, TX; Study Statistician: D Wang).*

GV06-03: The effect of adding ATG in the preparative regimen prior to unrelated donor HCT for acute leukemia. *(Study Chair: H Frangoul, Vanderbilt Children's Hospital, Nashville, TN; Study Statistician: D Wang).*

GV06-04: Current trends in chronic GVHD. *(Study Chair: S Arai, Division of Bone Marrow Transplant, Stanford University, Stanford, CA; Study Statistician: D Wang).*

3.11 Graft Sources and Manipulation Working Committee.

Co-Chair: John Wagner, MD, University of Minnesota, Minneapolis, MN
Co-Chair: Adrian Gee, PhD, Baylor College of Medicine, Houston, TX
Co-Chair: Richard Champlin, MD Anderson Cancer Center, Houston, TX
Statisticians: Fiona Kan, MS
Mei-Jie Zhang, PhD
Scientific Director: Mary Eapen, MD MS

3.11.1 Publications

HC98-02: Schmitz N, Eapen M, Horowitz MM, Zhang MJ, Klein JP, Rizzo JD, Loberiza FR, Gratwohl A, Champlin RE. **Long-term outcome of patients given transplants of mobilized blood or bone marrow: A report from the CIBMTR and the EBMT** *Blood 108:4288-4290, 2006.* We previously compared outcomes after allogeneic peripheral blood and bone marrow transplantation in 824 patients with leukemia, age ≥ 20 years and transplanted in 1995-1996. As the late consequences of peripheral blood transplantation are largely unknown, we analyszed follow-up information obtained on 483 surviving patients from the initial cohort, 173 recipients of peripheral blood and 310 recipients of bone marrow grafts. With longer follow up, chronic GVHD remained more frequent with peripheral blood compared to bone marrow (RR 1.65, 95% CI 1.28-2.11, p<0.0001). Relapse risks were similar in the two groups. Overall and leukemia-free survival were higher after peripheral blood transplants for patients with advanced CML but survival was lower after peripheral blood transplants for patients with chronic phase CML (RR of mortality 1.81, 95% CI 1.24-2.65, p=0.002). No differences in survival were seen between peripheral blood and bone marrow transplantation in acute leukemia. These data suggest cautious use of peripheral blood grafts for allogeneic transplantation in good risk patients as higher risks of chronic GVHD may increase late mortality.

HC98-05: Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Loberiza F, Champlin R, Scaradavou A, Klein J, Horowitz M, Wagner J. **Unrelated donor HCT in children with acute leukemia: Risks and benefits of umbilical cord blood versus HLA A, B, C, DRB1 allele-matched bone marrow.** *Submitted. Oral presentation at the American Society of Hematology meetings, December 2006.* CB has proven to be an acceptable alternative to BM for transplantation. However, it is unknown how CB mismatched at HLA 0-2 loci compares to HLA matched BM. Therefore, we compared results observed in 503 recipients of CB with those in 116 recipients of allele-matched BM (at HLA A, B, C, DRB1). Of CB recipients, 35 were matched at HLA A, B (antigen-level) and DRB1 (allele-level), 201 were mismatched at 1-locus and 267 were mismatched at 2-loci. All patients (aged <16 years) had acute leukemia and were transplanted between 1995-2003. Median follow up was 45 and 59 months for CB and BM recipients, respectively. Leukemia-free survival (LFS) rates was superior in recipients of HLA matched CB (p=0.040). Notably LFS and overall survival (OS) at 5-years were comparable between those receiving allele-matched BM and 1 or 2-loci mismatched CB. These results in LFS and OS are in part explained by differences in risks of transplant-related mortality (TRM) and relapse between patient populations. Compared to allele-matched BM transplants, TRM was similar in recipients of matched and 1-locus mismatched/high cell dose (>0.3 x 10^8/kg) CB and higher in recipients of 1-locus mismatched/low cell dose (≤0.3 x 10^8/kg) and 2-loci mismatched CB (any cell dose) (p=0.005, p<0.001, respectively). Conversely, relapse rates were lower in recipients of CB mismatched at 1 or 2-loci (p=0.037, p=0.003, respectively). The Table below shows the 5-year probabilities of TRM, relapse, LFS and OS by graft type. These results are the first to support the use of HLA matched or mismatched CB grafts with an adequate cell dose as first line transplant treatment regardless of the availability of a HLA allele-matched BM donor in the setting of actue leukemia in those <16 years.

	TRM	Relapse	LFS	OS
BM, allele-matched at A, B, C, DRB1	19%	41%	38%	45%
CB, A, B antigen-matched, DRB1 allele-matched	6%	34%	60%	63%
CB, 1-locus mismatched, high cell dose	29%	31%	41%	45%
CB, 1-locus mismatched, low cell dose	43%	21%	37%	36%
CB, 2-loci mismatched, any cell dose	49%	20%	33%	33%

D00-65: Eapen M, Logan B, Confer D, Haagenson M, Wagner JE, Weisdorf D, Wingard JR, Rowley S, Stroncek D, Leitman S, Gee A, Horowitz MM, Anasetti C. **Peripheral blood grafts from unrelated donors are associated with increased acute and chronic graft-versus-host disease without improved survival.** *Submitted.* Data from the CIBMTR indicate that approximately 70% of unrelated donor HCT in the U.S. utilize peripheral blood rather than bone marrow as a graft source. Comparative studies verifying its benefit, however, are lacking. We, therefore, performed a retrospective analysis comparing the results of 275 unrelated peripheral blood and 620 unrelated bone marrow transplants in adults 18-60 years of age with ALL, AML, CML or myelodysplasia, transplanted in 2000-2002. 73% of peripheral blood grafts were matched at HLA A, B, C (low resolution) and DRB1, 21% were mismatched at a single locus and 6% were mismatched at $\geq$ 2 loci. 69% of bone marrow grafts were matched, 26% were mismatched at a single locus and 5% were mismatched at $\geq$ 2 loci. Median follow-up was 24 (range, 6-48) and 34 (range, 6-54) months for peripheral blood and bone marrow recipients, respectively. Groups were similar except peripheral blood recipients were less likely to have CML, were more likely to have myelodysplasia and were transplanted more recently. Incidences of neutrophil recovery (95% versus 90% at day 100, p=0.01) and platelets $\geq$20,000/ul (81% versus 66%, at 1-year, p $<$0.0001) were significantly higher after peripheral blood than bone marrow transplants. Incidences of grades 2-4 but not grades 3-4 acute GVHD were significantly higher after peripheral blood than bone marrow transplants (56% versus 45% at day 100, p=0.003). Chronic GVHD was also significantly higher after peripheral blood transplants (54% versus 39%, at 3 years, p$<$0.0001). Despite higher rates of grade 2-4 acute and chronic GVHD after peripheral blood transplantation, incidence of relapse was similar in the two groups for both early and advanced leukemia. In multivariate analysis, risks of treatment-related mortality, treatment failure (relapse or death) and overall mortality during the first 9 months after transplantation were similar. However, among patients who survived the first 9 months, subsequent risks of treatment-related mortality (RR 1.90, 95% CI 1.14-3.17, p=0.01) and treatment failure (RR 1.60, 95% CI 1.06-2.44, p=0.03) were significantly higher in the peripheral blood cohort. Three-year adjusted (from multivariate models) probabilities of leukemia-free survival were 29% and 31%, p=0.5, after peripheral blood and bone marrow transplantation, respectively; corresponding probabilities of overall survival were 31% and 32%, p=0.8. While these data do not indicate a survival advantage with either stem cell source by disease or risk group, peripheral blood is associated with earlier engraftment. This advantage is offset by higher rates of grades 2-4 acute and chronic GVHD, leading to a higher risk of late adverse events. Randomized clinical trials are necessary to better define the relative risks and benefits of peripheral blood in the setting of unrelated donor HCT.

3.11.2 Preliminary Results

HC 03-01: Prevalence of microbially contaminated hematopoietic stem cell products. *(Study Chair: RE Champlin, MD Anderson Cancer Center, University of Texas, Houston, TX; Study Statistician: F Kan). Manuscript in preparation.* In 2001, the Docket Report from the Food and Drug

Administration expressed concerns regarding the potential of microbially contaminated hematopoietic stem cell products to produce morbidity and mortality in transplant recipients. This concern was the basis for development of regulatory standards for HCT products. We surveyed a total of 2972 transplants at 121 U.S. transplant centers that registered patients with the CIBMTR in the years 2000 and 2001. Information regarding microbial contamination of infused grafts was obtained from 94 transplant centers (80% response rate) for 2312 patients. 52 (2%) of 2286 infused grafts tested were culture positive for bacterial or fungal organisms. The microbial isolates included: coagulase negative staphylococcus (56%), gram negative organisms (15%), coagulase positive staphylococcus (10%), gram positive rods (10%), streptococcus (8%), and fungus (1%). Prophylactic antibiotics targeted at the contaminant were given to 17 of the 52 recipients of contaminated grafts. Antibiotic regimens included vancomycin alone (76%), aminoglycosides and vancomycin (12%), or cephalosporin and vancomycin (12%). 47 (50%) of the centers that participated have existing policies regarding contaminated products. Patients with non-malignant disorders or who received bone marrow were more likely to have a contaminated graft. No differences in age distribution, sex, race, type of transplant (allogeneic versus autologous) and year of transplant were noted between recipients of contaminated and non-contaminated grafts. The unadjusted 100-day survival of persons receiving contaminated grafts was 86 (72-93)% versus 81 (80-83)% among those receiving non-contaminated grafts, p=0.35. In summary, about 2% of hematopoietic stem cell products infused for allogeneic or autologous transplantations in U.S. centers will test positive for microbial contamination, but such contamination does not increase post-transplant mortality. The absence of significant 100-day mortality among patients infused with contaminated grafts suggests that stringent regulatory policies regarding the use of contaminated hematopoietic cell products may not be indicated.

R04-88: Higher cell dose and CD34+ content improves engraftment following unrelated donor cord blood transplantation: A report of the NMDP Cord Blood Experience. *(Study Chair: M Aurora, Texas Transplant Institute, San Antonio, TX; Study Statistician: J Klein). Manuscript in preparation.* Cord blood has become an important alternative unrelated donor allogeneic hematopoietic stem cell source. The NMDP has developed a comprehensive coordinated network of cord blood banks, search coordinating center and transplant programs with prospective collection of outcome data coordinated by the NMDP. Critical to cord blood transplantation has been limited cell dose with resultant prolonged engraftment time. The NMDP cord blood inventory has both TNC and CD34+ quantification on the units, allowing a comparison of the relative utility of either measure in identifying units producing rapid engraftment. Between 03/2000 and 03/2004, 12 NMDP banks (total inventory 31,976 units) released cord blood units to 144 patients at 44 NMDP transplant programs included in this analysis (median f/u 217 days, range, 26–1204 days). The median recipient age was 8.2 years (range, 0.2–63.1 years; 38 were $\geq$ 15 years) and median weight was 27 kg (range, 3–158 kg: 26% > 57 kg). Transplant indications included malignancy in 113 (ALL 36, AML 43, myelodysplasia 13, other 21), metabolic disorders (8) immune disorders (9) histiocytic disorders (3), erythrocytic abnormalities (6), platelet abnormality (1), aplastic anemia (3) and other nonmalignant disease (1). Most patients with malignancy had advanced disease (60 patients [53%] were beyond CR2 or in relapse). The median pre-freeze total nucleated cell count was 4.4 x 10^7/kg (range, 0.3–433 x 10^7/kg) and CD34+ cells 7.9 x 10^5/kg (range, 1.1–68.5 x 10^5/kg) in units selected for transplantation. Thus, the median cord blood total nucleated cell count was 142 x 10^7 cells (range, 54–396 x 10^7 cells); only 12 units under 80 x 10^7 cells were used. 114 patients engrafted by day +42 post-transplant with median time to neutrophil recovery > 500/mm^3 of 21 days (range, 8–62 days) and platelet count > 20,000 x 10^9/L of 64 days (range, 12–473) respectively. One-year survival and disease-free survival were 39% ± 9% and 38% ± 9%, respectively. The relapse rate was 16% ± 8% in this high-risk population. The 100-day treatment-related mortality rate was 26% ± 7%. For patients $\geq$ 15 years, treatment-related mortality was 42% ± 16% versus 21% ± 8% for patients < 15 years. Higher cell dose was associated with faster neutrophil and platelet engraftment. Units with both high total nucleated cells/kg and high CD34+/kg were associated with more rapid engraftment versus those with only high nucleated cells or only high CD34+ or neither (p<0.0001). In multivariate analysis,

recipient age > 15 years led to poorer survival (RR 3.4, 95% CI 1.7-6.7)) and disease-free survival (RR 2.8, 95% CI 1.5-5.2) compared to younger children, especially those < 3 years (p<0.0001). Male grafts into females yielded poorer survival than other gender combinations. These data confirm that cord blood is a valuable alternative unrelated donor histocompatible stem cell source. Since transplantation using cord blood units containing both high total nucleated cell and CD34+ content resulted in more rapid engraftment, optimal cord blood inventory should strive for both high cell count (> 80 x 10^7 cells) and high CD34+ cell content.

3.11.3 Planned Studies

R02-12: **Graft transport factors affecting engraftment and other transplant outcomes.** *(Study Chair: H Lazarus, Case Western Reserve University, Cleveland, OH; Study Statistician: F Kan).*

R02-42: Graft composition and outcomes. *(Study Chairs: N Collins, Memorial Sloan Kettering Cancer Center, New York, NY, D Weisdorf, University of Minnesota, Minneapolis, MN; Study Statistician: F Kan).*

GS05-01: Outcomes after transplantation of unrelated donor cord blood transplants: comparison of graft processing. *(Study Chair: R Chow, StemCyte International Cord Blood Center; Study Statistician: F Kan).*

GS05-02: Comparison of outcomes after transplantation of G-CSF mobilized bone marrow versus non-mobilized bone marrow grafts for severe aplastic anemia. *(Study Chair: R Chu, Emory University; Study Statistician F Kan).*

GS05-03: Comparison of outcomes after unrelated cord blood versus bone marrow grafts in children with severe aplastic anemia. *(Study Chair: J Wagner, University of Minnesota, Minneapolis, MN; M Eapen, Medical College of Wisconsin, Milwaukee, WI, Study Statistician M Eapen).*

3.12 Late Effects and Quality of Life Working Committee.

Co-Chair: Gerard Socié, MD PhD, Hôpital St. Louis, Paris, France
Co-Chair: John Wingard, MD, University of Florida, Gainesville, FL
Co-Chair: Brian Bolwell, MD, Cleveland Clinic Foundation, Cleveland OH
Statisticians: Kathleen A Sobocinski, MS
John Klein, PhD
Scientific Director: J Douglas Rizzo, MD MS
Assistant Scientific Director: Navneet Majhail, MD, MS

3.12.1 Publications

Rizzo JD, MD, Wingard JR, MD, Tichelli A, MD PhD, Lee SJ, MD, Van Lint MT, MD, Burns LJ, MD, Davies SM, MD, Ferrara JLM, MD, Socié G, MD PhD. **Recommended screening and preventive practices for long-term survivors after HCT: joint recommendations of the EBMT, the CIBMTR, and the American Society of Blood and Marrow *Transplantation.*** *Bone Marrow Transplant 37:249-261, 2006; Biol Blood Marrow Transplant, 12:138-151, 2006.* More than 40,000 HCTs are performed each year worldwide. With improvements in transplant technology, more transplant recipients now survive free of the disease for which they were transplanted. Cumulatively, there are tens of thousands of HCT survivors alive today. Although HCT is associated with considerable early morbidity and mortality, long-term survivors generally enjoy good health. Notwithstanding, there are sequelae that can cause substantial morbidity. Optimizing outcomes through prevention or early detection of

complications and mitigation of disability are high priorities. Many survivors are no longer under the care of transplant centers and many community health care providers may be unfamiliar with health matters relevant to HCT. Using data available through their large databases and extensive review of the literature, a consensus panel formed by members of the CIBMTR, the EBMT , and the American Society for Bone Marrow Transplantation has drafted recommendations to better inform care providers with regard to appropriate minimum screening and prevention practices for HCT survivors. The goal is to provide an overview of the late complications faced by transplant recipients, and provide reasonable recommendations for care, focusing on risks faced by patients beyond 6 months following transplantation.

A Guide to Protecting Your Health after Transplant: Recommended Tests and Procedures. The CIBMTR Consumer Advocacy Committee, working together with the Late Effects Working Committee, NMDP Office of Patient Advocacy and NMDP Education developed a version of the above publication for patients. This publication, A Guide to Protecting Your Health after Transplant: Recommended Tests and Procedures, provides guidelines that patients and their physicians can use to schedule long-term follow-up care after a marrow, blood stem cell or cord blood transplant. The patient guide includes information about side effects that may occur months or years after transplant, charts with recommended tests and procedures for patients' six-month, twelve-month and yearly post-transplant check-ups, space for patients to record important information about their own post-transplant care, and information for patients to share with their physicians about the tests and procedures they will need after transplant. Materials were created for allogeneic and autologous recipients separately. Copies of the guides can be found in downloadable format at http://cibmtr.org/PUBLICATIONS/guidelines.html. Additionally, a 4-hour symposium focusing on late effects after HCT and recommended screening practices was conducted at the American Society of Hematology meetings in December, 2006.

LE99-01: Bishop MM, Beaumont JL, Hahn EA, Cella D, Andrykowski MA, Brady MJ, Horowitz MM, Sobocinski KA, Rizzo JD, Wingard JR. **The late effects of cancer and HCT on spouses/partners compared to HCT survivors and survivor-matched controls.** *J Clin Oncol, In press.* Little is known about the long-term effects of cancer and HCT on spouse/partners. The purpose of this study was to examine the health-related quality of life (QOL) and posttraumatic growthof spouses/partners compared to survivors and controls and to identify factors associated with those outcomes. HCT survivor/partner pairs (n=177), coupled continuously since HCT, were drawn from 40 North American transplant centers. Married peer-nominated acquaintances (of survivors) served as controls (n=133). Outcomes were measured a mean of 6.7 years post-HCT (range,1.9–9.4 years). As expected, self-reported partner physical health was similar to controls, better than survivors (P<.001). However, partners reported more fatigue and cognitive dysfunction than controls (P<.001 for both), though less than survivors. Partners and survivors reported more depressive symptoms, sleep and sexual problems than controls (P<.001, P<.01, P<.01 respectively). Odds of partner depression were nearly 3.5 times that of controls (P<.002). Depressed partners were less likely than depressed survivors to receive mental health treatment (P<.04). Partners reported less social support (P<.001), dyadic satisfaction (P<.05), spiritual well-being (P<.05), and more loneliness (P<.05) than both survivors and controls. In contrast to survivors, partners reported little post-traumatic growth (P<.001). Factors associated with partner outcomes included partner health problems, coping, female gender, social constraint, survivor depression, optimism, multiple life changes, and social support. We concluded that spouses/partners experience similar emotional and greater social long-term costs of cancer/HCT than survivors without the potential compensatory benefits of post-traumatic growth. Some of the factors associated with partner outcomes are amenable to intervention.

3.12.2 Preliminary Results

LE98-05: Second cancers after allogeneic bone marrow transplantation. *(Study Chair: R Curtis, National Cancer Institute, Bethesda MD; Study Statistician: K Sobocinski). Manuscript in preparation.* This is a collaborative study with the National Cancer Institute and the Fred Hutchinson Cancer Research Center. We previously reported an increased risk of solid cancers in a large group of patients surviving more than five years after allogeneic HCT. That study had relatively few patients surviving more than 10 years post-transplant. We have continued surveillance of these and other transplant survivors to determine whether solid cancer risk changed beyond 10 years after transplantation. We assessed new cancers in 28,874 allogeneic transplant recipients and studied whether specific patient and transplant characteristics were associated with increased risk. 6,527 patients had survived for 5 or more years post-transplant and 1,925 for 10 or more years. Transplantation was done predominantly for leukemia (AML, CML, ALL; 74%), aplastic anemia (10%), lymphoma (5%) and myelodysplasia (5%). Average age at transplantation was 27 (range, <1-72) years. Sixty-seven percent of patients received TBI as part of their preparative regimen. The cumulative incidence of solid tumors increases steeply over time, reaching 5% 15 years after transplantation. Cancer incidence rates, adjusted for age, gender, calendar-year and geographic area taken from selected population-based cancer registries were used to calculate observed to expectedratios for solid cancers. Among one year survivors, the observed to expected ratio for all solid cancers combined is 2.2 (95% CI 1.9-2.6). Among 10 year survivors, the O/E ratio for all solid cancers is 4.9 (95% CI 3.2-6.7), and for these patients, the ratio for breast cancer is 3.3 (95% CI 1.1-7.6). Risk of breast cancer is not significant until 10 or more years after HCT. Multivariate analyses using Poisson regression modeling suggests that the risk of all solid cancers combined is increased for those who are exposed to total body irradiation (RR=1.8, 95%CI 1.0-3.4) or limited field irradiation (RR=5.6, 95%CI 1.9-15.6). Excess risk of solid cancers diminishes with increasing age at transplantation. These data indicate allogeneic transplant survivors face increasing risks of solid cancers with time after transplantation, supporting lifelong surveillance.

LE99-01: Preventive health behaviors of long-term hematopoietic cell transplant survivors. *(Study Chair: M Bishop, University of Florida, Gainsville, FL; Study Statistician: K Sobocinski). Manuscript in preparation. To be presented at the Tandem BMT meetings in February, 2007.* HCT is life-saving therapy for many patients with leukemia, lymphoma, and breast cancer. However, it is not known how many patients participate in healthy behaviors and recommended preventive services to avoid future health problems after transplant. We collected self-reported information on health-preserving behaviors as part of a large, cross-sectional study of long-term HCT survivors, spouses, and acquaintances. Self-reported information was classified as health provider independent [IND] (if medical contact not required, i.e., tobacco and alcohol avoidance, exercise) or health provider dependent [DEP] (e.g., cholesterol tests, stool guaiacs, sigmoidoscopy, blood pressure check, skin exam, breast exam, mammograms, immunizations, colon cancer screening), the latter adjusted for age and sex as appropriate. Participants included 662 HCT survivors (41% allogeneic and 59% autologous), 177 spouses, 158 controls matched to survivors on sex, age, martial status, and education level. 242 (36%) of HCT survivors had had acute leukemia, 132 (20%) CML, 132 (20%) lymphoma, and 156 (24%) breast cancer. Survivors were predominately Caucasian (90%), married (70%), female (62%), and well-educated (70% had post high school education). Mean age was 49 years (SD=10; range 21-77 years) and mean time since HCT was 7 years (SD= 3; range 2-23 years). 84% of survivors reported that they never smoke, 59% never drink alcohol, and 35% often/always exercise at least 20 minutes/day 3 times/week. Despite 94% of survivors reporting they had a physician and 92% had health insurance coverage, only 56% of survivors reported having received a flu shot in the last year. Although allogeneic survivors were more likely than autologous survivors to report having had a skin exam in the past year (54% versus 43%, p<.002), those rates were low given their vulnerability to melanoma. Other comparisons between allogeneic and autologous transplant survivors, as well as

between spouses and matched controls were made. Self-reported compliance with recommended health behaviors in HCT survivors was reasonably good, but there remains considerable room for improvement. Patients' frequent contact with the medical system and past experience with illness provide “teachable moments” to improve prevention screenings and to promote healthy behaviors in HCT survivors and their families.

LE99-01: Relationship quality and quality of life for HCT survivors and their partners. *(Study Chair: JR Wingard, University of Florida, Gainesville, FL; Study Statistician: K Sobocinski). Manuscript in preparation.* The object of this study was to examine the association between relationship quality and quality of life using couple level data from the quality of life study described above. Among the 663 HCT survivors who participated in the study, 350 participants, or 175 matched dyads where the HCT survivor and spouse who were married or living in a committed relationship participated in the study and provided complete data for our analyses. Only those HCT survivors who indicated that their marital status was never married (n=79), married/partnered (n=483) or divorced/separated (n=79) were considered. Analyses revealed that married/partnered survivors reported statistically less depression than never married survivors ($p<.05$) and divorced/separated survivors ($p<.01$). In addition, these analyses revealed that married/partnered survivors reported statistically better mental well-being than divorced/separated survivors ($p<.05$). No significant association was found between marital status and physical well-being. Further analyses are underway.

3.12.3 Planned Studies

LE98-07: Risk of early versus late PTLD after bone marrow transplantation. *(Study Chair: O Landgren, National Cancer Institute, Bethesda, MD; Study Statistician, E Gilbert)*

LE99-01: Clinical and demographic variables as predictors of long-term QOL. *(Study Chair: JR Wingard, University of Florida, Gainesville, FL; Study Statistician: K Sobocinski)*

LE99-01: Posttraumatic growth and spiritual well-being: Separate, related, or overlapping Constructs? *(Study Chair: MM Bishop, University of Florida, Gainesville, FL; Study Statistician: K Sobocinski)*

LE00-02: Late outcomes of autotransplants for leukemia and lymphoma. *(Study Chair: H Lazarus, Case Western Reserve University, Cleveland, OH; Study Statistician: K Sobocinski).*

D01-69: Donor leukocyte infusion for post transplant lymphoproliferative disorder. *(Study Chair: A Loren, University of Pennsylvania Cancer Center, Philadelphia, PA, D Porter, University of Pennsylvania Cancer Center, Philadelphia, PA; Study Statistician: K Sobocinski).*
LE05-01: Incidence of bronchiolitis obliterans after reduced-intensity HCT. *(S Mineishi, Vanderbilt University, Nashville, TN; Study Statistician: M Kukreja).*

LE05-02: Donor-derived cells contribute to second cancer development. *(Study Chair: C Cogle, University of Florida Shands, Gainsville, FL; Study Statistician: M Kukreja).*

LE06-01: Genetic susceptibility to therapy-related myelodysplasia and leukemia after autotransplantation in NHL *(Study Chair: T Fenske, Medical College of Wisconsin, Milwaukee, WI; Study Statistician: M Kukreja)*

3.13 Immunobiology Working Committee.

Co-Chair: Carolyn Hurley, PhD, Georgetown University Medical Center, Washington, DC
Co-Chair: Effie Petersdorf, MD, Fred Hutchinson Cancer Research Center, Seattle, Washington
Co-Chair: Machteld Oudshoorn, PhD, Europdonor Foundation, Leiden, The Netherlands
Statisticians: Michael Haagenson, MS, Fiona Kan, MS, MA
John Klein, PhD, Tao Wang, PhD
Scientific Directors: Mary Horowitz, MD, MS
Stephen Spellman, MS

3.13.1 Publications

SC 02-01: Loren AW, Bunin GR, Boudreau C, Champlin RE, Cnaan A, Horowitz MM, Loberiza FR, Porter DL**. Impact of donor and recipient sex and parity on outcomes of HLA-Identical sibling allogeneic hematopoietic stem cell transplantation.** *Biol Blood Marrow Transplant 12: 758-769, 2006.* Allogeneic HCT may cure patients with hematologic malignancies, but it carries significant risks. Careful donor selection is an important component of the clinical transplantation decision-making process and includes evaluation of HLA typing and other criteria, the most controversial of which is parity. We examined the effect of donor sex and parity on outcomes of HLA-identical sibling HCT. Because the effect of recipient sex/parity has never been explicitly evaluated, we also analyzed the effect of recipient sex/parity on outcomes of transplantation. We found that (1) parous female donors result in an increased risk of chronic GVHD in all recipients, (2) the magnitude of this increased risk is similar in male and female recipients, and (3) nulliparous female donors increase the risk of chronic GVHD in male recipients to a degree comparable to that from parous donors. A decrease in the risk of relapse was not observed, and there was no effect on overall survival, acute GVHD, or treatment-related mortality. Recipient parity had no independent effect on any endpoint. Until the effects of pregnancy on the maternal immune system are better understood, it is appropriate whenever possible to avoid parous female donors and to choose male donors for male recipients in HLA-identical related donor HCT.

R02-07: Farag SS, Bacigalupo A, Eapen M, Hurley C, Dupont B, Caliguiri MA, Boudreau C, Nelson G, Oudshoorn M, van Rood J, Velardi A. Maiers M, Setterhom M, Confer D, Posch PE, Anasetti C, Kamani N, Miller JS, Weisdorf DJ, Davies SM. **The effect of KIR ligand Incompatibility on the outcome of unrelated donor transplantation: A report from the Center for International Blood and Marrow Transplant Research, the Europeon Blood and Marrow Transplant Registry, and the Dutch Registry.** *Biol Blood Marrow Transplant 12: 876-884, 2006.* Matching for HLA class I alleles, including HLA-C, is an important criterion for outcome of unrelated donor transplantation. However, haplotype-mismatched transplantations for myeloid malignanacies, mismatched for killer immunoglobulin-like receptor (KIR) ligands in the graft-versus-host direction, is associated with lower rates of GVHD, relapse, and mortaility. This study investigated the effect of KIR ligand mismatching on the outcome of unrelated donor transplantation. The outcomes after 1571 unrelated donor transplantations for myeloid malignancies where donor-recipient pairs were HLA-A, -B, -C, and –DRB1 matched (n=1004), GVH KIR ligand-mismatched (n-137), host-versus-graft (HVG) KIR ligand-mismatched (n=170), and HLA-B and/or –C-mismatched but KIR ligand-matched (n=260) were compared using Cox regression models. Treatment-related mortality, treatment failure, and overall mortality were lowest after matched transplantations. Patients who received grafts from donors mismatched at the KIR ligand in the GVH or HVG direction and mismatched at HLA-B and/or C but matched at the KIR ligand had similar rates of treatment-related mortality, treatment failure, and overall mortality. There were no differences in leukemia recurrence between the 4 groups. These

results do not support the choice of an unrelated donor on the basis or KIR ligand mismatch determined from HLA typing.

D98-125: Wade JA, Hurley CK, Takemoto SK, Thompson J, Davies SM, Fuller TC, Rodey G, Confer DL, Noreen H, Haagenson M, Kan F, Klein J, Eapen M, Spelllman S, Kollman C. **HLA mismatching within or outside of cross-reactive Groups (CREG) is associated with similar outcomes after unrelated hematopoietic stem cell transplant.** *Blood, In Press.* The NMDP maintains a registry of volunteer donors for patients in need of HCT. Strategies for selecting a partially HLA-mismatched donor vary when a full match cannot be identified. Some transplant centers limit the selection of mismatched donors to those sharing mismatched antigens within HLA-A, -B cross reactive groups (CREG). To assess whether an HLA mismatch within a CREG group ("minor") may result in better outcome than a mismatch outside CREG groups ("major"), we analyzed validated outcomes data from 2709 bone marrow and peripheral blood stem cell transplants. 396 pairs (15%) were HLA-DRB1 allele matched but had an antigen-level mismatch at HLA-A or –B. Univariate and multivariate analyses of engraftment, graft-versus-host disease and survival showed that outcome is not significantly different between "minor" and "major" mismatches ($p=0.47$ from the log-rank test for Kaplan-Meier survival). However, HLA-A, -B, -DRB1 allele matched cases had significantly better outcome than mismatched cases ($p<0.0001$). For patients without an HLA match, the selection of a CREG compatible donor as tested does not improve outcome.

R02-33s: Mehta PA, Eapen M, Klein JP, Gandham S, Elliott J, Zamzow T, Combs M, Aplenc R, MacMillan ML,Weisdorf DJ, Petersdorf E Davies SM. **Interleukin-1 alpha genotype and outcome of unrelated donor hematopoietic stem cell transplantation for chronic myeloid leukemia.** *Submitted*. IL-1 is a pro-inflammatory cytokine implicated in initiation and maintenance of GVHD and the immune response to infection. A cytosine (C) to thymine (T) transition at codon -889 is believed to influence gene transcription. Previously we showed that the presence of at least one IL-1 T allele in the donor was associated with improved survival after unrelated donor HCT (survival at one year: 40% C/C donor, 68% T/C donor, 75% T/T donor, $p<0.01$). Multiple regression analysis showed reduced treatment-related mortality if the donor and recipient each possessed the IL-1T allele (RR 0.2, 95% CI 0.05-0.6, $p<0.01$). In the present study we sought to confirm these results in a larger more homogeneous patient population. The study included 426 adult patients (age > 18 years) with CML transplanted in first chronic phase between 1990 and 2002 with a CyTBI preparative regimen. Patients receiving peripheral blood stem cells, a second transplant, or a graft with > 1 HLA antigen mismatch were excluded. Donors and recipients were genotyped for the IL-1 polymorphism using a high throughput PCR assay. Donor recipient pairs were categorized into 4 groups according to the presence or absence of a T-allele in donor and in recipient (only recipient has T-allele, only donor has T-allele, both have T-allele and neither have a T-allele). Median patient age was 38 years (range 18-59); 57% were male; median donor age was 38 years (range 18-57 years) and 64% were HLA-matched at 6 antigens. Genotype categories were not significantly different in recipient and donor age, gender, year of transplant, performance status, GVH prophylaxis, HLA-match, interval from diagnosis to transplant, CMV serology and donor-recipient sex match. The impact of IL-1a genotype on univariate outcomes is shown below.

Endpoint	Recipient has T-allele	Donor has T-allele	Both have T-allele	Neither have T-allele	p-value
Treatment-related mortality @ 1 year	41%	43%	43%	43%	0.99
Acute GVHD	64%	67%	68%	72%	0.80
Chronic GVHD	50%	57%	52%	52%	0.81
Relapse@1year	7%	<1%	3%	1%	0.14
Relapse@2years	7%	4%	3%	3%	0.63
Leukemia-free survival @ 2 years	46%	51%	47%	47%	0.90
Survival@2 years	49%	52%	48%	48%	0.95

The data show no impact of IL-1 genotype on survival or treatment-related mortality. Multivariate analysis including donor and recipient age, performance status, year of transplant, CMV status, HLA disparity and donor patient sex mismatch confirmed that IL-1 genotype did not impact survival, leukemia-free survival, GVHD or treatment-related mortality. Survival (and leukemia-free survival) was significantly reduced in recipients of marrow with an allele or antigen level HLA-mismatch (RR 1.9, 95% CI 1.4-2.7; p< 0.0001) and T-cell depleted marrow (RR 1.43, 95% CI 1.07-1.92; p=0.017). Relapse was notably increased in recipients of T-cell depleted grafts (RR 4.1 95%CI 1.79-9.37; p=0.0008) and treatment-related mortality increased in recipients of an allele or antigen mismatched graft (RR 2.05 95% CI 1.44-2.91; p< 0.0001). In conclusion, these data from a large and relatively homogeneous population do not support a role for IL-1 genotype on outcome of unrelated donor transplantation for CML.

R03-57s: Hou L, Steiner N, Chen M, Belle I, Ng J, Hurley C. **KIR2DL1 Allelic Diversity: Four New Alleles Characterized in a Bone Marrow Transplant Population and Three Families.** *Submitted.* Transforming Growth Factor beta 1 (TGF-β1) is a multifunctional cytokine that plays a crucial role in immune regulation. Three of eight known polymorphic sites in the human TGF-β1 5' regulatory and signal peptide regions have been associated with higher secreted levels of TGFβ1. These single nucleotide polymorphisms (SNPs) have been linked to bone marrow transplant outcome but the results are inconsistent. As each of these studies examined single SNPs, the conflict could be due to different linkages between these SNPs and other functional SNPs and the corresponding phenotypes. A more comprehensive study of diversity and SNP linkages was undertaken here. Ten novel polymorphisms and 14 novel alleles were identified by sequence characterization of 38 unrelated individuals. The TGF-β1 alleles clustered into three phylogenetic groups based on the common functional SNPs -509C-T and +869T-C suggesting three phenotypic groups. However, the -509 and +869 SNP positions might not be as informative for predicting TGF-β1 phenotypes as suggested by the allelic groups. For example, individuals who carry allele p014 (intermediate phenotype) are more likely to have a low production phenotype due to the presence of +915C (decreased TGF-β1 expression) in this allele. This observation highlights why limited genotyping to predict phenotypes may not be definitive as linked SNPs likely affect the expected phenotypes that would be attributed to single SNPs. To assess impact of TGF-β1 promoter genotype on likelihood of developing and/or severity of GVHD in bone marrow transplant patients, we are characterizing 40 unrelated donor/recipient pairs in a pilot study. The genotype, p001/p003, was frequent (11/17, 64.7%) in recipients with grade 3 and 4 GVHD in comparison to recipients with GVHD grades 0-2 (7/16, 43.7%). These data target certain TGF-β1 promoter alleles for further study.

3.13.2 Preliminary Results

R04-97: Single or multiple HLA-A, B, C or DRB1 mismatches limit success of unrelated donor HCT. *(Study Chairs: S Lee, Fred Hutchinson Cancer Research Center, Seattle WA, C Anasetti, H. Lee Moffitt Cancer and Research Institute, Tampa FL; Study Statistician: M Haagenson). Manuscript in preparation. Oral presentation at American Society of Hematology meeting, December 2006.* Fewer than 50% of patients are able to identify an HLA-A, B, C, DRB1-sequence matched unrelated donor; the best partially matched donor must be chosen for the remainder. NMDP data from 3860 US transplants performed from 1988-2003 were analyzed to provide guidance in that choice. Patients had AML, ALL, CML or myelodysplasiz and received myeloablative conditioning regimens. Most received calcineurin-`based GVHD prophylaxis with T-cell replete grafts (79%). Nearly all received marrow grafts (94%). Median follow-up was 6 years. Patients and donors were retrospectively typed for HLA-A, B, C, DRB1, DQB1, DQA1, DPB1, and DPA1 by DNA sequencing and other high resolution typing methods. Matching was classified as low resolution (antigen-equivalent) or high resolution (allele sequence). Because of multiple comparisons, p-values <0.01 were considered significant. All analyses were adjusted for pt and transplant characteristics. RESULTS: Full matching for HLA-A, B, C, and DRB1 was associated with the best survival. A single mismatch at A, B, C or DRB1 was associated with increased mortality (RR 1.23, 95% CI 1.11-1.36, p=0.0001) with one-yr survival of 45% compared to 52% for fully matched pairs. Mismatches detected by low or high DNA resolution testing were associated with similar survival decrements (p=0.7). Survival differences were apparent in all disease risk categories. When mismatches at individual HLA loci were analyzed, a single mismatch at HLA-A was significantly associated with increased mortality (RR 1.35, 95% CI 1.14-1.59, p=0.0004); isolated HLA-A, B, C or DP mismatches were associated with increased risk of grades III-IV GVHD. Although the data set had few DRB1 mismatches (no antigen level and 58 allele level) limiting the power of this analysis, the RR of mortality (1.31, 95% CI 0.96-1.79, p=0.085) suggests an adverse outcome for DRB1 mismatching equivalent to A mismatching. Isolated DQ mismatching had no adverse impact. Mismatches at 2 HLA loci were associated with higher mortality risk than single mismatches (37% versus 45% one-yr survival), with HLA-A+C and HLA-B+C being the most frequent. We conclude that high resolution DNA typing of HLA-A, B, C, and DRB1 alleles facilitates optimal unrelated donor selection for patients with hematological malignancies because the best survival is associated with complete matching at these loci. When selecting among donors with single mismatches, HLA-DQ or DP disparity was not associated with worse survival. Examination of risks for mortality suggests single HLA-B or C mismatches are better tolerated than HLA-A or possibly DRB1 mismatches. Disparities for two loci, detected by either high or low resolution testing, compound the risk of mortality.

R04-91: KIR ligand absence in recipients of unrelated donor HCT is associated with less relapse and increased GVHD. *(Study Chair: J Miller, University of Minnesota Minneapolis, MN; Study Statistician: M Haagenson). Manuscript in preparation. Oral presentation at American Society of Hematology meetings, December 2006.* Natual killer (NK) cell alloreactivity in the GVH direction, defined by donor expression of inhibitory KIR for which the recipient lacks the corresponding class I MHC KIR ligand, can alter the outcome of HCT. All humans express at least one KIR ligand (C1, C2 and Bw4), and most genotypes frequently include the corresponding inhibitory KIR (e.g. in Caucasoid populations *KIR2DL2*, 49-60% and *KIR2DL3*, 85-93% (C1), *KIR2DL1*, 91-100% (C2); and *KIR3DL1*, 87-98% (Bw4)). Consequently, most donor-derived NK cells express inhibitory KIR recognizing all three MHC KIR ligands. Therefore NK cell alloreactivity after HCT may be operationally defined by the number and type of KIR ligands a recipient lacks. To evaluate the clinical effects of KIR ligand absence we studied 2062 patients with myeloid malignancies (556 AML, 1224 CML and 282 myelodysplasia) receiving unrelated donor HCT through the NMDP between 1988 and 2000, all part of the high-resolution typing project. Presence or absence of the C1, C2 and Bw4 KIR ligands was determined for each recipient from high resolution HLA class I typing. The median age and performance status of patients expressing all three KIR ligands (n=719) were not significantly different from those missing at

least 1 KIR ligand (n= 1343) (p=0.82 and p=0.71, respectively). A preliminary multivariate analysis of all patients showed no differences in the risk of relapse based on KIR ligand content. Significant differences emerged using stratification by disease stage. For patients with early disease (AML in CR1, 1st chronic phase CML <1 year from diagnosis, or myelodysplasia with refractory anemia) the absence of ≥1 KIR ligand was protective against relapse (RR 0.54, RR 0.30-0.95, n=534, P=0.03), independent of HLA-matching and consistent with reports of potentially beneficial NK cell mediated anti-tumor effects following HCT from HLA-matched sibling donors. In these early disease patients, three-year relapse rates were 11 (7-17)% with all KIR ligands present versus 6 (4-9)% with ≥1 ligand absent. In contrast, KIR ligand absence did not affect clinical outcomes for patients with more advanced myeloid disease. NK cells may also play an indirect role in GVHD through their effects on dendritic cells. Therefore we analyzed the impact on acute GVHD. HLA-matching was protective against acute GVHD, and generally, missing ≥1 KIR ligand had no effect on acute GVHD. Unexpectedly, in patients with late chronic phase CML > 1 year from diagnosis missing ≥1 ligand was associated with more frequent grade 3-4 acute GVHD (RR 1.6, 95% CI 1.1-2.2, n=481, P=0.008): 30 (23-37)% with all KIR ligands present versus 44 (39-50)% missing ≥1 KIR ligand. We noted more frequent pre-HCT interferon use late versus early chronic phase CML (63% versus 41%, P=<0.001) but prior interferon use did not independently affect GVHD. These data support the premise that NK cells have a genetically determined potential to affect outcomes following unrelated HCT in myeloid leukemia. A better understanding of how to manipulate KIR repertoires after HCT, by attenuation of inhibitory signals in patients who express all KIR ligands, for example, may allow extension of this clinical benefit to limit GVHD and relapse.

IB05-01: Multiplexed genotyping of human minor histocompatibility antigens: Clinical relevance of mHAg disparity in HCT. *(Study Chair: T Ellis, Blood Center of Wisconsin, Milwaukee, WI; Study Statistician: M Haagenson). Analyses in progress. Accepted for oral presentation at the BMT Tandem Meetings, February 2007.* This study assessed the effect of single and multiple minor histocompatibility antigen (mHAg) mismatches on outcomes of 730 unrelated donor, HLA-A, B, C, DRB1 and DQB1 allele-matched transplants facilitated by the NMDP between 1996 and 2003. The study population included patients with acute and chronic leukemia and myelodysplastic syndrome. Bone marrow was the predominant source of hematopoietic cells (85%). All patients received myeloablative conditioning regimens and calcineurin inhibitor-based GvHD prophylaxis. The median follow-up was 5 years (range: 0.9-8.9). DNA samples from both donor and recipient were obtained from the NMDP Research Sample Repository and genotyped for mHAg including: HA-1, HA-2, HA-3, HA-8, HB-1, and CD31. Patients carrying multiple relevant HLA alleles were evaluated for the impact of multiple mHAg mismatches. Primary outcomes included grades II-IV acute GvHD and survival; secondary outcomes tested included chronic GvHD, engraftment, and relapse. Single disparities at HA-1, HA-2, HA-3, HA-8, HB-1 and CD31 were not significantly associated with any of the outcomes analyzed. Significant associations with transplant outcomes were observed only when disparities existed at multiple mHAg loci. Significantly lower survival was observed for individuals mismatched for both CD31 and HA-3 in the GvH direction versus those matched (RR=2.01, 95% CI 1.14-3.55, p=0.017) or mismatched at a single locus for these mHAg (RR=2.38, 95% CI 1.32-4.35, p=0.0043). In addition, pairs mismatched at both CD31 and HA-3 in the GvH direction exhibited higher treatment-related mortality than pairs mismatched at a single locus (RR=2.50, 95% CI 1.27-4.76, p=0.009). The results for single mHAg mismatches at HA-1, HA-2, HA-3, HA-8, HB-1 and CD31 show no evidence of an effect on outcomes, but the power is limited by the population size. However, multiple mHAg mismatches are associated with significantly lower survival and increased treatment-related mortality when considering HA-3 and CD31 under the HLA-A*01 restriction.

R01-60: Use of HLA structure and function parameters to understand the relationship between HLA disparity and transplant outcomes. *(Study Chair: L. Baxter-Lowe, UCSF, San Francisco, CA; Study Statistician: M. Haagenson). Analysis.* The study aims to develop a scoring system for ranking

HLA mismatches based on the structural and functional changes imparted by various amino acid sequence differences. A preliminary analysis was conducted to investigate the immunogenicity of specific amino acid positions and differences to guide development of the scoring model. Transplant cases mismatched for single HLA-A alleles (7/8) were compared against transplants matched at 8/8 HLA-A, -B, -C and -DRB1 loci. The number of cases within each specific mismatch group was small ranging from 8 to 27 cases per group. Due to these small numbers, Fisher's Exact test and logistic regression were applied during the analysis of the outcomes. There was a trend for A*0101-*0201 to have less grades 3-4 acute GvHD but no statistically significant differences in outcome have been found in univariate analysis. Analyses are ongoing.

R02-27: HLA matchmaker analysis of HCT outcome. *(Study Chair, R. Duquesnoy, University of Pittsburgh, Pittsburgh, PA; Study Statistician: M. Haagenson). Manuscript in preparation.* This study evaluated the ability of the Matchmaker algorithm to predict the immunogenicity of HLA mismatches in unrelated donor transplants. The preliminary analysis evaluated cases matched at HLA-A, -B –C, DRB1 and DQB1 against cases that with a single allele mismatch for HLA-A, -B and -C. HLA mismatches were categorized based on the number of "Eplet" mismatches, i.e. immunogenic epitopes determined by the disparate amino acid sequences at the mismatched locus. Treatment related mortality was significantly worse after mismatched versus matched transplants and outcome did not seem to correlate with number of mismatched eplets.

R03-65s: Detection of H-Y antibodies in healthy female donors: Does H-Y presensitization predict male HCT outcome. ***(Study Chair, D. Miklos, Stanford University, Stanford, CA; Study Statistician: F. Kan).*** *Analysis.* 520 Normal Female donors have been tested by ELISA for H-Y antibodies and analysis thus far does not show an association with cGVHD, relapse or overall survival. Dr. Miklos et al. have developed a more sensitive microarray-based technique to test for H-Y antibodies and plan to repeat this analysis. In addition Dr. Miklos is obtaining blood samples from the surviving male recipients to evaluate the de novo development or adoptive transfer of pre-existing H-Y antibodies

R04-98: The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated HCT and their relationship to graft/patient outcome. *(Study Chair: R. Bray, Emory University, Atlanta, GA; Study Statistician: M. Haagenson). Analysis.* 37 patients with graft failure were matched with 78 controls achieving neutrophil engraftment by day 28 post transplant. Pre-transplant patient serum samples were tested for the presence of anti-HLA antibodies. Preliminary results suggest that the presence of donor-directed, HLA-specific alloantibody increases the risk of graft rejection after transplantation of hematopoietic stem cells from unrelated donors. Analyses are ongoing.

3.13.3 Planned Studies

R04-80s: Impact of HLA matching on outcome in pediatric patients undergoing unrelated umbilical cord blood transplantation. *(Study Chair: S Rodriguez-Marino, University of Chicago Hospitals, Chicago, IL; Study Statistician: M Haagenson).*

R04-93: Dissimilarity scoring in mismatched HCT pairs. *(Study Chair: R Blasczyk, Hannover Medical School, Hannover, Germany; Study Statistician: M Haagenson).*

IB05-02s: Effect of single MHC class I mismatch with numerous sequence differences on the clinical outcome of unrelated donor HCT. *(Study Chair: M Heemskerk, Europdonor Foundation, Leiden, The Netherlands; Study Statistician: M Haagenson).*

IB06-01: HLA disparity in unrelated bone marrow transplant donor-recipient pairs. *(Study Chairs: C Hurley, Georgetown University Medical Center, Washington, DC, USA; L Baxter-Lowe, Immunogenetics and Transplantation Laboratory, University of California, San Francisco, San Francisco, CA; Study Statistician: M Haagenson).*

IB06-02: Impact of mismatches in low expression HLA loci on the outcome of unrelated donor transplants. *(Study Chairs: M Fernandez-Vina, M. de Lima and R. Champlin, M. D. Anderson Cancer Center, Houston, TX; Study Statistician: M Haagenson).*

IB06-03: One antigen mismatched related versus HLA-matched unrelated donor HCT in patients with acute leukemia: Results in the era of molecular typing. *(Study Chairs: D Valcarcel and J Sierra, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Study Statistician: F Kan).*

IB06-04: Effect of age on outcome in patients undergoing related HLA mismatched/haploidentical stem cell transplantation. *(Study Chair: L Dong, Peking University People's Hospital, Dao-Pei Hospital, Beijing, China; Study Statistician: F Kan).*

IB06-13: HLA disparity in unrelated cord blood transplants: Delineation of factors contributing to transplant outcomes. *(Study Chair: L Baxter-Lowe, Immunogenetics and Transplantation Laboratory, University of California - San Francisco, San Francisco, CA; Study Statistician: M Haagenson).*

IB06-05: Use of high-resolution HLA data from the NMDP for the International Histocompatibility Working Group in HCT. *(Study Chair: E Petersdorf, Fred Hutchinson Cancer Research Center, Seattle, WA; Study Statistician: M Haagenson).*

IB06-06: Transplant outcomes using related donors other than matched siblings for transplantation in pediatric patients: the effect of low-resolution or allelic mismatches on GVHD and survival. *(Study Chairs: P Shaw, Children's Hospital at Westmead, Sydney, Australia; M Pulsipher, University of Utah, Salt Lake City, Utah; Study Statistician: F Kan).*

3.13.3.2 Cytokines/Chemokines

R03-70s: Candidate gene study to examine the impact of chemokine and chemokine receptor gene polymorphisms on the incidence and severity of acute and chronic GvHD. *(Study Chair: R Abdi, University of Queensland Toowoomba Hospital, Toowoomba, Queensland, Australia; Study Statistician: F Kan).*

R04-75s: Functional significance of cytokine gene polymorphisms in modulating risk of post-transplant complications. *(IHWG) (Study Chair: E Petersdorf, Fred Hutchinson Cancer Research Center, Seattle, WA; Study Statistician: M Haagenson).*

IB05-03s: Genetic polymorphisms in the genes encoding human interleukin-7 receptor-α: Prognostic significance in allogeneic HCT. *(Study Chair: K Muller, Paediatric Clinic, Copenhagen, Denmark; Study Statistician: M Haagenson).*

3.13.3.3 NK/KIR

R02-40s: KIR reconstitution after unrelated HCT. (Study Chair: J Miller, University of Minnesota, Minneapolis, MN; Study Statistician: M Haagenson).

R03-63s: The role of KIR and their HLA ligands in unrelated blood and marrow transplants: The genetics and heterogeneity of KIR genes and haplotypes in ethnically diverse donor-recipient transplant pairs. *(Study Chairs: E Trachtenberg, Children's Hospital and Research Center, Oakland, CA; J Miller, University of Minnesota, Minneapolis, MN; Study Statistician: M Haagenson).*

R04-74s: Functional significance of KIR-Ligand genes in HLA matched and mismatched unrelated HCT. *(IHWG) (Study Chairs: B Dupont, Memorial Sloan-Kettering Cancer Center, New York, NY, K Hsu, Memorial Sloan-Kettering Cancer Center, New York, NY; Study Statistician: M Haagenson).*

IB06-12s: Study on the role of Natural Killer Cells activating KIR genes in protection against lymphoma relapse in HCT. *(Study Chair: C Demanet, Academic Hospital-Brussels Free University, Brussels, Belgium; Study Statistician: M Haagenson).*

3.13.3.4 Other Genes

R02-10s: MICA, MICB and TCRDV1 genotypes influence the outcome of HCT in African-Americans. *(Study Chair: P Fraser, CBR Laboratories, Inc., Boston, MA; Study Statistician: M Haagenson).*

R03-58s: The role of MICA in GVHD following matched unrelated donor HCT. *(Study Chair: M Verneris, University of Minnesota Cancer Center, Minneapolis, MN; Study Statistician: M Haagenson).* Incorporated into IB06-08 study.

R04-76s: Identification of functional SNPs in unrelated HCT. *(Study Chair: E Petersdorf, Fred Hutchinson Cancer Research Center, Seattle, WA, Study Statistician: M Haagenson).*

IB06-07s: NOD2/CARD15 mutations in the donor or recipient increase the risk of acute GvHD and treatment-related mortality following allogeneic stem cell transplantation. *(Study Chairs: N Davidson and Y Nguyen, Washington University School of Medicine, St. Louis, MO; Study Statistician: M Haagenson).*

IB06-08: The role between certain HLA-B alleles and the development of gastrointestinal GVHD following matched unrelated donor transplantation. *(Study Chair: M Verneris, University of Minnesota Cancer Center, Minneapolis, MN; Study Statistician: M Haagenson).*

3.13.3.5 Sensitization and Tolerance

GV04-01: Outcome of non-identical twin transplant for leukemia. *(Study Chair: A J Barrett, NHLBI, NIH, Bethesda, MD; Study Statistician: M Haagenson).*

IB06-09s: Detection of HLA antibody to the mismatched antigen in single antigen HLA-mismatched unrelated donor transplants: Is it a predictor of Graft-versus-Host Disease outcome? *(Study Chairs: S Arai and D Miklos, Stanford University, Stanford, CA; Study Statistician: M Haagenson).*

IB06-10: Evaluation of the impact of the exposure to Non-Inherited Maternal Antigens (NIMA) during fetal life and breast feeding and to the Inherited Paternal Antigens (IPA) during pregnancy on the clinical outcome of HCT from haploidentical family members. *(Study Chair: J van Rood, Europdonor Foundation, Leiden, The Netherlands; Study Statistician: F Kan).*

IB06-11s: The effect of Non-Inherited Maternal Antigens (NIMA) in cord blood transplantation. *(Study Chair: L Baxter-Lowe, University of California-San Francisco, San Francisco, CA; Study Statistician: F Kan)*

3.14 Regimen-related Toxicity/Supportive Care Working Committee.

Co-Chairs: Karen Ballen, MD, Massachusetts General Hospital, Boston, MA
Co-Chair: Andrea Bacigalupo, MD, Ospedale S. Martino, Genova, Italy
Statisticians: Manza-A Agovi, MPH
Brent Logan, PhD
Scientific Director: J. Douglas Rizzo, MD, MS

3.14.1 Publications

D01-08: Giralt S, Logan B, Rizzo JD, Zhang M-J, McGaha O, Ballen K, Emmanouilides C, Nath R, Parker P, Porter D, Sandmaier B, Waller E, Barker J, Pavletic S, Weisdorf D. **Reduced intensity conditioning regimens with volunteer unrelated donor progenitor cell transplantation: Lessons learned from the first 286 patients reported to the National Marrow Donor Program. An analysis from the Center for International Blood and Marrow Transplant Research**. *Submitted.* To determine the long-term outcome of patients undergoing unrelated donor transplantation after a reduced intensity conditioning regimen we performed a retrospective analysis of transplant outcomes of the first five years of reduced intensity experience as reported to the NMDP. Patients were included for this analysis if they were older than 18 years and had undergone an unrelated donor transplant procured through the NMDP from 1/1/96 until 05/31/01 for a hematologic malignancy. The numbers of unrelated donor transplants performed using reduced intensity conditioning increased from 59 during 1996 to 1999, to 149 in the year 2000. Patients receiving reduced intensity recipets were older (53 versus 33 years) and had a higher likelihood of having advanced disease (81% versus 51%) when compared to patients undergoing a myeloablative conditioning regimen during the same time period. The five-year survival rate was 23 (18-28)%; the five-year incidence of progression/relapse was 43 (37-49)%. In multivariate analysis, prognostic factors for overall survival were disease stage, time from diagnosis to transplant, degree of HLA match, Karnofsky performance score, and source of stem cells. This analysis demonstrates that long term survival and disease control can be obtained with unrelated donor HCT after reduced intensity conditioning. However, only prospective trials will define the optimal role of this therapy in patients with hematologic malignancies.

3.14.2 Preliminary Results

RT05-04: Outcomes after HCT using fludarabine, busulfan and Thymoglobulin: A matched comparison to allogenic transplants conditioned with busulfan and cyclophosphamide. *(Study Chair: C Bredeson, Medical College of Wisconsin, Milwaukee, WI; Study Statistician: M-J Zhang). Manuscript in Preparation.* Allogeneic HCT after standard myeloablative conditioning is associated with significant risks of regimen related mortality and GVHD. Over the past five years, a novel fludarabine-based conditioning regimen using a low dose of rabbit ATG (Thymoglobulin) with fludarabine and intravenous busulfan has been used at a single transplant center where initial data suggest a lower incidence of acute GVHD in a diverse population of patients with acute leukemia (n=48), CML (n= 21), CLL (n= 9), myelodysplasia (n=22), lymphoma (n= 23) and multiple myeloma (n=11). We performed a

retrospective analysis comparing outcomes using this new approach with matched controls receiving HCT after conditioning with standard busulfan and Cy during the same time period. All patients were 18 to 65 years of age, received HLA-identical sibling peripheral blood or bone marrow transplants for the diseases noted above from 1999-2003 and were given cyclosporine and methotrexate for GVHD prophylaxis. Controls were selected from eligible patients reported to the CIBMTR to match on disease and disease status at transplant and to minimize age differences. Two matches were found for 95 cases, 1 for 26 and none for 13. The latter 13 were excluded from further study leaving 121 cases and 216 matched controls available for comparison. Median follow-up was 30 (range, 12-61) months for cases and 35 (range, 2-72) months for controls (p=0.47). Compared to the 216 controls, the 121 cases had lower Karnofsky scores before transplant, and were more likely to receive a peripheral blood transplant. Outcome comparisons used multivariate Cox regression, stratified on the matched pair, to adjust for these differences. The risk of grades II-IV acute GVHD (RR 0.34, 95% CI 0.20-0.59, p=0.0001) and overall mortality (RR 0.48, 95% CI, 0.29-0.77, p=0.003) were significantly lower in cases versus controls. The risk of chronic GVHD was similar in the cases and controls. These results suggest that the novel regimen fludarabine, busulfan and Thymoglobulin decreases the risk of acute GVHD and improves survival after HLA-identical sibling HCT and support the development of a prospective multi-center randomized clinical trial to confirm these findings.

3.14.3 Planned Studies

D98-70: Comparative analysis of busulfan and Cy versus Cy/TBI in unrelated donor transplantation for AML, CML and myelodysplasia. *(Study Chair: J Uberti, University of Michigan, Ann Arbor, MI; Study Statistician: M Agovi).*

CK00-03: Effect of type of TBI on outcome of HLA identical sibling HCT. (*Study Chair: J Cahn, Centre Hospitalier Universitaire de Grenoble, Grenoble, France; Study Statistician: M Agovi).*

SC03-01/ R02-26: A retrospective study on the impact of obesity on toxicity and outcomes in HCT for AML. (*Study Chair: W Navarro, UCSF, San Francisco, CA; Study Statistician: M Agovi)*.

LE03-01: Effect of smoking on transplant outcome*. (Study Chair: D Marks, Bristol Royal Hospital for Children, Bristol, UK; Study Statistician: K Sobocinski).*

RT05-01: Role of gemtuzumab ozogamicin in the development of hepatic veno-occlusive disease*. (Study Chair: S Bearman, Rocky Mountain Cancer Center, Denver, CO; Study Statistician: M Agovi).*

RT05-02: L**ower BMI prior to transplantation as an indicator of increased risk for morbidity and mortality during the first 100 days after the transplantation process***. (Study Chair: C Barker, BC Children's Hospital, Vancouver, Canada; Study Statistician: M Agovi).*

RT05-03: Second matched unrelated donor transplant as a rescue strategy for patients who fail to engraft after initial transplantation. *(Study Chair: J Schriber, City of Hope National Medical Center, Phoenix, AZ; Study Statistician: M Agovi).*

RT06-01: Evaluation of TGF-β1 promoter and signal peptide polymorphisms as risk factors for renal dysfunction in HCT patients treated with cyclosporine A *(Study Chair: R Shah, Georgetown University Medical Center, Washington DC, DC; Study Statistician: M Agovi).*

RT06-02: A longitudinal study of treatment related mortality to determine how innovations in clinical care over the past two decades have affected the safety of myeloablative allogeneic transplantation. *(Study Chair: J Horan, Emory University, Atlanta, GA; Study Statistician: M Agovi).*

3.15 Infection and Immune Reconstitution Working Committee.

Co-Chair: Jan Storek, MD, PhD, University of Calgary, Calgary, Alberta, Canada
Co-Chair: Jo-Anne van Burik, MD, University of Minnesota, Minneapolis, MN;
Co-Chair: Ronald Gress, MD, National Institutes of Health, Bethesda, Maryland;
Statisticians: Manisha Kukreja, MBBS, MPH
Sergey Tarima, PhD
Scientific Director: Marcie Tomblyn, MD, MS.

3.15.1 Preliminary Results

LE04-02: Outcome of HCT in Human Immunodeficiency Virus (HIV)-positive patients with hematological malignancies. *(Study Chair: V Gupta, Princess Margaret Hospital, Toronto, Ontario, Canada; A Keating; Study Statistician: T Pedersen). Analyses in progress.Accepted for Oral Presentation at BMT Tandem Meetings in February 2007.* Previous reports suggest feasibility and curative potential of autologous transplantation for HIV-associated lymphomas. Anecdotal reports suggest that allogeneic HCT may be feasible in HIV-positive patients. We retrospectively evaluated 27 HIV-positive patients with malignant (n=20) or non-malignant disorders (n=7), who received an allogeneic HCT between 1987 and 2003 and were reported to the CIBMTR. The median age at transplant was 32 years (range 9-49) and 78% of recipients were male. The donors were: HLA identical siblings, 19 (70%); syngeneic, 5 (19%); and unrelated, 3 (11%). Indications for HCT were diverse and included: non-Hodgkin lymphoma, 10; CML, 3; AML, 2; myelodysplastic syndrome, 2; ALL, 2; other acute leukemia, 1; aplastic anemia, 2; and other non-malignant disorders including HIV disease, 5. Twenty-one (78%) patients were transplanted prior to 1996. The conditioning regimens included high-dose (≥1000 cGY) TBI, 13 (48%); chemotherapy only, 13 (48%); and, low-dose (200cGY) TBI, 1 (4%). Twenty-three (85%) patients received bone marrow and 4 (15%) peripheral blood grafts. The rate of neutrophil engraftment at 28 days was 77%. The cumulative incidenceof grades II–IV acute GVHD (excludes syngeneic transplants) was 9 (1-25)%. For patients alive at 100 days (n=11), the cumulative incidence of chronic GVHD at one and two years was 36 (12-65)%. At a median follow-up of 59 months, 6 patients are alive. Twenty-one patients died at a median of 58 days (range, 2–479) but only 3 (14%) due to relapse. The probability of survival at 2-years was 22%. Treatment related mortality probabilities at 100 days and 2-years were 44% and 67%, respectively. Causes of treatment-related mortality were: pulmonary toxicity, 7; infections, 3; organ failure, 3; HIV disease, 2; and others, 3. Deaths related to pulmonary toxicity appear to be higher in patients receiving high-dose TBI based conditioning (5/13) compared to the other conditioning regimens (2/14). CD4 counts ($x10^9$/L) and viral loads (log copies) are available on few patients and some patients had multiple values post-transplant. In the 3 months prior to transplant, the median CD4 count (n=8) was 106 (range, 0 -1200) and the median viral load (n=5) was 1.7 (range, 1.6–5). At 3 months post transplant, the median CD4 count (n=15) was 20 (range, 0–286). After 6 months post transplant, the median CD4 count (n=9) and viral load (n=9) were 640 (range, 302–1061) and 1.7 (range, 1.7–4.4), respectively. Of the 6 patients transplanted after 1996, 4 survive compared to 2 of 21 patients transplanted prior to 1996, presumably related to the effect of improved supportive care strategies and highly active anti-retroviral therapy. These data suggest that allogeneic HCT is feasible for HIV-positive patients with malignant and non-malignant disorders and provide the framework for the design of future prospective studies.

3.15.2 Planned Studies

LE00-01: Impact of CMV infection by day 100 after allogeneic HCT for leukemia. (*Study Chair: J Wingard, University of Florida, Gainesville, FL; Study Statistician: M Kukreja).*

GV02-02: Outcome of patients with hematologic malignancy receiving HLA-matched sibling allogeneic HCT from hepatitis B and/or hepatitis C positive donors. *(Study Chair: K Ballen, Massachusetts General Hospital, Boston, MA; Study Statistician: M Kukreja).*

LE04-01: CMV infection and mortality after HCT. *(Study Chair: M Boeckh, Fred Hutchinson Cancer Research Center, Seattle, WA; Study Statistician: M Kukreja).*

R04-90: KIR-ligand: NK cell interaction and infection after unrelated donor transplantation. *(Study Chair: J van Burik, University of Minnesota, Minneapolis, MN; Study Statistician: M Haagensen).*

IN05-01: Determining risk factors for very late-onset invasive aspergillus infection among HCT recipients. *(Study Chair: B Park, Centers for Disease Control and Prevention, Atlanta, GA; Study Statistician: M Kukreja).*

IN05-02: Atypical molds infections in HCT patients. *(Study Chairs: M Tomblyn,* University of Minnesota, Minneapolis, MN; Steven Trifilio, RPh, Northwestern University, Chicago, IL*; Study Statistician: M Kukreja).*

IN06-01 The rate of breakthrough of *Pneumocystis jiroveci* pneumonia as a function of prophylaxis regimens *(Study Chairs: K* Williams, Johns Hopkins Hospital, *Baltimore; Study Statistician: M Kukreja).*

3.16 Donor Health and Safety Working Committee.

Co-Chairs: Michael Pulsipher, MD, University of Utah School of Medicine, Salt Lake City, UT
Co-Chair: Paolo Anderlini, MD, M D Anderson Cancer Center, Houston, TX
Co-Chair: Susan Leitman, MD, NIH Clinical Center Blood Bank, Bethesda, MD
Statisticians: Tanya Pedersen, BS
Brent Logan, PhD
Scientific Director: Dennis Confer, MD

3.16.1 Preliminary Results

D01-84a: Volunteer unrelated donor peripheral blood collection efficacy and recipient outcomes: Results of a prospective NMDP trial, 1999-2003. *(Study Chair: M. Pulsipher, University of Utah, Salt Lake City, Utah, Study Statistician, P. Chitphakdithai). Manuscript in preparation. Oral presentation at the American Society of Hematology meetings, December 2006.* In spite of limited multi-institutional outcome data and concern about high rates of chronic GvHD, peripheral blood has become the most frequently used unrelated donor stem cell source. We present an analysis of 1178 non-T-cell depleted donor/recipient pairs enrolled on a prospective trial conducted by the NMDP (1999-2003). Multivariate analysis revealed that donors who were younger, heavier, or who had higher pre-apheresis CD34+ cell numbers gave higher CD34+ yields. Recipients were more likely to engraft neutrophils if Karnofsky scores (KS) were ≥90 (RR 0.31 for <90, p<0.001) or if the donor blood volume processed was about 24 L (RR 2.88 for 24L versus <19L, p=0.006). Platelet engraftment was associated with KS ≥90 (RR 0.66 for <90, p=0.005), CMV seronegative recipients (RR 0.66 for CMV+, p=0.004), and high CD34+ cells/kg recipient wt infused (RR 2.94 for >$9.5x10^6$ CD34+ cells/kg versus

<3.6, p<0.001). Surprisingly, a higher incidence of grade II-IV acute GVHD at 100 days was noted in pediatric compared to adult patients (58% versus 45%, *p*=0.011), although rates of grade III-IV acute GVHD were similar (31% versus 26%, p= 0.29). Lower rates of grade II-IV acute GVHD were also noted for HLA matched versus mismatched (45% versus 56%, *p*=0.023), reduced intensity versus myeloablative conditioning (39% versus 51%, *p*<0.001), and FK506 versus CsA-based prophylaxis regimens (RR 0.73, p=0.003). An advantage in survival at one year was noted for early versus intermediate versus high risk disease (one year overall survival 57% versus 45% versus 33%, *p*<0.001) and 6/6 HLA matched versus mismatched groups (one year overall survival 48% versus 38%, *p*=0.031). The risk of dying was higher in recipients who had a performance score <90 (RR 1.55, p<0.001), were CMV seropositive (RR 1.21, p=0.012), had an HLA-mismatched donor (RR 1.48, p=0.001), or received a myeloablative transplant (RR 1.39, p<0.001). In conclusion, unrelated donor peripheral blood results in rapid engraftment and acceptable long-term survival outcomes, but chronic GVHD occurs in >50% of recipients. Better outcomes are associated with use of FK-506, 24L of collection, higher product cell counts, reduced intensity regimens, HLA-matched donors, low risk disease and high Karnofsky scores.

D01-84a: The burden of the volunteer unrelated hematopoietic cell donor: Results of a prospective NMDP trial assessing toxicities associated with peripheral blood collections, 1999-2005. *(Study Chair: M. Pulsipher, University of Utah, Salt Lake City, Utah, Study Statistician, P. Chitphakdithai). Manuscript in preparation.* Limited data is available describing donor toxicity associated with G-CSF mobilized peripheral blood collection in normal unrelated volunteers. We report detailed toxicity outcomes in 2408 unrelated peripheral blood donors facilitated by the NMDP (1997-2004). Female donors had significantly higher rates of toxicity, requiring central line placement more often (20% versus 4%, *p*<0.0001), experiencing more apheresis related adverse events (20% versus 7%, *p*<0.0001), more bone pain (RR 1.49), and higher rates of grade II-IV and III-IV adverse events (RR 2.22 and 2.13). Larger or obese donors experienced more bone pain (RR 4.2) and higher rates of toxicities (RR 1.4). More than 80% of donors reported bone pain, with 10% describing severe and 1% intolerable pain. Six percent of donors experienced grade III-IV toxicities and 0.6% experienced toxicities that were considered severe and unexpected. No deaths were reported and no long-term adverse events were noted, however, the study was not designed to address late toxicities. In conclusion, G-CSF mobilized peripheral blood collection in unrelated donors is generally safe, but donors must understand that nearly all will experience pain, one in four may have moderate to severe nausea or citrate toxicity, and a small percentage may experience significant short-term adverse events. In addition, women and larger donors are at higher risk for donation related toxicities. This large, comprehensive study using common toxicity measures should serve as a baseline for future donor safety studies.

D01-84b: Serious complications following unrelated donor marrow collection: Experiences of the NMDP. *(Study Chair: D. Confer, National Marrow Donor Program, Minneapolis, Minnesota, Study Statistician: B. Logan). Manuscript in preparation.* Marrow has been collected as source of hematopoietic progenitor cells for transplantation for more than 30 years, yet relatively little has been reported concerning serious donor complications. Minor side-effects such as hypotension, syncope and collection site pain are reported in up to 75% of marrow collections facilitated by the NMDP. The purpose of this study was to document the incidence and nature of serious complications among NMDP marrow donors. All NMDP marrow collections between December 1987 and December 1999 (n=9245) were included for review. Using data from standardized individual follow-up forms, 345 donors who experienced potentially serious medical complications (e.g., excessive pain, adverse acute anesthesia reaction, delayed return to normal activities, need for additional medical intervention) were identified. A panel of five physicians reviewed each of these cases and identified 125 (1.35% of the 9245 total) that all agreed were serious post-donation complications. The panel further identified these by cause and duration. Of the 125 serious cases, proximal cause fell into five categories: (1)

mechanical injury to tissue, bone, or nerve (n= 69, or 55% of the serious subset and 0.7% of the total); (2) anesthesia (n=45, or 36% of the serious subset and 0.5% of the total); (3) infection (n=1, or 0.8% of the serious subset and 0.01% of the total); (4) other (n=1 [grand mal seizure], or 0.8% of the serious subset and 0.01% of the total); and (5) serious events thought to be unrelated to donation (n=9 [6 cases of cancer and 3 cases of herniated spinal disk requiring major intervention], or 7% of the serious subset and 0.09% of the total). The 116 donors with complications directly related to donation were further categorized according to symptom nature and duration. Sixty-seven donors (58% and 0.7% of the total) experienced prolonged recovery periods (from months to years), with symptoms stemming mostly from mechanical injury and requiring interventions ranging from limited physician involvement and/or physical therapy at one end, to surgical procedures and ongoing (one to >10 years) disability at the other. Forty-nine donors (42% and 0.5% of the total) experienced severe acute reactions, mostly related to anesthesia (e.g., complicated post-spinal headaches, cardiac arrythmias, pulmonary edema). These severe acute reactions were short-lived and typically resolved within hours to days after collection. In conclusion, the incidence of serious complications from marrow donation is low (1.35%) and mechanical injury is the most frequent cause of prolonged post collection recovery. The risks of collecting hematopoietic progenitor cells by marrow aspiration should be compared with those associated with the collection of G-CSF mobilized progenitors from the blood by apheresis.

DS05-01: Donor form development. *(Study Chairs: M Pulsipher, University of Utah, Salt Lake City, Utah, P Anderlini, MD Anderson Cancer Center, Houston, Texas, S. Leitman, NIH Clinical Center Blood Bank, Bethesda, Maryland, Study Statistician: T Pedersen).* First draft completed.

3.16.2 Planned Studies

DS05-02: RDSafe: A multi-institutional study of HCT donor safety and quality of life. *(Study Chair: M Pulsipher, University of Utah, Salt Lake City, Utah, Study Statistician: B Logan).*

DS05-03: RDSafe2: A multi-institutional study of HCT donor safety and quality of life. *(Study Chair: M Pulsipher, University of Utah, Salt Lake City, Utah, Study Statistician: B Logan).* This protocol was rolled into the above study.

DS06-01: Related donor and recipient management practice pattern survey. *(Study Chair: P O'Donnell, Fred Hutchinson Cancer Research Center, Seattle, Washington, Study Statistician: T Pedersen).*

DS06-02: LDSafe: A multi-institutional study of unrelated HCT donor long-term safety. *(Study Chair: D Confer, National Marrow Donor Program, Minneapolis, Minnesota, Study Statistician: B Logan).*

3.17 Health Policy and Psychosocial Issues Working Committee.

Co-Chair: Stephanie Lee, MD, Dana Farber Cancer Institute, Boston, MA
Co-Chair: Galen Switzer, PhD, University of Pittsburg Medical Center, Pittsburg, PA
Statisticians: Anna Hassebroeck, MPH
John Klein, PhD
Scientific Director: J. Douglas Rizzo, MD, MS
Assistant Scientific Director: Navneet Majhail, MD, MS

3.17.1 Publications

HS05-06: Nietfeld JJ, Pasquini MC, Logan BR, Verter F, Horowitz MM. **Lifetime probabilities of HCT in the US: Implications for umbilical cord blood storage.** *Submitted.* The purpose of this study was to estimate the probabilities of HCT in general and a cord blood transplantation in particular, based

upon current HCT practices in the United States. We estimated the probabilities of autologous and/or allogeneic HCT using data from the CIBMTR and the U.S. Surveillance, Epidemiology and End Results Program. Probabilities were calculated as cumulative incidences. Estimates were considered under several scenarios: under current indications for HCT, when assuming universal donor availability, and when broadening HCT use in hematologic malignancies. The incidences of diseases treated with HCT and of actual HCTs increase with age, rising strongly after age 40. After that age, these incidences are higher for men than for women, independent of race. The lifetime probabilities of undergoing an HCT range from 0.23% to 0.98% under the various scenarios considered. Given current indications, the lifetime probability of undergoing autologous or allogeneic HCT is much higher than reported by others and could rise even higher with expansion of applicability in persons with hematologic malignancies. Whether the probability of undergoing HCT in general corresponds to the probability of using stored cord blood for transplantation depends upon assumptions regarding the development of transplantation practices and the availability and quality of cord blood cells after long term storage.

3.17.2 Preliminary Results

HS05-02: The volume effect for matched unrelated donor bone marrow transplants for three kinds of leukemia (ALL, AML, CML)-Learning by doing versus selective referral. *(Study Chair: F Schneider, Harvard University, Cambridge, MA, Study Statistician: JD Rizzo). Manuscript in preparation.* The purpose of this study is to determine whether a relationship exists between the number of transplants performed at a given hospital/transplant center and the outcomes for the patients, after adjusting for patient severity, and if such a relationship exists, whether it may be due to selective referral (higher quality hospitals are sought by patients and their referring physicians) or due to a causal relationship where higher volume leads to better outcomes. In evaluating this relationship, there is interest in learning whether changes in market structure, such as introduction of new transplant programs in an existing market affect outcomes, or whether consolidation of transplant programs may be justified by a causal relationship between volume and outcomes. This study will fulfill the requirements for a PhD Thesis in Economics for the PI, once analysis and thesis preparation is complete.

HS06-06: Access to HCT: Effect of Race and Gender. *(Study Chairs: T Joshua, JD Rizzo, M Horowitz, Medical College of Wisconsin, Milwaukee, WI; Study Statisitician: MJ Zhang.) Manuscript in preparation. To be presented at Tandem BMT Meetings in Keystone, CO on Monday, February 12, 2007.* Although HCT has the potential to increase survival for patients with many diseases, particularly hematologic cancers, it is a complex and costly procedure with substantial risk of morbidity and mortality. Increasing numbers of uninsured and underinsured persons and health care marketplace competition raise concerns about patients' access to HCT in the United States. Many studies demonstrate that African-Americans are more likely to be diagnosed at advanced stages of cancer and are less likely to receive optimal care for cancer than Caucasians and that women are less likely to receive some aggressive interventions than men. In this study, we addressed the question of whether African-Americans and women are would be less likely to receive HCT for hematologic malignancy.We estimated the annual incidence of leukemia, lymphoma and multiple myeloma for African-Americans, Caucasians, men and women under the age of 70 years in the U.S. using the SEER Cancer Registry data for 1997 to 2002 and U.S. Census reports for the year 2000. We estimated the annual incidence of autologous, HLA-identical sibling and unrelated HCT performed in these groups in the U.S. using CIBMTR registration data for 1997 to 2002. Logistic regression was used to calculate the age-adjusted odds ratio of receiving HCT in groups defined by race, gender and disease. The overall likelihood (or odds) of undergoing HCT for the diseases considered was higher for Caucasians than for African-Americans [OR=1.40, (1.34-1.46), P<0. 0001]. This difference in likelihood persisted for each type of HCT: autologous [OR=1.24(1.19-1.30), p<0.0001], HLA identical sibling [OR=1.59, (1.46-1.74), p <0.0001], and unrelated donor [OR=2.02(1.75-2.33), p <0.0001]. Men were somewhat more likely to

receive HCT than women [OR=1.07(1.05-1.1) p<0.0001]; however, this difference pertained only to autologous transplantation [OR=1.1(1.06-1.13), p<0.0001]. The likelihoods of HLA identical sibling [OR=1.05(0.99-1.10), p =0.063] and unrelated donor HCT [OR=0.94(0.88-1.01), p =0.11] did not differ significantly by gender. We conclude utilization of HCT for leukemia, lymphoma and multiple myeloma varies by race, with Caucasians more likely to receive HCT than African-Americans. Lower HCT rates for African-American were seen for both autologous and allogeneic HCT, indicating that donor availability cannot fully explain the differences. Women with lymphoma and multiple myeloma are also less likely than men to receive autologous HCT for reasons unexplained by age or disease status.

3.17.3 Planned Studies

HS05-01: Ethnicity and unrelated donor transplant outcomes. *(Study chairs: S Davies, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH; KS Baker, University of Minnesota, Minneapolis, MN, K Ballen, Massachusetts General Hospital, Boston, MA, C Bigelow and C Hardy, University of Mississippi Medical Center, Jackson, MS; H Frangoul, Vanderbilt University, Nashville, TN; Study Statistician: A Hassebroek).*

HS05-07: Feasibility of collecting social, economic, health insurance, cultural, spiritual well-being and social support data among different ethnic groups receiving allogeneic HCT. *(Study Chair: F Loberiza, University of Nebraska Medical Center, Omaha, NE; Study Statistician: K Cao).*

HS06-01: Outcomes of autologous stem cell transplants for multiple myeloma between the African-American and Caucasian-American populations. *(Study Chairs: P Mehta, Central Arkansas Veterans Healthcare System, Little Rock, AR; P Hari, Medical College of Wisconsin, Milwaukee, WI; Study Statistician: A Hassebroek).*

HS06-02: Comparison of cord blood utilization and transplant outcomes among different racial/ethnic groups undergoing HCT. *(Study Chair: K Ballen, Massachusetts General Hospital, Boston, MA; Study Statistician: A Hassebroek).*

HS06-03: Survival trends among adolescent and young adult recipients of sibling allogeneic HCT for the treatment of leukemia or lymphoma. *(Study Chair: B Hayes-Lattin, Oregon Health and Science University, Portland, OR; Study Statistician: A Hassebroek).*

HS06-04: Presenting survival data to patients considering HCT. *(Study Chair: C Cutler, Dana Farber Cancer Institute, Boston, MA; Study Statistician: A Hassebroek)*.

HS06-05: Self-report form. *(Study Chair: Committee, Study Statistician: A Hassebroek).* Form development in progress. Collection of racial and ethnic background, education, occupation, insurance and employment status on CIBMTR forms is critical to the ability to conduct meaningful studies in health policy. These data are currently collected on the CIBMTR research forms. However, some questions are difficult for transplant centers to collect and report, others may be more accurately reported by the patients themselves. The committee has been exploring whether data collection can be improved at transplant centers by developing a data collection instrument that can be completed by the patient for those centers wishing to introduce this process. The questions will be in patient-friendly language, and the data items collected will be directly convertible to the CIBMTR research forms. Surveys completed at Data Management meetings and by a sample of transplant center directors demonstrate relatively high interest in this process. Once completion of conversion to new harmonized research forms is complete, development of patient self-report sections will be finalized with plans to distribute during 2007.

3.18 Statistical Center Methodologic Studies

3.18.1 Multistate Models

Statistical Center PhD biostatisticians focused on investigating new approaches and techniques for analyzing HCT data using multistate regression models resulting in several papers:
Shu Y and Klein JP **Additive hazards Markov regression models illustrated with bone marrow transplant data.** *Biometrika 92:283-302, 2005.* This work develops alternatives to Cox proportional hazards modeling for multistate models. It shows how additive hazards regression models can be used to estimate transition rates and then how these regression models can be synthesized to obtain estimates of the probability a patient will be in a given state at any time after transplant.

Bhattacharyya M. and Klein JP. **A random effect model for multistate survival analysis with application to bone marrow transplantation.** *Math Biosci, 194:37-48, 2005*. In this paper, a random effect is added to the usual Cox Markov model for multistate data. The developed method was applied to an HCT data analysis.

Shu Y, Klein JP and Zhang MJ. **Asymptotic theory for the Cox Semi-Markov Illness-Death Model.** *Lifetime Data Anal DOI.1007/s10985-006-9018-9*, 2006. This paper describes asymptotic variance estimations for the transition hazards under a semi-Markov multi-state model.

Andersen PK and Klein JP. **Regression analysis for multistate models based on a pseudo-value approach, with applications to bone marrow transplantation studies.** *Scan JStat, In Press.* In this paper, direct regression models for the current leukemia free survival based on pseudo-value approach were studied and applied to HCT data sets.

Zhang MJ and Scheike TH. **Directly modeling the regression effects in multistate models.** *Scan J of Stat, In Press*. In this paper, direct regression modelling for the transition probability in a multistate model based on inverse censoring weighting technique was studied, and the proposed approach applied to an HCT data set.

3.18.2 Competing Risks

Statistical Center biostatisticians have been investigating methods for making inference for competing risks data. Competing risks arise in a variety of problems in HCT studies including analyses of relapse, GVHD and treatment-related mortality. Summary curves for competing risks are typically made by using the cumulative incidence curve and comparison of treatments is typically made by comparing hazard rates.

Bajorunaite R and Klein JP. **Two sample test of the equality of two cumulative incidence functions,** *J Planning and Inference, In Press.* In this paper, the focus was on testing for the equality of two or more cumulative incidence functions using several new tests.

Klein JP. **Modeling competing risks in cancer studies.** *Stat in Med* 25:1015-1034, 2006. In this paper, it is argued that the Aalen's additive hazards model is more appropriate and internally consistent than the usual Cox Regression model.

Scheike TH and Zhang MJ. **Predicting cumulative incidence probability: Marginal and cause-specific modeling.** *Submitted.* In this paper, we suggested a new simple approach based on inverse censoring probability technique for estimating and assessing the covariate effect for the cumulative incidence function in the competing risk model. Cox type multiplicative model, Aalen's additive model,

mixed alternative model (See Scheike and Zhang, *Biometrics 59, 1033-1045, 2003*) and nonparametric model were studied.

Sun LQ, Liu JX, Sun, JG and Zhang MJ. **Modeling the subdistribution of a competing risk.** *Statistica Sinica 16:1367-1385, 2006.* In this paper, the subdistribution hazard is designed through a general model. Robust variance estimates are presented and the model-fitting problem investigated.

Zhang, MJ and Fine, J. **Summarizing time-dependent differences in cumulative incidence functions.** *Submitted.* This paper proposed nonparametric inferences for general summary measure, which may be time-varying, and for time-averaged versions of the measures.

3.18.4 Techniques for Censored and Truncated Data

Boudreau C. and, Lawless JF. **Survival analysis based on the proportional hazards model and survey data,** *Can 34:203-216, 2006.* Methods were proposed based on the stratified Cox proportional hazards model that account for the complex survey design often used to collect such data. Our methods are based on the theory of estimating equations in conjunction with empirical process theory.

Klein JP, Logan B and Andersen PK. **Analyzing survival curves at a fixed point in time.** *Submitted.* Here the focus was on testing for the equality of survival curves at a fixed point in time.

3.19 Other Statistical Center Scientific Activities

3.19.1 Clinical Trial Support

U24-CA-76518 does not directly fund clinical trials. However, the Statistical Center makes its resources available to support clinical trials in several ways:

- *Trial Planning*: Investigators planning clinical trials in HCT use the CIBMTR database to assess patient populations potentially available for trials under specific eligibility criteria. With the aid of CIBMTR staff, they can estimate the effect of changing eligibility criteria on patient accrual. Additionally, the database provides a more precise and less biased estimate of the baseline outcomes of interest than literature reviews, “expert opinions” or experience in limited numbers of centers. The database can identify the most common supportive care and other practices in potentially eligible patients so that clinical protocols can be written to be acceptable to most transplant centers. CIBMTR routinely makes these types of information available to Protocol Teams of the BMT CTN. It also has made them available to other investigators including those at Baylor College of Medicine, the International Working Group on Non-myeloablative Stem Cell Transplant, the University of Florida, the Fred Hutchinson Cancer Research Center, several pharmaceutical companies and others.
- *Data collection instruments*: The CIBMTR has an open policy for sharing data collection forms and database structures. The latter reflect the knowledge and expertise not only of Statistical Center personnel but also many transplant experts on our Working Committees who evaluate and revise the data collection forms. They are a resource for investigators doing any HCT research that involves collection of clinical data. The forms are freely available on our website. They have been used as the basis for data collection instruments in several clinical trials including those sponsored by the BMT CTN.
- *Statistical Consultation:* Statistical Center personnel have provided statistical review of several HCT clinical trial protocols and are increasingly seen as a resource of expertise in this area. CIBMTR statisticians also serve as statisticians for the BMT CTN.
- *Trial interpretation:* The CIBMTR database is a valuable tool for evaluating results of clinical trials,

especially single arm studies. The Statistical Center has made the database available to provide matched controls for patients treated in single and multi-institution studies of transplant strategies, providing some basis for evaluating treatment effects after controlling for patient characteristics.

The CIBMTR has now created a formal clinical trial support program, Resource for Clinical Investigations in BMT, RCI BMT, to make its resources more available to individuals and groups outside the BMT CTN seeking to plan, implement and/or interpret clinical trials. In some instances, the CIBMTR has partnered with other groups to seek funding for these trials but U24-CA76518 does not directly fund clinical trials.

3.19.2 Statistical Education

Dr. J.P. Klein serves as Statistical Director of the CIBMTR and has authored, or contributed to, chapters in critical texts on blood and marrow transplantation as well as numerous peer-reviewed publications. He and Mei-Jie Zhang, PhD have collaborated often on professional writings. They, along with Brent Logan, PhD, Tao Wong, PhD and Sergey Tarima, PhD participate in ongoing CIBMTR research studies, contributing to statistical integrity, and advising Working Committee members. Drs. Klein and Zhang have been involved in providing surveys of statistical methods for survival analysis which can be applied to cancer data in general and transplant data more specifically. In 2006, Drs. Klein and Zhang wrote overview of modern techniques in survival analysis for the Handbook of Statistics (Klein, JP and Zhang, MJ. **Survival Analysis**, *Handbook of Statistics, In Press*.)

All CIBMTR PhD statisticians are members of the Division of Biostatistics (Department of Population Health/Medical College of Wiscosni) and function as consultants for CIBMTR research activity including the BMT CTN. Statisitical personnel are involved and in planning and presenting sessions on statistical design and analysis at the CIBMTR annual meetings and at biannual training sessions for data management personnel in participating CIBMTR centers. CIBMTR statisticians also regularly write articles on statistical HCT issues for a clinical audience in the following published this past year: Logan BR, Zhang MJ and Klein JP. **Regression Models for Hazard Rates Versus Cumulative Incidence Probabilities in Bone Marrow Transplant Data.** *Biol. of Blood and Marrow Transplantation,* 12:107-112, 2006.

4.0 OTHER ACTIVITIES

4.1 Presentations

In 2006, there were 177 presentations at national and international meetings of data provided by the CIBMTR. Data from the CIBMTR were also used innumerable times for local and regional meetings and for teaching purposes.

4.2 Information Dissemination

It is the policy of the CIBMTR to provide maximum access to data collected. In 2006, the CIBMTR, through its Information Resource Program, provided information in response to more than 1100 requests for information. Table 4.2.1 summarizes these requests. The most frequent users of the CIBMTR Information Resource Program are physicians or patients seeking information regarding outcome of transplants in specific situations for assistance in clinical decision-making. The CIBMTR is generally able to provide such information, not readily available from the medical literature, within 24-48 hours. Individuals and organizations also increasingly use registry data in planning and interpreting results of clinical trials. Additionally, the Statistical Center provides educational materials (slides, graphics) for many presentations and distributes a set of slides summarizing current use and outcome of blood and marrow transplants to all participating teams. It also maintains a website (www.cibmtr.org) where answers to the most frequently asked questions can be found. During 2006, there were 197,422 visits to the cibmtr.org website. This site is housed at the Minneapolis website and was developed in collaboration with the NMDP web team. Visits to the website were from physicians, patients, and other individuals interested in blood and marrow transplantation.

Table 4.2.1. Requests for information received by the CIBMTR, January 1 to December 31, 2006.

Type of Organization	Total
Physician	614
Pharmaceutical Company	361
Patient or Relative	36
Market Research Firm	22
Federal Government Agency	14
State Government	0
Insurance Company	33
Medical Society	19
Consulting Firm	12
Law Firm	0
Donor Registry/Blood Bank	25
Student	9
News Media	3
TOTAL	**1148**

4.3 Meetings/Newsletters

CIBMTR meetings date back to January 1996 when the IBMTR first held the first stand-alone annual meeting of its membership. The meetings expanded in 1999 through an alliance with the American Society of Blood and Marrow Transplantation to hold annual meetings of the two organizations jointly

as the BMT Tandem Meetings. The joint efforts have proved successful, with more than 2000 participants attending the BMT Tandem Meetings in 2006. In addition to a full scientific program addressing timely issues in HCT, the programs include summaries of CIBMTR activities, reviews of completed studies and discussion of planned studies as well as educational workshops for data management personnel, BMT pharmacists, nurses and BMT center administrators. Continuing Medical Education and Continuing Education credits are issued through the Medical College of Wisconsin for physicians and allied health professionals from the United States who attend these meetings. Dr. Horowitz serves as the Continuing Medical Education director.

Meetings of the CIBMTR Working, Advisory and Executive Committees, the Consumer Advocacy Committee and the International Studies Committee are held during the BMT Tandem Meetings, as well as by teleconference or in conjunction with meetings of national hematology (American Society of Hematology) and oncology (American Society of Clinical Oncology) societies. Working Committee chairs, statisticians and scientific directors meet every 4-6 weeks by teleconference.

To further enhance communication between the Statistical Center and CIBMTR participants, the CIBMTR Statistical Center publishes a biannual newsletter summarizing activities. Two newsletters including the Summary Slides on the state of the art in blood and marrow transplantation were published in 2006.

5.0 DATA MANAGEMENT

Data collection and management activities of the CIBMTR are restricted to collection and management of data from IBMTR (not NMDP) centers. Data collection, entry, and auditing for NMDP centers are not under the purview of NMDP-Research and have not involved CIBMTR personnel. Data from both campuses however are merged in a research dataset, evaluated for duplication and made available for use on CIBMTR studies on a monthly basis.

5.1 Data Collection

CIBMTR data collection forms are continually reviewed to assess needs for revision and are updated accordingly. TED and TED follow-up (TEDFU) forms can be submitted via paper, StemSoft software, or TED on the Web, an Internet application. CIBMTR and EBMT representatives met several times in 2006 to revise the TED forms. In 2007, CIBMTR and NMDP will introduce a single set of co-sponsored research Report Forms, a single, harmonized series of forms and one set of instructions for their completion, to ease the data management burden to transplant centers.

Work continues on AGNIS (A Growable Network Information System) project, a system for automated data exchange for transplant outcomes data funded by N01-HC-45215. An AGNIS Steering Committee which includes members of CIBMTR, NMDP, EBMT and others has defined hundreds of treatment-related data elements for curation in the NCI's cancer Data Standards Repository (caDSR). Members of the group are working with the EMMES Corporation and representatives from the Children's Oncology Group (COG) and the American Society of Blood and Marrow Transplantation (ASBMT) to further develop a dictionary of *common data elements* for HCT clinical research. The first transmission of data via AGNIS between the Milwaukee campus of CIBMTR and the Minneapolis offices of NMDP is targeted for early 2007. For additional information on AGNIS please contact Dennis Confer at the National Marrow Donor Program (dconfer@nmdp.org) or Doug Rizzo at CIBMTR (rizzo@mcw.edu).

5.2 Data Manager Education

Continuing the program of education for data managers in participating centers, the CIBMTR conducted a three-day training session in February 2006, in conjunction with the Annual BMT Tandem Meetings in Honolulu, HI. 301 data managers attended. Participants indicated a high level of satisfaction with topics covered and training provided. Another training session was conducted by CIBMTR personnel in November 2006 in Minneapolis in conjunction with the NMDP annual Council meeting, with 128 in attendance. We plan to continue biannual in-person training sessions in 2007 but will also add availability of self-learning packets and Web casts for use on-site at participating centers.

5.3 Audits

On-site audits for participating CIBMTR centers have been used to confirm data accuracy and consecutive reporting. Kathleen Kovatovic has been the Milwaukee based CIBMTR Audit Director since 1999. Ms. Kovatovic is a registered pharmacist with experience in blood and marrow transplantation, oncology and clinical trials. In addition to performing most of the on-site audits, her responsibilities include:

- working with the Statistical Center to identify teams to be audited,
- scheduling audits,
- providing data to the auditor (if done by someone else) and audited team regarding cases to be reviewed,

- reviewing and summarizing audit worksheets completed by the auditor,
- supplying a written audit report to the team,
- preparing a summary of audit results for the ExecutiveCommittee.

Fourteen allogeneic and 20 autologous HCT programs were audited in 2006; an additional seven programs will be audited by February 28, 2007, the end of the current U24 funding period. To date, overall accuracy is slightly improved to 98.7% with <1% major errors. There is no evidence of biased or selective reporting. All audit reports are reviewed by the CIBMTR Executive Committee during the annual BMT Tandem meetings. In 2007, the NMDP and CIBMTR will be unifying its audit system, with the aim of auditing all research centers once every three years.

5.4 Computer Capabilities

Computer resources for the CIBMTR Statistical Center (Milwaukee Campus) are shared with the 7 other divisions of the Medical College of Wisconsin. The resources consist of a network of 2 SUN Ultra-4 UNIX servers, Sun-Fire V 250 Server, 23 SUN/Unix workstations, an Intel based PC network server, a backup PC server and Dell PC workstations for each staff member. Both networks reside on the Medical College of Wisconsin network infrastructure The Intel PC server has 2G of RAM, dual processors with RAID and tape backup capabilities. MS Outlook 2003 Exchange and MS Server 2003 are the applications on this server that provide a departmental mail server and capability to synchronize documents and other files on and off line.

The intra-departmental networks are separated from other college departments on the Unix side by a dedicated sentry SUN workstation and on the PC side by the departmental PC server authenticating users for departmental staff only.

All research patient data resides on a SUN Ultra 4 workstation configured as a database server. Data is housed in ORACLE relational tables with access and security limited by the ORACLE DBMS. Entry, administrative and statistical staff access the appropriate level of ORACLE data depending on their job description. The ORACLE data is accessible from the staff PC desktops through custom screens built using Visual Basic 6.0. Administrative data are stored on the PC file server and are secured by Windows network passwords as needed for confidentiality.

Specific projects in 2006 include the following:

- There has been continued upgrade to the *TED on the Web* interactive application for secure, uninterrupted access to entry of TED and TED-FU forms.

- Harmonized CIBMTR Research Forms to replace and update the research forms of the NMDP and the CIBMTR were finalized in October 2006 and the collection instruments for the Stem Cell Transplant Outcomes Database (SCTOD) are now in the final stages of approval (see Section 1.3). The data elements of the Harmonized Research Form and the SCTOD minimum transplant data collection form are being curated to the caDSR metadata repository

- Testing is underway using the Univeral Translater component of AGNIS to facilitate mapping between the AGNIS data elements in the caDSR repository and the local database structure of AGNIS users.

- An environment has been developed for the secure exchange of SAS data sets of essential demographic and outcome data between the Minneapolis and Milwaukee campuses. Work continues on the identification of patients who have data residing at both campuses and actually merging the data from the Minneapolis campus and the Milwaukee campus for a common data set for statistical analysis.

6.0 HUMAN SUBJECTS/ HIPAA COMPLIANCE

All work funded by U25-CA76518 uses existing data derived from records of patients treated in participating CIBMTR institutions. In no instance does the CIBMTR direct or suggest how patients in participating institutions are treated. Studies performed using this database have been continuously reviewed by the Institutional Review Committee (IRC) of the Medical College of Wisconsin since 1987. **The IRC of the Medical College of Wisconsin has reviewed the CIBMTR Research program and approved its activities for the current year (HRCC# 56-87).** A waiver of informed consent for the research activities covered by this grant was granted in accordance with 45 CFR part 46.116(d) based upon the following criteria:

- the research involved no more than minimal risk to the subjects,
- the waiver will not adversely affect the rights and welfare of the subjects,
- the research could not practicably be carried out without the waiver,
- and, whenever appropriate, the subjects will be provided with additional pertinent information after participation.

CIBMTR institutions are required to provide a unique patient number for each patient to facilitate communication regarding submitted cases, however the link between the unique number and other identifying patient information is kept only by the HCT center. All participating centers must sign a data use agreement (DUA), generated with approval of the Medical College of Wisconsin IRC and the Medical College of Wisconsin privacy officer, in compliance with HIPAA regulations. In accordance with HIPAA regulations, no patient names or other protected health information are maintained in the database aside from those items considered acceptable in a "limited dataset" as outlined in 45 CFR 164.514(e)(2) (see below). Data are never released in a way that individual patients or centers can be identified.

All Statistical Center personnel, including administrative and data entry staff, are trained in ethical conduct of clinical research and have completed the NIH tutorial on clinical research ethics available on the web (http://ohsr.od.nih.gov). Starting in 2006, all CIBMTR personnel are required to also complete the more complex training tool, Collaborative Insitutional Review Board (IRB) Training Initiative Program (CITI). All certificates are on file in the CIBMTR administrative offices or in the Department of Medicine, Division of Neoplastic Diseases office.

6.1 Health Insurance Portability and Accountability Act (HIPAA)

The NMDP (including NMDP-Research, the Minneapolis campus of the CIBMTR) is exempt from HIPAA requirements. NMDP has been designated a "public health authority" (PHA) under HIPAA and, as a result, network centers, regardless of their status as a covered entity, are allowed to disclose protected health information to the NMDP without an individual's written consent or authorization so the NMDP can carry out its statutory requirements. Because the NMDP is designated as a public health authority under HIPAA, and because it obtains IRB-approved consent from all recipients and donors who participate in NMDP research activities (including CIBMTR activities), centers can provide patient and donor information for NMDP-faciliated transplants to the NMDP/CIBMTR without any additional business associate or data disclosure agreements.

Extensive measures were taken on the CIBMTR Milwaukee campus in previous years to ensure compliance with HPIAA, which went into effect April 14, 2003. These measures are documented below. However, due to certain requirements of the SCTOD Contract (see Section 1.3), the CIBMTR will also apply for PHA status which will mandate a change in current consent practices. Initiatives towards resolution of these issues are in progress.

6.1.1 HIPAA Security Measures and Beyond

The terms of the CW Bill Young Program SCTOD contract commit the CIBMTR and the Milwaukee Data center to a new level of data security certification. Data system components of the SCTOD must comply with Department of Health and Human Services Information Security Program Policy and HRSA Office of Information Technology (OIT) certification and accreditation to operate. The data collection for the SCTOD will be operationalized by using the NMDP FormsNet 2.0 web-based application to a server in the NMDP network at the NMDP offices in Minneapolis. NMDP Information Systems have been subject to HRSA OIT oversight since 1995 and the annual Certification and Accreditation process was completed and achieved in October 2006. Since SCTOD data from FormsNet 2.0 will be received and integrated into the CIBMTR computer system in Milwaukee for analysis and dissemination, the CIBMTR has begun the process leading to certification and authorization of CIBMTR Milwaukee computer systems. Much of the effort of defining Security Policies and Procedures at the Medical College of Wisconsin institutional level as well as at the CIBMTR departmental level have provided an excellent starting point for this much more rigorous requirement.

The process includes evaluation and compliance with system security controls in 17 control families defined by the National Institute of Standards and Technology (NIST). These control areas fall into 3 major categories; 1) Managerial, 2) Operational and 3) Technical. Management controls include development and documentation of Risk Assessment Policies and Procedures and Systems Security Planning and Procedures. Operational controls include documentation of Security Awareness policies, Contingency Planning procedures, Personnel Security policies and system rules of behavior, and Physical and Environmental Protection procedures. The controls included in the Technical group include areas such as System Access Control procedures, Identification and Authentication procedures, Communications protection and Audit Accountability.

Policies and procedures are being defined and documented to address the 170 controls defined in NIST Special Publication 800-53. Evaluation and approval of this formal Security Self Assessment by HRSA OIT and other OIT input will lead to the completion and approval of a Systems Security Plan for CIBMTR-Milwaukee. Interim Authority to Operate (IATO) from HRSA OIT is expected in July 2007 based on approval of the documented plans. The security Certification and Accreditation schedule following IATO will involve site visits from the OIT team to test security controls and contingency plans. The goal is achievement of full Certification and Accreditation and authority to operate the SCTOD system components at CIBMTR-Milwaukee by July 2008.

As part of the SCTOD security program, CIBMTR-Milwaukee will install a new SUN Fire V240 dual processor UltraSparc IIIi to function as a CIBMTR dedicated fileserver early in 2007. This system will be configured according to the Health and Human Services Security Configuration Standards and will provide the file-sharing and analysis platform previously shared with several other Medical College of Wisconsin research departments. CIBMTR is also currently recruiting for a Systems Security Specialist/Systems Administrator to oversee security responsibilities on our UNIX and Windows networks.

6.1.2 HIPAA Confidentiality Measures

HIPAA regulations also specify requirements to maintain confidentiality of Protected Health Information. The CIBMTR and its participating centers ("covered entities") have chosen to address the HIPAA privacy regulations by maintaining and exchanging a "limited dataset" in the setting of a data use agreement as specified in 45 CFR 164.514(e). With this arrangement, written authorization from each patient for release of data contained on current CIBMTR data inserts is not required. The primary reason to pursue such an approach was to allow use of exact onset times for post-transplant complications that are essential to the evaluation of transplant outcome. Limited datasets can contain town, city, state, zip code; birth, admission, discharge, complication, service and death dates; as well as age. Other direct patient identifying information considered protected health information, other than these items and a unique identification number, as mentioned above (linked only by the transplant center), have been removed from our data forms (Registration and Research Inserts) and databases. Patient names, social security numbers, hospital medical record numbers and other protected health information have been removed from our database, and teams may not use such numbers as their unique patient identification number.

Data use agreements were approved by the legal counsel of the Medical College of Wisconsin and by the institutional privacy officer early in 2003 and again in November 2004. These agreements have been mailed to all participating CIBMTR teams in the United States as well as international participants. Extensive efforts have been undertaken to achieve high compliance. As of the time of this report, data use agreements have been executed between CIBMTR and 92.7% of participating centers in the United States. Data use agreements have been executed with 81.9% of international participating centers. The lower rate in the latter group is expected given the complex nature of international privacy regulations. **Data submitted after April 14, 2003 from centers where a data use agreement has not yet been executed has been subjected to quarantine procedures that preclude use of this data.** Such data are not entered in the database, and are kept in locked, private filing space. Teams are notified at time of data submission that a data use agreement has yet to be executed and to refrain from submitting additional data until an agreement is in place. Attempts to achieve full compliance with data use agreements are ongoing.

6.2 Gender and Minority Inclusion

CIBMTR rules require that participating centers report all consecutive transplant recipients. The population available for study, therefore, includes women and minorities in the same proportion as they are found in the general transplant population. None of the proposed studies exclude patients on the basis of race or sex, except those that are specifically exploring issues related to race or ethnic background.

Table 6.2 Gender and Racial distribution of transplant recipients in CIBMTR databases.

		Native American	Asian/Pacific Islander	Black	Hispanic	White	Other Unknown	Total
Registration All Years	Male	187	6324	5581	4309	84607	24979	125987 (52.9%)
	Female	158	4589	5648	3382	72970	24037	110784 (46.6%)
	Unknown	0	23	23	22	191	918	1177 (0.5%)
	Total	345 (0.1%)	10936 (4.6%)	11252 (4.7%)	7713 (3.3%)	157768 (66.3%)	49934 (21.0%)	237948 (100%)
Registration 2002-2006	Male	52	1833	2391	1085	29617	4835	39813 (58.6%)
	Female	53	1336	2139	770	20292	3287	27877 (41.0%)
	Unknown	0	16	9	14	78	179	296 (0.4%)
	Total	105 (0.1%)	3185 (4.7%)	4539 (6.7%)	1869 (2.8%)	49987 (73.5%)	8301 (12.2%)	67986 (100%)
Research All Years	Male	103	3126	2155	2483	39037	2149	49053 (53.7%)
	Female	83	2263	2175	1771	33994	1841	42127 (46.2%)
	Unknown	0	2	5	5	41	17	70 (0.1%)
	Total	186 (0.2%)	5391 (5.9%)	4335 (4.8%)	4259 (4.6%)	73072 (80.1%)	4007 (4.4%)	91250 (100%)
Research 2002-2006	Male	30	667	504	899	7182	555	9837 (58.8%)
	Female	27	485	465	522	4978	376	6853 (41.0%)
	Unknown	0	1	2	3	25	12	43 (0.2%)
	Total	57 (0.3%)	1153 (6.9%)	971 (5.8%)	1424 (8.5%)	12185 (72.8%)	943 (5.7%)	16733 (100%)

7.0 SUMMARY

Activities funded under U24-CA76518 continue to provide a unique resource of information and expertise to the medical and scientific community. The affiliation of IBMTR with NMDP Research to form the CIBMTR is increasing the availability of these resources for blood and marrow transplant research.

CIBMTR studies deal with a wide spectrum of disease- and treatment-related issues using sophisticated statistical techniques and the power of large numbers to answer many important questions.

These include:

1.) determination of transplant outcome in rare diseases, such as Chediak-Higashi syndrome, in common diseases for which transplants are rarely performed, such as low grade NHL and in new indications, such as autoimmune disease;
2.) description of trends in transplant activity such as increasing use and success in older patients, improved outcome in specific diseases and availability and appropriateness of use
3.) identification of factors affecting transplant outcome including 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;
4.) the relative efficacy of HLA-identical sibling, alternative allogeneic donor and autologous transplants in specific diseases;
5.) the relative efficacy of transplant and non-transplant treatment;
6.) long-term effects on quality of life and late complications like second cancers; and,
7.) optimal statistical models to study post-transplant events.

The inclusive nature of our Working Committees and data access policies means that CIBMTR data are available to a broad range of investigators in the field. Additionally, the Statistical Center provides access to collected data in a meaningful way for physicians and patients dealing with difficult clinical decisions.

The funding provided through U24-CA76518 is leveraged by thousands of hours of voluntary effort from physicians and scientists using these data to address important issues in HCT and cancer treatment. Intergration with other NIH and HRSA funded efforts (eg. AGNIS, BMT CTN, SCTOD) assures that these funds are used efficiently to provide maximum value to the scientific community.

List of Appendices

APPENDIX 1

CIBMTR Participating Centers

Fundaleu Dr Mainetti	Buenos Aires	Argentina	CIBMTR Registration
Fundaleu-Angelica Ocampo	Buenos Aires	Argentina	CIBMTR Research
Hospital Priv De Onc-Buenos Aries	Buenos Aires	Argentina	CIBMTR Research
Hospital De Pediatria	Buenos Aires	Argentina	CIBMTR Registration
Hospital Jose De San Martin	Buenos Aires	Argentina	CIBMTR Registration
Hospital Universitario Austral	Buenos Aires	Argentina	CIBMTR Research
Institutos Medicos Antartidica	Buenos Aires	Argentina	CIBMTR Registration
Hospital Priv Cordoba	Cordoba	Argentina	CIBMTR Research
Sanatorio Allende	Cordoba	Argentina	CIBMTR Research
Hospital De Ninas La Plata	La Plata	Argentina	CIBMTR Research
Cetramor	Santa Fe	Argentina	CIBMTR Registration
Hanson Center Cancer Research	Adelaide	Australia	CIBMTR Research
Royal Child Hospital	Brisbane	Australia	CIBMTR Registration
Royal Brisbane Hospital	Brisbane	Australia	CIBMTR Research
Royal Price Alfred Hospital	Camperdown	Australia	CIBMTR Research
St. Vincent's Hospital	Darlinghurst	Australia	CIBMTR Registration
Alfred Hospital	Melbourne	Australia	CIBMTR Research
Royal Children's Hospital	Parkville	Australia	CIBMTR Research
Royal Melbourne Hospital	Parkville	Australia	CIBMTR Research
Princess Margaret Hospital	Perth	Australia	CIBMTR Research
Royal Perth Hospital	Perth	Australia	CIBMTR Research
Prince of Wales Children’s Hospital	Randwick	Australia	CIBMTR Research
Children’s Hospital at Westmead	Sydney	Australia	CIBMTR Research
Prince Of Wales Hospital	Sydney	Australia	CIBMTR Research
Newcastle Mater Hospital	Newcas	Australia	CIBMTR Research
Westmead Hospital	Westmead	Australia	CIBMTR Research
University of Graz	Graz	Austria	CIBMTR Research
Akh Vienna	Vienna	Austria	CIBMTR Registration
Ludwig Blotzmann Institute	Vienna	Austria	CIBMTR Registration
St. Anna Children’s Hospital	Vienna	Austria	CIBMTR Registration
Az Sint-Jan	Brugge	Belgium	CIBMTR Registration
Children’s University Hospital	Brussels	Belgium	CIBMTR Registration
Cliniques Universitaires St-Luc	Bruxelles	Belgium	CIBMTR Research
University Hospital Antwerp	Edegem	Belgium	CIBMTR Research
U Ziekenhuis Gasthuisberg	Leuven	Belgium	CIBMTR Research
University De Liege	Liege	Belgium	CIBMTR Registration
Hospital De Barretos	Barretos	Brazil	CIBMTR Registration
University Estadual De Campinas	Campinas	Brazil	CIBMTR Research
Hospital De Clinicas Curitiba	Curitiba	Brazil	NMDP/CIBMTR Research
Hospital De Clin De Porto Alegre	Porto Alegre	Brazil	CIBMTR Registration
Hospital De Porto Alegre	Porto Alegre	Brazil	CIBMTR Registration
Centro De Tx –Hemope	Pernambuco	Brazil	CIBMTR Registration
Real Institute De Medula Ossea	Recife	Brazil	CIBMTR Research
University Sao Paulo	Ribeirao Preto	Brazil	CIBMTR Registration
Instituto Nacional de Cancer	Rio de Janeiro	Brazil	CIBMTR Research
Hemorio	Rio de Janeiro	Brazil	CIBMTR Registration

CIBMTR Participating Centers

University Federal Rio De Janeiro	Rio de Janeiro	Brazil	CIBMTR Research
Albert Einstein Hospital	Sao Paulo	Brazil	CIBMTR Registration
Hospital A.C. Camargo	Sao Paulo	Brazil	CIBMTR Research
Hospital de Base Sao Jose	Sao Paulo	Brazil	CIBMTR Research
University Sao Paulo- Incor	Sao Paulo	Brazil	CIBMTR Research
Instituto De Oncologia Pediatrica	Sao Paulo	Brazil	CIBMTR Registration
Alberta Children's Hospital	Calgary-Alberta	Canada	CIBMTR Research
T. Baker Cancer Center	Calgary-Alberta	Canada	CIBMTR Registration
Victoria Gen Hos-Qe Ii Hsc	Halifax	Canada	CIBMTR Registration
Chedoke-Mcmaster	Hamilton-Ontario	Canada	CIBMTR Research
Queen's University	Kingston Ontario	Canada	CIBMTR Registration
London Health Science Center	London-Ontario	Canada	CIBMTR Research
Hospital St Justine	Montreal	Canada	CIBMTR Research
Northeastern Ontario Center	Ontario	Canada	CIBMTR Research
Ottawa General Hospital	Ottawa	Canada	CIBMTR Registration
Hotel-Dieu De Quebec	Quebec	Canada	CIBMTR Registration
Mcgill University Health Center	Quebec	Canada	CIBMTR Registration
Hopital Du St. Sacre	Quebec City	Canada	CIBMTR Registration
St Johns Health Sciences Center	St Johns	Canada	CIBMTR Registration
Toronto General	Toronto	Canada	CIBMTR Research
Princess Margaret Hospital	Toronto Ontario	Canada	CIBMTR Research
Hospital for Sick Children	Toronto-Ontario	Canada	CIBMTR Research
British Columbia Children's Hospital	Vancouver-Bc	Canada	CIBMTR Research
Cancer Care Manitoba	Winnipeg-Manito	Canada	CIBMTR Research
Institute De Transplant de Medula Os	Barranquilla	Columbia	CIBMTR Registration
Fundacion Clinica Valle Del Lili	Cali-Valle	Columbia	CIBMTR Registration
Instituto de Cancerologia	Medellin	Columbia	CIBMTR Registration
University Hospital	Bratislava	Czech.	CIBMTR Registration
Charles University Hospital	Pilsen	Czech.	NMDP/CIBMTR Research
Institute of Hem-Blood Transfusion	Prague	Czech.	CIBMTR Registration
University Hospital Motol	Prague	Czech.	CIBMTR Registration
Rigshosp-Copenhagen	Copenhagen	Denmark	NMDP/CIBMTR Research
NCI Cairo University	Cairo	Egypt	CIBMTR Registration
Mansoura University Hospital	Mansoura	Egypt	CIBMTR Registration
Birmingham Heartlands Hospital	Birmingham	England	CIBMTR Registration
Queen Elizabeth Hospital-Birmingham	Birmingham	England	CIBMTR Research
Bristol Children's Hospital	Bristol	England	CIBMTR Research
Addenbrooke's NHS Trust	Cambridge	England	CIBMTR Research
Great Ormond Street Hospital	London	England	CIBMTR Research
Imperial College School of Medicine	London	England	CIBMTR Research
London Clinic	London	England	CIBMTR Registration
Royal Free Hospital	London	England	NMDP/CIBMTR Registration
Royal London Hospital, Whitechapel	London	England	CIBMTR Research
St George's Hospital	London	England	CIBMTR Research
St. Mary's Hospital	London	England	CIBMTR Research
Royal Victorian Hospital-Newcastle	Newcastle	England	CIBMTR Research
Royal Marsden Hospital	Sutton	England	CIBMTR Registration
Helsinki University Central Hospital	Helsinki	Finland	NMDP/CIBMTR Registration
Turku University	Turku	Finland	CIBMTR Research
Centre Hospitalier Régional Univ.	Angers	France	CIBMTR Registration

CIBMTR Participating Centers

Hopital Jean Minjoz	Besancon	France	CIBMTR Research
Hopital Claude Huriez, Lille	Lille	France	CIBMTR Registration
Hospital Edouard Herriot	Lyon	France	CIBMTR Registration
Institute J. Calmettes	Marseille	France	CIBMTR Research
Hopital Saint Louis	Paris	France	CIBMTR Research
Hospital Jean Bernard	Poitiers	France	CIBMTR Research
Heinrich-Heine University	Dusseldorf	Germany	NMDP/CIBMTR Registration
University Children's Hospital	Frankfurt	Germany	CIBMTR Research
Albert-Ludwig University	Freiburg	Germany	NMDP/CIBMTR Research
Martin-Luther-University Halle-Witt	Halle	Germany	CIBMTR Registration
Universitaetslinikum Hamburg	Hamburg	Germany	NMDP/CIBMTR Research
Medical School Of Hannover	Hannover	Germany	CIBMTR Registration
Ruprecht-Karls-University	Heidelberg	Germany	NMDP/CIBMTR Research
Christian Albrechts University	Kiel	Germany	CIBMTR Research
University Hospital Mainz	Mainz	Germany	NMDP/CIBMTR Registration
Blinik Grosshadern, Munich	Munich	Germany	NMDP/CIBMTR Research
U-Kinderk. Munich	Munich	Germany	CIBMTR Research
Children’s Hospital	Tubingen	Germany	NMDP/CIBMTR Registration
Medical University-Tubingen	Tubingen	Germany	NMDP/CIBMTR Registration
Universitat Ulm	Ulm-Donau	Germany	NMDP/CIBMTR Registration
Deutsche Klinik für Diagnostik	Wiesbaden	Germany	NMDP/CIBMTR Research
Chinese University Hong Kong	Shatin	Hong Kong	CIBMTR Research
National Institute Haematology	Budapest	Hungary	NMDP/CIBMTR Registration
Tata Memorial Hospital	Mumbai	India	CIBMTR Research
All India Institute of Medical Science	New Delhi	India	CIBMTR Registration
Institute Rotary Cancer Hospital	New Delhi	India	CIBMTR Research
Christian Medical College Hospital	Tamil Nadu	India	CIBMTR Research
Dr Shariati Hospital	Tehran	Iran	CIBMTR Research
St James Hospital	Dublin	Ireland	CIBMTR Research
Haddasah University	Jerusalem	Israel	NMDP/CIBMTR Research
Chaim Sheba Medical Center	Tel-Hashomer	Israel	NMDP/CIBMTR Research
Chaim Sheba Medical Center	Tel-Hashomer	Israel	NMDP/CIBMTR Registration
San Orsola University Hospital	Bologna	Italy	CIBMTR Registration
University Bologna-Pediatric	Bologna	Italy	CIBMTR Registration
Universita Degli Studi di Brescia	Brescia	Italy	CIBMTR Research
Ospedale St. Martino	Genoa	Italy	NMDP/CIBMTR Registration
Ospedale Civile-Pesaro	Pesaro	Italy	CIBMTR Research
Ospedale St. Camillo	Rome	Italy	CIBMTR Research
St. Eugenio Hospital	Rome	Italy	CIBMTR Research
Universita Cattolica Sacro Cuore	Rome	Italy	CIBMTR Registration
University Torino	Torino	Italy	CIBMTR Registration
Udine University Hospital	Udine	Italy	CIBMTR Research
Osaka City University	Osaka	Japan	CIBMTR Research
Osaka University Medical School	Osaka	Japan	CIBMTR Research
National Cancer Center Hospital	Tokyo	Japan	CIBMTR Research
Toranomon Hospital	Tokyo	Japan	CIBMTR Registration
Asan Medical Center	Seoul	Korea	CIBMTR Research
Samsung Medical Center	Seoul	Korea	CIBMTR Research
St Mary's-Seoul	Seoul	Korea	NMDP/CIBMTR Research
Ajou University Medical Center	Suwon	Korea	CIBMTR Research

CIBMTR Participating Centers

Fauclty of Medican Kuwait University	Safat K	Kuwait	CIBMTR Research
University Malaya	Kuala Lumpur	Malaysia	CIBMTR Registration
Institute Nacional de Pediatria	Coyoacan	Mexico	CIBMTR Research
Hospital Civil de Guadalajara	Guadalajara	Mexico	CIBMTR Research
Hos.Espec. Centro Medico La IMSS	Mexico D.F.	Mexico	CIBMTR Research
Hospital San Jose-Tec De Monterrey	Monterrey	Mexico	NMDP/CIBMTR Research
University Hospital	Monterrey	Mexico	CIBMTR Registration
Center de Hematology Med Int	Puebla	Mexico	CIBMTR Registration
Acad H Maastricht	Maastricht	Netherlands	CIBMTR Registration
University Hosp S Radboud, Nijmegen	Nijmegen	Netherlands	NMDP/CIBMTR Registration
Auckland City Hospital	Auckland	New Zealand	CIBMTR Research
Starship Children's Hospital	Auckland	New Zealand	CIBMTR Research
Christchurch Hospital	Christchurch	New Zealand	CIBMTR Research
Wellington School of Medicine	Wellington	New Zealand	CIBMTR Research
Bismillah Taqee Insitute of Health Sci	Karachi	Pakistan	CIBMTR Research
Bone Marrow Transplant Center	Rawai Pindi	Pakistan	CIBMTR Registration
Institute Oncologica Nacional	Panama	Panama	CIBMTR Research
Medical University Of Gdansk	Gdansk	Poland	CIBMTR Research
Silesian Medical Academy	Katowice	Poland	NMDP/CIBMTR Research
Medical University of Warsaw	Warsaw	Poland	CIBMTR Research
Inst Portugues de Oncologia – Lisbon	Lisbon	Portugal	CIBMTR Research
Inst Portugues de Oncologia – Porto	Porto	Portugal	CIBMTR Registration
Petrov Medical University	St Petersburg	Russia	CIBMTR Research
King Faisal Hospital & Research Ctr	Riyadh	Saudi Arabia	NMDP/CIBMTR Research
King Faisal Hosp-Pediatrics	Riyadh	Saudi Arabia	NMDP/CIBMTR Research
Royal Infirmary Edinburgh	Edinburgh	Scotland	CIBMTR Registration
Glasgow Royal Infirmary	Glasgow	Scotland	CIBMTR Research
Royal Hospital for Sick Children	Glasgow	Scotland	CIBMTR Research
Children's Med Inst. Nat Univ Hospital	Singapore	Singapore	CIBMTR Research
National University Hospital	Singapore	Singapore	CIBMTR Research
Singapore General Hospital	Singapore	Singapore	CIBMTR Research
University of Cape Town Leuk Center	Cape Town	South Africa	CIBMTR Research
Constantiaberg Medi-Clinic	Capetown	South Africa	NMDP/CIBMTR Research
Medical Oncology Rosebank	Johannesburg	South Africa	CIBMTR Registration
University of Witwatersrand	Johannesburg	South Africa	CIBMTR Research
Mary Potter Oncology Center	Pretoria	South Africa	CIBMTR Registration
Hospital Santa Creui Sant Pau	Barcelona	Spain	CIBMTR Research
Hospital Infantil Vall d'Hebron	Barcelona	Spain	CIBMTR Research
University Barcelona	Barcelona	Spain	CIBMTR Registration
Hospital Gregorio Maranon	Madrid	Spain	CIBMTR Research
Hospital Puerta Hierro	Madrid	Spain	CIBMTR Registration
Hospital Nino Jesus	Madrid	Spain	CIBMTR Research
Hospital Carlos Haya	Malaga	Spain	CIBMTR Research
Son Dureta Hospital	Palma De Mallor	Spain	CIBMTR Research
Clinica University De Navarra	Pamplona	Spain	CIBMTR Registration
Hospital La Fe	Valencia	Spain	CIBMTR Research
Sahlgrenska University Hospital	Goteborg	Sweden	NMDP/CIBMTR Research
Huddinge University Hospital	Huddinge	Sweden	NMDP/CIBMTR Research
Basel Kantonsspital	Basel	Switzerland	CIBMTR Research
University Hospital Bern	Bern	Switzerland	CIBMTR Registration

CIBMTR Participating Centers

Hopitaux University De Geneva	Geneva		Switzerland	CIBMTR Research
University Hospital-Zurich	Zurich		Switzerland	CIBMTR Registration
National Taiwan-Pediatrics	Taipei		Taiwan	CIBMTR Research
Veterans General Hospital	Taipei		Taiwan	CIBMTR Research
Chang Gung Children's Hospital	Taoyuan		Taiwan	CIBMTR Registration
Ankara University	Ankara		Turkey	CIBMTR Registration
Gulhane Military Medical Academy	Ankara		Turkey	CIBMTR Research
Hacettepe Univ Inst of Oncology/Hem	Ankara		Turkey	CIBMTR Registration
Erciyes Medical School	Kayseri		Turkey	CIBMTR Research
Asoc. Espanola Primera de Socorros	Montevideo		Uruguay	CIBMTR Research
British Hospital	Montevideo		Uruguay	CIBMTR Research
Center de Medula Osea	Montevideo		Uruguay	CIBMTR Research
Hospital Maciel	Montevideo		Uruguay	CIBMTR Research
Hospital de Clinicas Caracas	Caracas		Venezuela	CIBMTR Research
Hospital Center Valencia	Valencia		Venezuela	CIBMTR Research
Univ of Alabama Birmingham	Birmingham	AL	USA	NMDP/CIBMTR Research
Comprehensive Cancer Institute	Huntsville	AL	USA	CIBMTR Research
City of Hope Samaritan	Phoenix	AZ	USA	NMDP/CIBMTR Registration
Mayo Clinic	Scottsdale	AZ	USA	CIBMTR Research
Arizona Oncology Assoc	Tucson	AZ	USA	CIBMTR Research
University of Arizona Cancer Center	Tucson	AZ	USA	NMDP/CIBMTR Registration
Alta Bates Medical Center	Berkeley	CA	USA	CIBMTR Registration
City Of Hope	Duarte	CA	USA	NMDP/CIBMTR Registration
Scripps Clinic Research Foundation	La Jolla	CA	USA	NMDP/CIBMTR Research
University of California-San Diego	La Jolla	CA	USA	NMDP/CIBMTR Research
Loma Linda University Medical Center	Loma Linda	CA	USA	CIBMTR Research
Cedars Sinai Medical Center	Los Angeles	CA	USA	NMDP/CIBMTR Registration
Childrsn's Hospital of Los Angeles	Los Angeles	CA	USA	NMDP/CIBMTR Research
UCLA-Medicine	Los Angeles	CA	USA	NMDP/CIBMTR Research
UCLA-Pediatrics	Los Angeles	CA	USA	NMDP/CIBMTR Research
Hoag Cancer Center	Newport Beach	CA	USA	CIBMTR Registration
Children's Hospital Oakland	Oakland	CA	USA	NMDP/CIBMTR Research
St Joseph Hospital Irvine	Orange	CA	USA	CIBMTR Research
UCI Medical Center	Orange	CA	USA	CIBMTR Research
Children's Hospital	Orange Co	CA	USA	NMDP/CIBMTR Research
Sutter Cancer Center	Sacramento	CA	USA	CIBMTR Registration
Univ of Calif.-Davis Cancer Center	Sacramento	CA	USA	NMDP/CIBMTR Registration
Children's Hospital of San Diego	San Diego	CA	USA	NMDP/CIBMTR Registration
Univ. of California-San Francisco	San Francisco	CA	USA	NMDP/CIBMTR Research
University Of California	San Francisco	CA	USA	NMDP/CIBMTR Registration
Stanford University Medical Center	Stanford	CA	USA	NMDP/CIBMTR Research
Children's Hospital University of CO	Denver	CO	USA	NMDP/CIBMTR Research
Rocky Mountain Transplant, Denver	Denver	CO	USA	NMDP/CIBMTR Registration
Yale Cancer Center	New Haven	CT	USA	NMDP/CIBMTR Research
Bennett Cancer Center	Stamford	CT	USA	CIBMTR Research
Children's National Medical Center	Washington	DC	USA	NMDP/CIBMTR Registration
Alfred I Dupont Hospital for Children	Wilmington	DE	USA	NMDP/CIBMTR Research
Medical Center of Delaware	Wilmington	DE	USA	NMDP/CIBMTR Registration
Medicine Hematology/Oncology B	Boynton Beach	FL	USA	CIBMTR Research
Shands Hospital	Gainesville	FL	USA	NMDP/CIBMTR Research

CIBMTR Participating Centers

Mayo Clinic Jacksonville	Jacksonville	FL	USA	CIBMTR Research
Nemours Children's Clinic	Jacksonville	FL	USA	CIBMTR Registration
Miami Children's Hospital	Miami	FL	USA	NMDP/CIBMTR Registration
University of Miami School	Miami	FL	USA	NMDP/CIBMTR Registration
All Children's Hospital	St Petersburg	FL	USA	NMDP/CIBMTR Registration
H Lee Moffitt Cancer Center	Tampa	FL	USA	NMDP/CIBMTR Research
Good Samaritan Medical Center	Beach	FL	USA	CIBMTR Registration
Phoebe Cancer Center	Albany	GA	USA	CIBMTR Registration
Blood & Marrow GA	Atlanta	GA	USA	NMDP/CIBMTR Research
Egleston Children's Hosp	Atlanta	GA	USA	NMDP/CIBMTR Research
Emory University	Atlanta	GA	USA	NMDP/CIBMTR Research
Medical College Of Georgia	Augusta	GA	USA	CIBMTR Research
Dekalb Medical Ctr – Transplant Unit	Decatur	GA	USA	CIBMTR Registration
University of Iowa Hospital & Clinics	Iowa City	IA	USA	NMDP/CIBMTR Research
St Lukes Regional Medical Center	Boise	ID	USA	CIBMTR Research
Children's Memorial Hosp	Chicago	IL	USA	NMDP/CIBMTR Research
Northwestern Memorial Hospital	Chicago	IL	USA	NMDP/CIBMTR Research
Rush University Medical Center	Chicago	IL	USA	NMDP/CIBMTR Registration
Univ. of Chicago-Children's Hospital	Chicago	IL	USA	NMDP/CIBMTR Registration
University of IL at Chicago Med Ctr	Chicago	IL	USA	NMDP/CIBMTR Research
Universtiy of Chicago	Chicago	IL	USA	CIBMTR Research
Loyola University Medical Center	Maywood	IL	USA	NMDP/CIBMTR Research
Lutheran General Hospital	Parkridge	IL	USA	CIBMTR Registration
Methodist Medical Center Peoria	Peoria	IL	USA	CIBMTR Research
Cancer Treatment Cen of Amer - Mid	Zion	IL	USA	CIBMTR Research
Methodist Hospital Indiana	Indianapolis	IN	USA	NMDP/CIBMTR Research
Oncology Hematology Associates	Indianapolis	IN	USA	CIBMTR Research
Riley Hospital for Children	Indianapolis	IN	USA	NMDP/CIBMTR Registration
St. Vincent Hospital Indianapolis	Indianapolis	IN	USA	CIBMTR Research
University of Kansas	Kansas City	KS	USA	NMDP/CIBMTR Research
Via Christi/St. Francis	Wichita	KS	USA	CIBMTR Research
University of Kentucky	Lexington	KY	USA	NMDP/CIBMTR Registration
Univ Med. Ctr Univ. of Louisville Hosp	Louisville	KY	USA	NMDP/CIBMTR Research
LSU Children's Hospital	New Orleans	LA	USA	NMDP/CIBMTR Research
Tulane University Medical Center	New Orleans	LA	USA	NMDP/CIBMTR Research
LSU Medical Center	Shreveport	LA	USA	NMDP/CIBMTR Research
Dana Farber Cancer Institute	Boston	MA	USA	NMDP/CIBMTR Registration
Massachusetts General Hospital	Boston	MA	USA	CIBMTR Registration
Tufts New England Medical Center	Boston	MA	USA	CIBMTR Registration
Lahey Hitchcock Clinic	Burlington	MA	USA	CIBMTR Research
UMASS Memorial Health Care	Worcester	MA	USA	NMDP/CIBMTR Registration
Johns Hopkins Oncology Center	Baltimore	MD	USA	NMDP/CIBMTR Research
Greenbaum Cancer Center, U of MD	Baltimore	MD	USA	NMDP/CIBMTR Research
National Heart Lung & Blood Institute	Bethesda	MD	USA	CIBMTR Registration
National Institute Of Health	Bethesda	MD	USA	CIBMTR Registration
National Cancer Institute	Bethesda	MD	USA	CIBMTR Research
Maine Medical Center	Scarborough	ME	USA	CIBMTR Registration
University of Michigan-Pediatrics	Ann Arbor	MI	USA	NMDP/CIBMTR Registration
Henry Ford Hospital	Detroit	MI	USA	NMDP/CIBMTR Research
Wayne State University	Detroit	MI	USA	NMDP/CIBMTR Registration

CIBMTR Participating Centers

Devos Children's Hospital	Grand Rapids	MI	USA	NMDP/CIBMTR Research
Abbott Northwest Hospital	Minneapolis	MN	USA	CIBMTR Registration
Childrens Hospital & Clinics	Minneapolis	MN	USA	CIBMTR Research
Universtiy MN-Minneapolis	Minneapolis	MN	USA	NMDP/CIBMTR Research
Mayo Clinic Rochester	Rochester	MN	USA	NMDP/CIBMTR Research
Minn. Oncology Hem-St.Paul	St.Paul	MN	USA	CIBMTR Registration
Children's Mercy Hospital	Kansas City	MO	USA	CIBMTR Research
St Lukes Hospital Kansas City	Kansas City	MO	USA	NMDP/CIBMTR Research
Cardinal Glennon Children's Hospital	St Louis	MO	USA	NMDP/CIBMTR Research
St Louis Children's Hospital	St Louis	MO	USA	NMDP/CIBMTR Research
Washington Univ. School Of Medicine	St Louis	MO	USA	NMDP/CIBMTR Research
U of MS Medical Center - Jackson	Jackson	MS	USA	NMDP/CIBMTR Registration
Deaconess Billings Clinic	Billings	MT	USA	CIBMTR Registration
Missoula Onconolgy Inf Disease	Missoula	MT	USA	CIBMTR Registration
U Of NC-Chapel Hill	Chapel Hill	NC	USA	NMDP/CIBMTR Research
Carolinas Medical Center	Charlotte	NC	USA	CIBMTR Research
Duke University – Pediatrics	Durham	NC	USA	NMDP/CIBMTR Research
Duke University – Adults	Durham	NC	USA	NMDP/CIBMTR Registration
Piedmont Hematology Onco Assoc	Winston Salem	NC	USA	CIBMTR Registration
Bowman Gray Wake-Forest	Winston-Salem	NC	USA	NMDP/CIBMTR Research
Univ Of Nebraska Medical Center	Omaha	NE	USA	NMDP/CIBMTR Research
Dartmouth-Hitchcock	Lebanon	NH	USA	CIBMTR Research
Hackensack Medical Center	Hackensack	NJ	USA	NMDP/CIBMTR Research
Cancer Institute of New Jersey	New Brunswick	NJ	USA	NMDP/CIBMTR Research
New York Oncology/Hematology PC	Albany	NY	USA	CIBMTR Registration
Our Lady Of Mercy Medical Center	Bronx	NY	USA	CIBMTR Research
Roswell Park Cancer Institute	Buffalo	NY	USA	NMDP/CIBMTR Research
Schneider Children's Hospital	New Hyde Park	NY	USA	NMDP/CIBMTR Research
Children's Hospital of NY	New York	NY	USA	NMDP/CIBMTR Research
Columbia Presbyterian Hospital	New York	NY	USA	CIBMTR Research
Memorial Sloan-Kettering Cancer Ctr	New York	NY	USA	NMDP/CIBMTR Registration
Mountt Sinai Hospital	New York	NY	USA	NMDP/CIBMTR Research
New York Presbyterian Hospital	New York	NY	USA	NMDP/CIBMTR Research
NYU Med Ctr Hassenfield Children's	New York	NY	USA	CIBMTR Research
St Vincents Hospital Manhatten	New York	NY	USA	CIBMTR Registration
Strong Memorial Hospital	Rochester	NY	USA	NMDP/CIBMTR Research
Suny Stony Brook	Stony Brook	NY	USA	CIBMTR Research
Suny-Health Center	Syracuse	NY	USA	CIBMTR Research
New York Medical College	Valhalla	NY	USA	NMDP/CIBMTR Research
Children's Hospital Medical Center	Akron	OH	USA	CIBMTR Research
Cincinnati Children's Hospital	Cincinnati	OH	USA	NMDP/CIBMTR Research
Jewish Hospital Cincinnati	Cincinnati	OH	USA	NMDP/CIBMTR Research
Cleveland Clinic	Cleveland	OH	USA	NMDP/CIBMTR Research
University Hospital of Cleveland	Cleveland	OH	USA	NMDP/CIBMTR Research
Rainbow Babies-Case Western	Cleveland	OH	USA	NMDP/CIBMTR Research
Children's Hospital	Columbus	OH	USA	NMDP/CIBMTR Research
The Ohio State University	Columbus	OH	USA	NMDP/CIBMTR Research
Miami Valley Hospital	Dayton	OH	USA	CIBMTR Research
St Vincent Mercy Medical Ctr Toledo	Toledo	OH	USA	CIBMTR Research
Cancer Care Assoc Ok City	Oklahoma City	OK	USA	CIBMTR Research

CIBMTR Participating Centers

Univ Oklahoma	Oklahoma City	OK	USA	NMDP/CIBMTR Research
Cancer Care Associates	Tulsa	OK	USA	CIBMTR Research
St Francis Hospital	Tulsa	OK	USA	CIBMTR Registration
Health & Sci University-Pediatrics	Portland	OR	USA	NMDP/CIBMTR Research
Health & Sci University-Adult	Portland	OR	USA	NMDP/CIBMTR Research
Legacy Good Samaritan Hospital	Portland	OR	USA	CIBMTR Research
Providence Portland Medical Center	Portland	OR	USA	CIBMTR Research
Geisinger Medical Center	Danville	PA	USA	CIBMTR Research
Hershey Medical Center	Hershey	PA	USA	NMDP/CIBMTR Research
Hahnemann University Hospitals	Philadelphia	PA	USA	NMDP/CIBMTR Research
Philadelphia Children's Hospital	Philadelphia	PA	USA	NMDP/CIBMTR Registration
Temple University Cancer Center	Philadelphia	PA	USA	NMDP/CIBMTR Registration
Thomas Jefferson University	Philadelphia	PA	USA	NMDP/CIBMTR Research
Univ. Of Pennsylvania Hospital	Philadelphia	PA	USA	NMDP/CIBMTR Research
Children's Hospital	Pittsburgh	PA	USA	NMDP/CIBMTR Research
University of Pittsburgh Medical Ctr	Pittsburgh	PA	USA	NMDP/CIBMTR Research
West Pennsylvania Cancer Institute	Pittsburgh	PA	USA	NMDP/CIBMTR Research
Guthrie Clinic, Ltd	Sayre	PA	USA	CIBMTR Research
R Williams Medical Center	Providence	RI	USA	CIBMTR Registration
Medical University of South Carolina	Charleston	SC	USA	NMDP/CIBMTR Registration
Roper Care Alliance	Charleston	SC	USA	NMDP/CIBMTR Research
Cancer Center of Carolinas	Greenville	SC	USA	CIBMTR Research
Spartanburg Regional Medical Center	Spartanburg	SC	USA	CIBMTR Registration
Avera Mckennan Transplant Institute	Sioux Falls	SD	USA	NMDP/CIBMTR Research
Thompson Cancer Survival Center	Knoxville	TN	USA	CIBMTR Registration
Baptist Centers for Cancer Care	Memphis	TN	USA	CIBMTR Registration
St.Jude Children's Hospital	Memphis	TN	USA	NMDP/CIBMTR Registration
UT - Blood & Marrow Transplant Ctr	Memphis	TN	USA	NMDP/CIBMTR Registration
Vanderbilt University	Nashville	TN	USA	NMDP/CIBMTR Registration
Harrington Cancer Center	Amarillo	TX	USA	CIBMTR Research
Arlington Cancer Center	Arlington	TX	USA	CIBMTR Registration
Spohn Hospital	Corpus Christi	TX	USA	CIBMTR Registration
Baylor Medical Center - Dallas	Dallas	TX	USA	NMDP/CIBMTR Research
Children's Medical Center - Dallas	Dallas	TX	USA	NMDP/CIBMTR Research
Medical City Dallas	Dallas	TX	USA	NMDP/CIBMTR Research
Univ Of Texas SW Medical Ctr Dallas	Dallas	TX	USA	NMDP/CIBMTR Research
El Paso Cancer Treatment Center	El Paso	TX	USA	CIBMTR Registration
Cook Children's Medical Center	Fort Worth	TX	USA	NMDP/CIBMTR Research
MD Anderson Cancer Center	Houston	TX	USA	NMDP/CIBMTR Research
Texas Children's Hospital	Houston	TX	USA	NMDP/CIBMTR Research
The Methodist Hospital	Houston	TX	USA	NMDP/CIBMTR Research
Wilford Hall USAF Medical Center	Lackland	TX	USA	CIBMTR Registration
University Medical Center	Lubbock	TX	USA	NMDP/CIBMTR Research
South Texas Cancer	San Antonio	TX	USA	NMDP/CIBMTR Research
University of Texas-HSCSA	San Antonio	TX	USA	CIBMTR Research
Scott & White Clinic & Hospitals	Temple	TX	USA	CIBMTR Research
Latter Day Saints Hospital	Salt Lake City	UT	USA	CIBMTR Research
Univ of Utah Medical Center	Salt Lake City	UT	USA	NMDP/CIBMTR Research
Fairfax Stem Cell Transplant Program	Falls Church	VA	USA	NMDP/CIBMTR Registration
VA Oncology Associates	Norfolk	VA	USA	CIBMTR Registration

CIBMTR Participating Centers

Medical College of Virginia	Richmond	VA	USA	NMDP/CIBMTR Research
Fletcher Allen Health Center	Burlington	VT	USA	CIBMTR Registration
Fred Hutchinson Cancer Center	Seattle	WA	USA	NMDP/CIBMTR Registration
UW-Madison Hospital & Clinics	Madison	WI	USA	NMDP/CIBMTR Research
Marshfield Clinic	Marshfield	WI	USA	CIBMTR Research
MCW-Milwaukee	Milwaukee	WI	USA	NMDP/CIBMTR Research
St Lukes Medical Center Milwaukee	Milwaukee	WI	USA	CIBMTR Research
Waukesha Memorial Hospital	Waukesha	WI	USA	CIBMTR Research
West VA University Hospital	Morgantown	WV	USA	NMDP/CIBMTR Research

APPENDIX 2

CIBMTR ADVISORY COMMITTEE

Chair: **Sergio Giralt**, MD, MD Anderson Cancer Center, Houston, TX

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Naynesh R. Kamani, MD, Children's National Medical Center, Washington, DC
Claudio Anasetti, MD, Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Vice Chairs:
North America: **Mark Litzow**, MD, Mayo Clinic, Rochester, MN
Europe: **Eliane Gluckman**, MD, Hopital St. Louis, Paris, France
South America: **Ricardo Pasquini**, MD, Hospital de Clinicas, Curitiba, Brazil
Asia/Africa/ Australia: **Jeffrey Szer**, MD, Royal Melbourne Hosp., Parkville, Victoria, Australia

At Large North America: **Steven Devine**, MD, Arthur G. James Cancer Institute, Columbus, OH
Ginna Laport, MD, Stanford University Medical Center, Stanford, CA
Christopher Bredeson, MD, Cancer Care Manitoba, Winnipeg, Canada
David Porter, MD, University of Pennsylvania Hospital, Philadelphia, PA
Jeff Lipton, MD, Schneider Children's Hospital, New Hyde Park, NY
Nancy Bunin, MD, Children's Hospital of Philadelphia, Philadelphia, PA

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Jakob Passweg, MD MS, Geneva University Hospital, Geneva, Switzerland
Andrea Bacigalupo, MD, San Martino Hospital, Genova, Italy
Jane Apperley, MD, Imperial College London, London, England
Stephen Mackinnon, MD, Royal Free Hospital, London, England
Katarina LeBlanc, MD, Huddinge University Hospital, Stockholm, Sweden

Appointed Members:

Patient/Family Representatives: **Art Flatau**, Co-Chair, Consumer Advocacy Committee
Susan K. Stewart, Co-Chair, Consumer Advocacy Committee

Donor Center Representative: **Thomas H. Price**, MD, Medical Director, Puget Sound Blood Center

Collection Center Representative: **Zbigniew (Ziggy) Szczepiorkowski**, MD, Medical Director, Dartmouth-Hitchcock Medical Center

Bioethicist:	**Raquel Schears,** MD MPH, FACEP, Mayo Clinic, Rochester, MN
Information Technology:	**James Nelson,** Chief Applications Architect for Unitedhealth Group, Minnetonka, MN
Business Executive:	**Alan Leahigh,** Executive Vice President, Executive Administration, Inc., Chicago, IL

Ex Officio:

Executive Director:	Jeffrey Chell, MD, NMDP, Minneapolis, MN
Chief Scientific Director:	Mary M. Horowitz, MD, MS, CIBMTR, Milwaukee, WI
Research Advisor:	Daniel Weisdorf, MD, University of Minnesota, Minneapolis, MN
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MCW/NCI Project Officer:	Roy Wu, PhD
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MCW/NIAID Project Officer:	Linda Griffith, MD, PhD
CIBMTR Program Leaders:	
Statistical Methodology:	John P. Klein, PhD
Observational Research:	J. Douglas Rizzo, MD, MS
Clinical Trials Support:	Marcie Tomblyn, MD, MS
Immunobiology:	TBD

***** These positions are a residual component of a Transitional Advisory Committee formed after the affiliation between IBMTR & NMDP Research these indivduals chaired prior committees of the IBMTR and NMDP-Research. These terms as past-chair were designed to provide continuity through the first year of the elected officer terms.

APPENDIX 3

CIBMTR EXECUTIVE COMMITTEE

- **Chair**: Sergio Giralt, MD, MD Anderson Cancer Center, Houston, TX
- **Vice-Chair North America:** Mark Litzow, MD, Mayo Clinic, Rochester, MN
- **Vice-Chair South America:** Ricardo Pasquini, MD, Hospital de Clinicas, Federal University of Parana, Curitiba, Brazil
- **Vice-Chair Europe:** Eliane Gluckman, MD, Hopital St. Louis, Paris, France
- **Vice-Chair Asia/Australia/Africa:** Jeffrey Szer, MD, Royal Melbourne Hospital, Parkville, Victoria, Australia
- **Past Chair/NMDP RAP Committee:** Naynesh R. Kamani, MD, Children's National Medical Center, Washington, DC
- **Past Chair/NMDP Histocompatibility Committee:** Claudio Anasetti, MD, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
- **Past Chair/IBMTR:** Olle Ringdén, MD, PhD, Huddinge University Hospital, Huddinge, Sweden
- **Past Chair/ABMTR:** Richard Champlin MD, MD Anderson Cancer Center, Houston, TX
- **CIBMTR Executive Director*^:** Jeffrey Chell, NMDP, Minneapolis, MN
- **CIBMTR Chief Scientific Director*^:** Mary M. Horowitz, MD, MS, Medical College of Wisconsin, Milwaukee, WI
- **CIBMTR Research Advisor*^:** Daniel Weisdorf, MD, University of Minnesota, Minneapolis, MN
- **CIBMTR Statistical Director*:** John P. Klein, PhD, Medical College of Wisconsin, Milwaukee, WI
- **CIBMTR Program Leader/Clinical Trials*:** Marcie Tomblyn, MD, MD, University of Minnesota, Minneapolis, MN
- **CIBMTR Program Leader/Observational Studies*:** J. Douglas Rizzo, MD, Medical College of Wisconsin, Milwaukee, WI
- **Four appointed members of the Advisory Committee:**

Patient/Family
Representatives (2): Art Flatau, Co-Chair, Consumer Advocacy Committee
Susan K. Stewart, Co-Chair, Consumer Advocacy Committee

Donor Center Representative (1): Thomas H. Price, MD, Medical Director, Puget Sound Blood Center

Collection Center Representative (1): Zbigniew (Ziggy) Szczepiorkowski, MD, Medical Director, Dartmouth-Hitchcock Medical Center

* ***ex officio***
^ ***ex officio with voting privileges***

APPENDIX 4

CIBMTR WORKING COMMITTEES

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Jorge Sierra, MD, de la Santa Creu i Sant Pau, Barcelona, Spain
Martin Tallman, MD, Northwestern Memorial Hospital, Chicago, IL
Scientific Director: Daniel Weisdorf, MD
Statisticians: Waleska Pérez, MPH, Mei-Jie Zhang, PhD

Chronic Leukemia Working Committee
Chairs: Sergio Giralt, MD, MD Anderson Cancer Center, Houston, TX
Jeffrey Szer, MD, Royal Melbourne Hospital, Parkville, Victoria, Australia
Ann Woolfrey, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Scientific Director: Mukta Arora, MD, MS
Statisticians: Manisha Kukreja, MBBS, MPH, Sergey Tarima, PhD

Lymphoma Working Committee
Chairs: Julie Vose, MD, University of Nebraska Medical Center, Omaha, NE
Hillard Lazarus, MD, Case Western Reserve University, Cleveland, OH
Koen van Besien, MD, University of Chicago, Chicago, IL
Scientific Director: Parameswaran Hari, MD
Statisticians: Jeanette Carreras, MPH, Mei-Jie Zhang, PhD

Plasma Cell Disorder Working Committee
Chairs: David Vesole, MD, PhD, St. Vincent's Comprehensive Cancer Center, NY, NY
Donna Reece, MD, Princess Margaret Hospital, Toronto, Ontario, Canada
Gustavo Milone, Angelica Ocampo-Hospital and Research Center - Fundaleu, Buenos Aires, Argentina
Scientific Director: Parameswaran Hari, MD
Statisticians: Waleska S. Pérez, MPH, Mei-Jie Zhang, PhD

Solid Tumors Working Committee
Chairs: Patrick Stiff, MD, Loyola University Medical Center, Maywood, IL
Richard Childs, MD, National Institutes of Hematology, Bethesda, MD
Didier Blaise, MD, Institut J. Paoli I. Calmettes, Marseille, France
Scientific Director: Mukta Arora, MD, MS
Statisticians: Kathleen A. Sobocinski, MS, Sergey Tarima, PhD

Pediatric Cancer Working Committee
Chairs: Bruce Camitta, MD, Midwest Children's Cancer Center, Milwaukee, WI
Stephan Grupp, MD, Children's Hospital of Philadelphia, Philadelphia, PA
Stella Davies, MD, Children's Hospital Medical Center, Cincinnati, OH
Scientific Director: Mary Eapen, MD, MS
Statisticians: Dan Wang, MS, Mei-Jie Zhang, PhD

Non-Malignant Marrow Disorders Working Committee
Chairs: Ricardo Pasquini, MD, Hospital de Clinicas, Federal University of Parana, Curitiba, Brazil
Judith Marsh, MD, St. George's Hospital Medical School, London, UK
Mark Walters, MD, Children's Hospital of Oakland, Oakland, CA
Scientific Director: Mary Eapen, MD, MS
Statisticians: Jeanette Carreras, MPH, Sergey Tarima, PhD

Immune Deficiencies/Inborn Errors Working Committee
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Mitchell Horwitz, MD, Duke University, Chapel Hill, NC
Carmem Maria Sales Bonfim, MD, Hospital de Clinicas, Federal University of Parana, Curitiba, Brazil
Scientific Director: Mary Eapen, MD, MS
Statisticians: Anna Hassebroek, MPH, Sergey Tarima, PhD

Autoimmune Diseases Working Committee
Chairs: Richard Nash, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Harold Atkins, MD, Ottawa General Hospital, Ottawa, Ontario, Canada
Scientific Director: Marcelo Pasquini, MD
Statisticians: Manza Agovi, MPH, Brent Logan, PhD

Immunobiology Working Committee
Chairs: Effie Petersdorf, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Carolyn Hurley, PhD, Georgetown University School of Medicine, Washington, DC
Machteld Oudshoorn, PhD, Leiden University Medical Center, Leiden, The Netherlands
Scientific Directors: Mary Horowitz, MD, MS, Stephen Spellman, MS
Statisticians: Michael Haagenson, MS, Fiona Kan, MS, MA, John P. Klein, PhD, Tao Wang, PhD

Graft Sources and Manipulation Working Committee
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Adrian Gee, PhD, Baylor College of Medicine, Houston, TX
Scientific Director: Mary Eapen, MD, MS
Statisticians: Fiona Kan, MS, MA, Mei-Jie Zhang, PhD

Regimen-Related Toxicity/Supportive Care Working Committee
Chairs: Karen Ballen, MD, Massachusetts General Hospital, Boston, MA
Andrea Bacigalupo, MD, San Martino Hospital, Genova, Italy
Scientific Director: J. Douglas Rizzo, MD, MS
Statisticians: Manza Agovi, MPH, Brent Logan, PhD

Infection and Immune Reconstitution Working Committee
Chairs: Jan Storek, MD, PhD, University of Calgary, Calgary, Alberta, Canada
JoAnne van Burik, MD, FACP University of Minnesota, Minneapolis, MN
Ronald Gress, MD, National Institutes of Health, Bethesda, MD
Scientific Director: Marcie Tomblyn, MD, MS
Statisticians: Manisha Kukreja, MBBS, MPH, Sergey Tarima, PhD

Graft-vs-Host Disease Working Committee
Chairs: A. John Barrett, MD, National Institutes of Health, Bethesda, MD
Olle Ringdén, MD, PhD, Huddinge University Hospital, Huddinge, Sweden
Claudio Anasetti, MD, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL
Steven Pavletic, MD, National Cancer Institute, Bethesda, MD
Scientific Directors: Mukta Arora MD, MS, Stephen Spellman, MS
Statisticians: Dan Wang, MS, Tao Wang, PhD

Late Effects and Quality of Life Working Committee
Chairs: Gérard Socié, MD, PhD, Hôpital Saint-Louis, Paris, France
John Wingard, MD, University of Florida, Shands Hospital, Gainesville, FL
Brian Bolwell, MD, Cleveland Clinic Foundation, Cleveland, OH
Scientific Director: J. Douglas Rizzo, MD, MS
Assistant Scientific Director: Navneet Majhail, MD, MS
Statisticians: Kathleen A. Sobocinski, MS, John P. Klein, PhD

Donor Health and Safety Working Committee
Chairs: Michael Pulsipher, MD, Utah Blood & Marrow Transplant Program, Salt Lake City, UT
Paolo Anderlini, MD, MD Anderson Cancer Center, Houston, TX
Susan Leitman, MD, National Institute of Health, Bethesda, MD
Scientific Director: Dennis Confer, MD
Statisticians: Tanya Pedersen, Brent Logan, PhD

Health Policy Working Committee
Chairs: Stephanie Lee, MD, Dana-Farber Cancer Institute, Boston, MA
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Scientific Director: J. Douglas Rizzo, MD
Assistant Scientific Director: Navneet Majhail, MD, MS
Statisticians: Anna Hassebroek, MPH, John P. Klein, PhD

APPENDIX 5

IMMUNOBIOLOGY STEERING COMMITTEE (NMDP HISTOCOMPATIBILITY COMMITTEE)

Robert A. Bray, PhD, dip. ABHI (Chair)
Emory Univ. Hospital School of Medicine

Carolyn K. Hurley, PhD
Georgetown University Medical Center

Naynesh Kamani, MD
Children's National Medical Center

Craig Kollman, PhD
Jaeb Center for Health Research

Edgar Milford, MD
Brigham and Women's Hospital

Carlheinz Müller, MD, PhD
German National Bone Marrow Donor Registry

Harriet Noreen CHS
University of Minnesota-Fairview

Ann Woolfrey, MD
Fred Hutchinson Cancer Center

Neng Yu, MD, dip ABHI
American Red Cross Blood Services, NE Division

Pablo Rubinstein
The Lindsley F. Kimball Research Institute
The New York Blood Center

Robert J. Hartzman, MD, Capt, MC, USN (Ret.) (Navy Representative)
C.W. Bill Young Marrow Donor Recruitment and Research Program

Robert Baitty (HRSA Representative)
Health Resources & Services Admin., HHS

Robyn Ashton (HRSA Representative)
Health Resources & Services Admin., HHS

Juliet N. Barker, MBBS (Hons), FRACP
Memorial Sloan-Kettering Cancer Center

CIBMTR Staff
Brent Logan, PhD
Center for International Blood & Marrow Transplant Research, Milwaukee Campus

Mary Eapen, MD, MS
Center for International Blood & Marrow Transplant Research, Milwaukee Campus

NMDP Staff
Michelle Setterholm
National Marrow Donor Program

Dennis Confer, MD
National Marrow Donor Program

Pat Coppo
National Marrow Donor Program

APPENDIX 6

CLINICAL TRIALS ADVISORY COMMITTEE

Arthur Flateau: Association of Cancer Online Resources

Brent R. Logan: Center for International Blood & Marrow Transplant Research

Daniel Weisdorf: University of Minnesota

Dennis Confer: National Marrow Donor Program

Ed Stadtmauer: University of Pennsylvania

Hillard Lazarus: Ireland Cancer Center

John Wingard: University of Florida

Marcie Tomblyn: National Marrow Donor Program

Mary Eapen: Center for International Blood & Marrow Transplant Research

Mary Horowitz: Center for International Blood & Marrow Transplant Research

Naynesh Kamani: Children's National Medical Center

Rebecca Drexler: National Marrow Donor Program

Sergio Giralt: MD Anderson Cancer Center

Sue Stewart: BMT Infonet

APPENDIX 7

2007 Consumer Advocacy Committee

Co-Chairs

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Susan Stewart (Co-chair)
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APPENDIX 8

CIBMTR NOMINATING COMMITTEE

Chair: **Ed Stadtmauer,** University of Pennslvania

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Joe Antin, Dana Farber Cancer Center
Brenda Sandmaier, Fred Hutchinson Cancer Researh Center
Jose Borbolla-Escoboza, Instituto Tecnológico y de Estudios Superiores de Monterrey

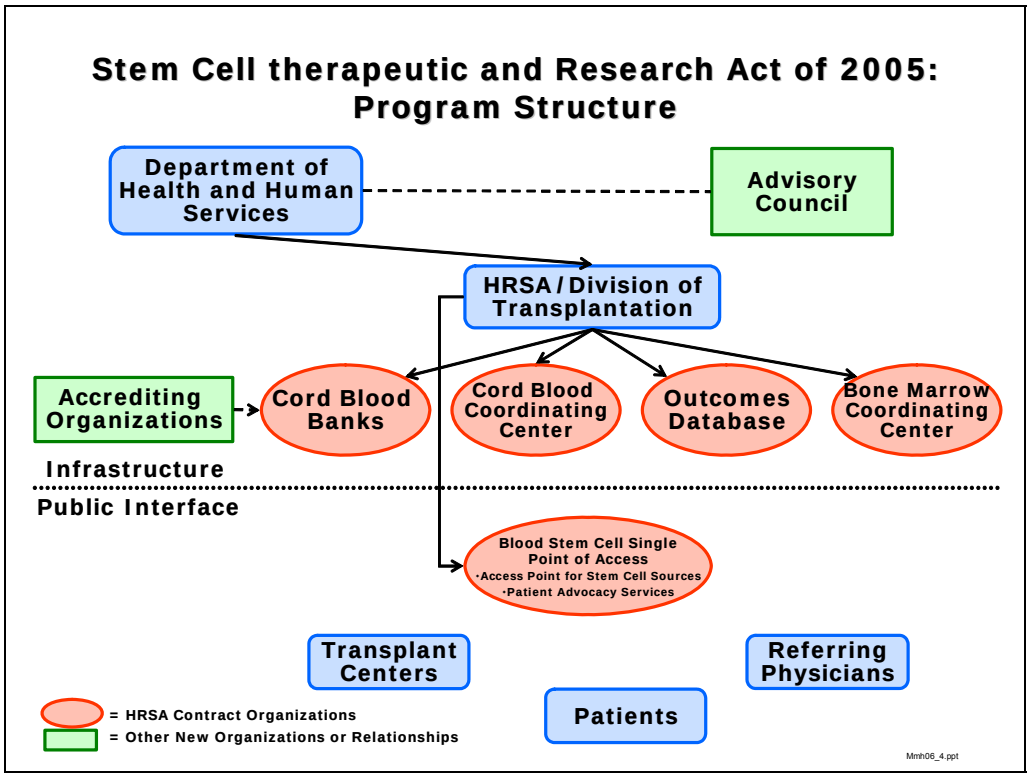
APPENDIX 9

CIBMTR Awarded HRSA Contract to Administer the C.W. Bill Young Cell Transplantation Program Outcomes Database

By J. Douglas Rizzo, MD, MS
Associate Scientific Director, Center for International Blood and Marrow Transplant Research
Associate Professor of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

CIBMTR Newsletter, Volume 12, Issue 2, December 2006

The Center for International Blood and Marrow Transplant Research (CIBMTR) is pleased to be the recipient of the contract (administered by the United States Health Resources and Services Administration (HRSA)) to establish and maintain the Stem Cell Therapeutic Outcomes Database (SCTOD) for the C.W. Bill Young Cell Transplantation Program. This is the beginning of an exciting new era for research in hematopoietic cell transplantation (HCT). The C.W. Bill Young Cell Transplantation Program (the Program) builds on the infrastructure for donor procurement and outcomes analysis developed by the National Marrow Donor Program (NMDP), which has held the U.S. contract to maintain a National Bone Marrow Donor Registry (NBMDR) for unrelated donor transplantation since its inception in 1987. In December 2005, the U.S. Stem Cell Therapeutic and Research Act of 2005 (Public Law 109-129) established the C.W. Bill Young Cell Transplantation Program to succeed (and enhance) the NBMDR. The Program is named after C.W. Bill Young, a recently re-elected 36 year veteran Congressman from Florida who has been a strong advocate of biomedical research and who was instrumental in the founding of the U.S. donor registry. The Program will include five key components: a Bone Marrow Coordinating Center (BMCC); a Cord Blood Coordinating Center (CBCC); an Offi ce of Patient Advocacy and Single Point of Access for health care professionals and patients (OPA/SPA); and a Stem Cell Therapeutics Outcomes Database (SCTOD). Several cord blood banks will also receive contracts to develop a National Cord Blood Inventory. See Figure 1. Working with its NMDP partner, the CIBMTR submitted the winning proposal to administer the SCTOD. The NMDP also was awarded the BMCC, CBCC and the OPA/SPA contracts. Although the landscape of HCT will change because of this legislation, the contract awards to CIBMTR and NMDP represent a substantial benefi t
to transplant centers, who have become accustomed to collaborating with these organizations. Current, long-standing relationships will not be disrupted as the NMDP and CIBMTR work to implement new and modified requirements of the Program. The CIBMTR and NMDP will use their substantial experience and adapt proven, in-place methods and systems to ensure a successful transition to
the new Program. Implementation of the new Program will present new challenges and opportunities for the HCT community. Important aspects of the program are: development of new systems to collect HCT data electronically, enhanced efforts to develop a standard dataset of HCT data, new requirements for U.S. centers to report outcomes data for all allogeneic transplantations, development of a related donorrecipient research sample repository, systems to make more data publicly available, broadened reporting of U.S. transplant center-specifi c survival rates, and data collection on uses of stem cells for new therapeutic applications (e.g., regenerative medicine).



Data collection for the SCTOD component of the Program will include collection of data for: allogeneic HCTs done in the U.S. using related or unrelated donors; allogeneic HCTs done using cells obtained through the Program, whether the transplantation is done in the U.S. or elsewhere: and use of allogeneic hematopoietic cells for emerging clinic applications other than HCT. In order to minimize the burden of data collection and assure that the most relevant data is collected, CIBMTR has begun discussions with U.S. authorities, the American Society of Blood and Marrow Transplantation (ASBMT), the European Blood and Marrow Transplant Group (EBMT), the Foundation for Accreditation of Cellular Therapy, the World Marrow Donor Association, cord blood banks and others in the international HCT community arrive at consensus on a reasonable set of common data elements to be collected for all patients. The current Transplant Essential Data form (corresponding to the EBMT Med-A form) will serve as a starting point (http://cibmtr.org/DATA/registering_centers.html). [Of note, centers participating as Research Centers in the CIBMTR will still be asked to complete comprehensive Report Forms on a subset of these patients; in a separate initiative the NMDP and CIBMTR have been working to harmonize the forms used for related and unrelated donor transplants.] The CIBMTR and NMDP are adapting established electronic data collection systems to collect these data under the HRSA contract. It is anticipated that these electronic systems will also allow centers to access their own HCT data as one of the benefi ts of participation. CIBMTR will work with consultants from PACT (Production Assistance for Cellular Therapies) and the SCCT (Specialized Centers for Cell-Based Therapy) and others to develop an approach to collect and analyze data on the use of hematopoietic cells for clinical applications other than HCT. Finally, CIBMTR and NMDP will work to expand the current unrelated donor-recipient specimen repository to include specimens obtained from related donor-recipient pairs. The databases and specimen repository created by these additional requirements of the C.W. Bill Young Program will serve as a resource for HCT investigators to address important research questions. The new Program will also require publication of an annual report of Transplant center-specifi c outcomes similar to the report currently generated by the NMDP for unrelated HCT. CIBMTR strongly believes in the importance of adjusting for difference in “case-mix” of patients across

transplant centers using parameters for disease status and comorbidities at the time of HCT. The experience held by the NMDP will facilitate generation of these reports, and CIBMTR will work closely with the ASBMT Quality Outcomes Committee, the CIBMTR Consumer Advocacy Committee, transplant center director representatives and HRSA to prepare a fair report that is useful for the transplant community and understandable to the general public. Although change is often diffi cult, and will certainly require patience as new systems are implemented, the transition to the C.W. Bill Young Cell Transplantation Program promises to offer an enhanced platform from which to conduct clinical investigation into the outcomes of HCT for traditional and emerging indications.

The C.W. Bill Young Cell Transplantation Program and the NMDP
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CIBMTR Newsletter, Volume 12, Issue 2, December 2006

The National Marrow Donor Program (NMDP) is a non-profit corporation that since 1987 has held a series of government contracts to operate the “National Bone Marrow Donor Registry”. In this role NMDP has facilitated more than 25,000 unrelated donor transplants for patients with blood disorders, such as leukemia and aplastic anemia, as well as immune system and genetic disorders. Currently more than 6.1 million adult donors and 52,000 cord blood units are listed on NMDP’s registry. New adult donors are recruited at about 280,000 annually. Cord blood unit numbers will grow signifi cantly as a result of the Stem Cell Therapeutic and Research Act of 2005. The new act created the C.W. Bill Young Cell Transplantation Program, a totally revamped system for delivering hematopoietic stem cell transplantation options to the U.S. public. This legislation is sweeping in its scope, but emphasizes a federal commitment to development of umbilical/placental cord blood. The legislation creates a National Cord Blood Inventory (NCBI), established by contracts awarded to individual cord blood banks that are charged with responsibility to begin collection of 150,000 new, high-quality cord blood units (CBU). The CBU inventories (both NCBI and non- NCBI units) of these contracted banks, as well as the inventories of other qualifi ed member banks, will be listed, searched and distributed through the National Cord Blood Coordinating Center (CBCC). An analogous National Bone Marrow Coordinating Center (BMCC) will oversee adult donor recruitment, donor search, product collection and product distribution activities of the adult donor registry. The public interface to these coordinating centers will be provided through another contract awarded to establish an Offi ce of Patient Advocacy/ Single Point of Access (OPA/SPA) function. Six cord blood banks are charter members of the NCBI. They are: Carolinas Cord Blood Bank at Duke University Medical Center, MD Anderson Cord Blood Bank, Milstein National Cord Blood Bank Program at the New York Blood Center, Puget Sound Blood Center, StemCyte, Inc., and the University of Colorado Cord Blood Bank. As described elsewhere in this issue, a contract for the outcomes database was awarded to CIBMTR. Contracts to operate the CBCC, BMCC and OPA/SPA were awarded to the NMDP. Because NMDP received these latter three contracts, much of the complexity inherent in the Program will be shielded from the public and from the transplant community. Federal oversight of the Program rests with the Department of Transplantation in the Health Resources and Services Administration (HRSA). HRSA is a federal agency dedicated to improving health care access in the U.S. In HRSA’s own words, “HRSA is the nation’s access agency – improving health and saving lives by making sure the right services are available in the right places at the right time.” Accordingly, the new contracts with NMDP include many requirements related to improving access to transplantation therapies. Some of the most interesting requirements relate to enhancing the information supplied to patients, their families and the public. For example, NMDP must develop software that allows patients, families, and the public at large, to conduct searches of the adult donor and CBU registries. This is envisioned as a public web site where

any individual with HLA data can obtain information about the potential for matching adult donors and CBU. While this service clearly provides patients with greater access to health-related information, it also creates obligations to ensure that the information is accurate, properly represented and accompanied with important disclaimers. For example, the public search report cannot fully anticipate the transplant center's eligibility rules or HLA matching requirements. The new contracts also require that patients are periodically updated about the status of their donor/CBU search that is being managed by a transplant center. If the search is interrupted or cancelled, the contractor must notify the patient. These requirements will be difficult to implement in a "fool-proof" manner, but will work best with solid collaboration between NMDP and the transplant centers. Additional contract requirements relate to increasing transplantation activity, improving effi ciency and developing performance measures. These and other requirements will challenge NMDP, CIBMTR and their partners to create a working environment for innovation and collaboration. The C.W. Bill Young Cell Transplantation Program has created a vision for the future of transplantation therapies in the U.S. Implementation of this vision has been entrusted to two well-known organizations, CIBMTR and NMDP, working in collaboration with federal officials and the transplant community. The demands are numerous, but rewards for our transplant community and the patients we serve are innumerable.

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