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CENTER FOR INTERNATIONAL BLOOD
& MARROW TRANSPLANT RESEARCH

PROGRESS REPORT

JANUARY-DECEMBER
2005

RESEARCH SCIENCE INNOVATION

Progress Report for January – December 2005

List of Abbreviations

Acronym	Definition
ABMTR	Autologuous Blood and Marrow Transplant Registry
AE	Adverse Event
ALL	Acute Lymphoblastic (Lymphocytic) Leukemia
AML	Acute Myelogenous Leukemia
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ATG	Anti-Thymocyte Globulin
BMT	Blood and Marrow Transplant
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
Bu	Busulfan
CALGB	Cancer and Leukemia Group B
CIBMTR	Center for International Blood and Marrow Transplant Research
CGP	Cytokine Gene Polymorphism
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogeneous Leukemia
CMML	chronic Myelomonocytic Leukemia
CMV	Cytomegalovirus
CNS	Central Nervous System
COBLT	Cord Blood Transplantation Study
CP	Chronic Phase
CR	Complete Remission
CSA	Cyclosporine
CSF	Cerebro-spinal Fluid
CT	Computerized Tomography
Cy	Cyclophosphomide
DLI	Donor Leukocyte or Lymphocyte Infusion
ECOG	Eastern Cooperative Oncology Group
G-CSF	Granulocyte-Colony Stimulataing Factor
GVHD	Graft versus Host Disease
HCT	Hematopoietic Stem Cell Transplant
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
IBMTR	International Blood and Marrow Transplant Registry
IRB	Institutional Review Board
IV	Intravenous
KIR	Killer Immunoglobulin-like Receptor
KPS	Karnofsky Performance Score

MDS	Myelodysplasic Syndrome
mHAg	Human Minor Histocompatibility Antigen
MM	Multiple Myeloma
MTX	Methotrexate
NIH	National Institutes of Health
NHL	Non-HodgkinLymphoma
NHLBI	National Heart, Lung and Blood Institute
NMDP	National Marrow Donor Program
PBMTC	Pediatric Bone Marrow and Stem Cell Transplant
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFT	Pulmonary Function Test
PR	Partial Response
QOL	Quality of Life
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Stable Disease
SNP	Single Nucleotide Polymorphism
SWOG	South Western Oncology Group
TBI	Total Body Irradiation
TRM	Treatment Related Mortality
UCB	Umbilical Cord Blood
VOD	Veno-Occlusive Disease
WBC	White Blood Cell

Progress Report for January – December 2005

1.0 INTRODUCTION

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research program formed in July 2004 through an affiliation of the International Bone Marrow Transplant Registry (IBMTR) and Autologous Blood and Marrow Transplant Registry (ABMTR) of the Medical College of Wisconsin (MCW) and the research arm of the National Marrow Donor Program (NMDP-Research). Both the IBMTR and the NMDP had broad expertise in the field of blood and marrow transplantation, including observational research and clinical trials. The IBMTR was a voluntary organization involving more than 400 transplant centers in 47 countries (see Appendix 1) that 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 hematopoietic stem cell transplants and also conducted research to improve the outcome of such transplants. The NMDP Network includes 164 transplant centers, 80 donor centers, 101 collection centers, 89 apheresis centers and 17 cord blood banks (see Appendix 1).

The CIBMTR brings together the research efforts of both organizations, each with complementary strengths that are instrumental in bringing the proposed projects to completion.

The IBMTR contributes:

- a strong record of clinical research and publications in hematopoietic stem cell transplantation and statistical methodology;
- a long history of effective collaborations with a large network of transplant centers;
- key personnel with acknowledged leadership in the field and combined training in both HCT (hematopoietic stem cell transplantation) and biostatistics;
- an extensive database of clinical information on autologous, related and unrelated donor transplantation with information on >65% of the transplants done in the U.S.

The NMDP contributes:

- experience with a large network of donor, collection and transplant centers;
- a database that includes almost all unrelated donor transplants in the U.S. and with stored donor-recipient biologic samples for a large subset of these transplants;
- an experienced business office with contractual relationships with specimen repositories, contract laboratories, pharmacies and other organizations essential for trial-related activities;
- an experienced patient advocacy office that can provide educational and counseling services to patients treated in or considering participation in clinical trials.

This affiliation represents a commitment of the two organizations to coordinate their

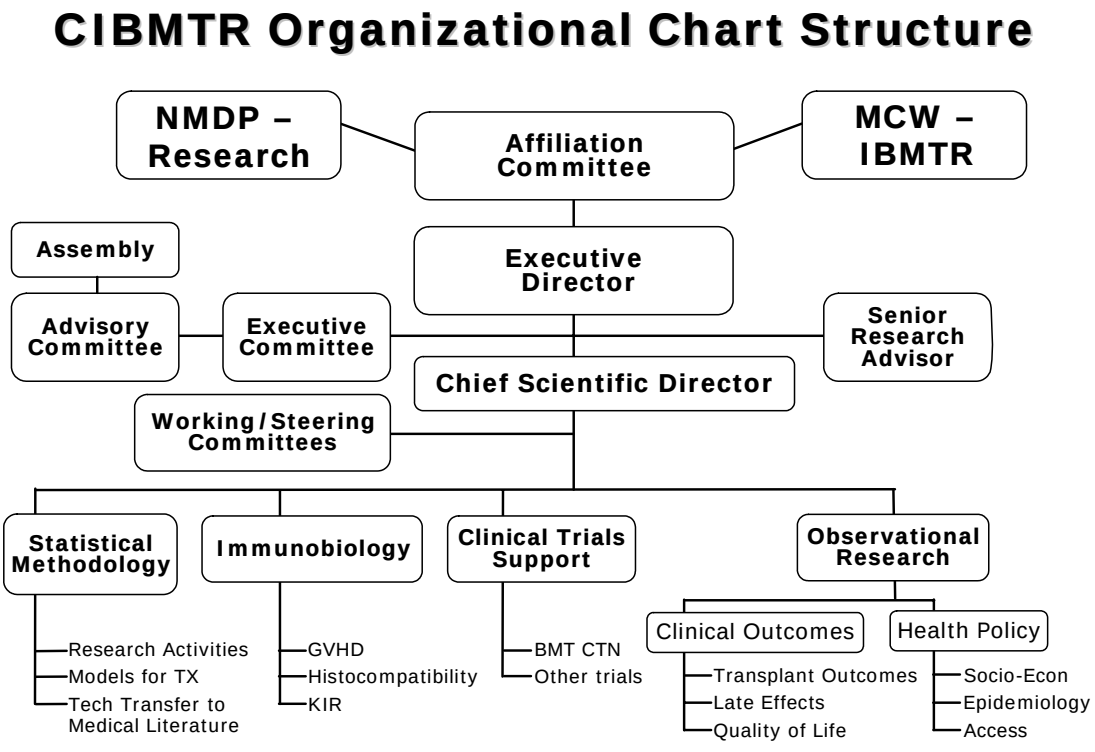
efforts and resources and to provide a single point of focus for development and support of transplant-related clinical research. CIBMTR Statistical Center activities are funded primarily by an NIH (National Institutes of Health) grant (U24-CA76518) which provides funding to establish a resource of data and statistical expertise for clinical research in blood and marrow transplantation. All of this work is now done under the umbrella of the CIBMTR, with policy and scientific oversight by CIBMTR Scientific, Executive and Advisory (Appendix 2) Committees. This Progress Report deals primarily with those CIBMTR activities related to this resource.

In July 2004, a Transitional Advisory Committee was established to include previous IBMTR Executive Committee members, NMDP Research and Publications (RAP) Committee members and NMDP Histocompatibility Committee members. In October, 2004 this group met, voted for interim officers and nominated chairs for expanded scientific Working Committees. The first CIBMTR Assembly elections occurred in late 2005 to select representatives to the permanent Advisory Committee for terms beginning 3/1/06. CIBMTR Committees, as did IBMTR Committees, include many of the leaders in the fields of transplantation, hematology and oncology who are committed to using the data and statistical expertise made available through this resource grant to address important issues in blood and marrow transplantation.

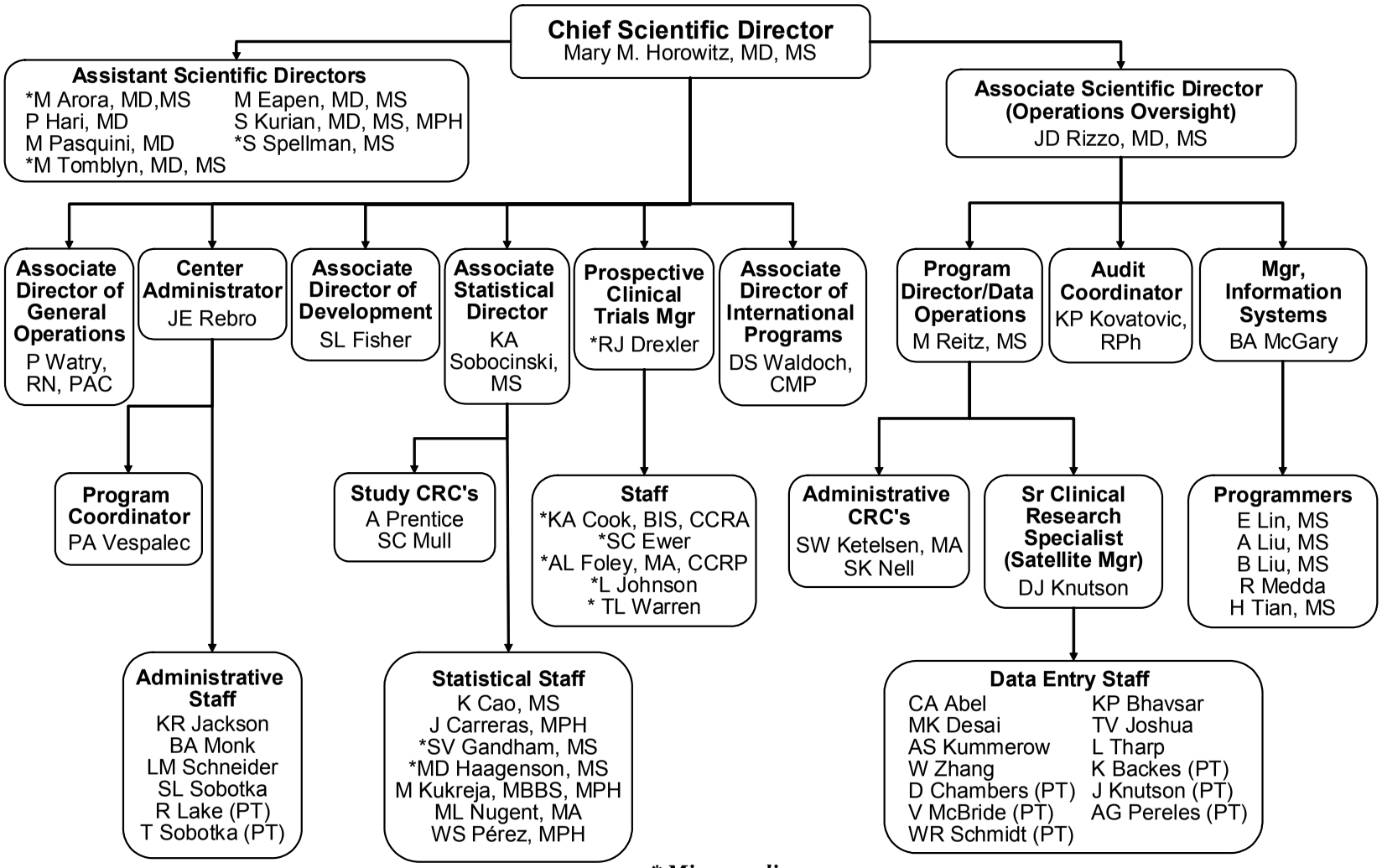
The organizational structure of the CIBMTR is shown in Figures 1.1 and 1.2. The Chief Scientific Director has primary responsibility for administrative and scientific operations. The Executive Director provides additional administrative leadership. The CIBMTR Statistical Director has responsibility for 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

Figure 1.1



CIBMTR Organizational Chart



**** Minneapolis campus***
PT = Part-time

Figure 1.2

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Each of these areas is (or will be) directed by a Program Leader who is an M.D. or Ph.D.

A detailed description of the CIBMTR structure including the plans for transitioning from the previous IBMTR and NMDP structures can be found in Appendix 3. A summary of the committee structure and responsibilities is included below.

1.1 Committee Responsibilities

The new CIBMTR Committee structure is designed to ensure that the activities of the CIBMTR are consistent with the priorities of the transplant community it serves and that the CIBMTR operates with broad input from members of that community.

CIBMTR **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;
- planning and conducting workshops at CIBMTR meetings.

Working Committees have responsibility for setting priorities for CIBMTR observational studies using the large clinical databases of the IBMTR and NMDP. These observational studies are a core activity of the CIBMTR.

There are 17 Working Committees with the following indicated areas of responsibility for scientific oversight (Appendix 2):

- **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 (MM) 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, autoimmune cytopenias and other non-malignant hematopoietic disorders
- **Immune Deficiencies/Inborn Errors of Metabolism (IEOM):** cellular therapy for congenital and acquire immune deficiencies and inborn errors of metabolism
- **Autoimmune Diseases:** cellular therapy for autoimmune disorders other than autoimmune cytopenias
- **Graft Sources and 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 Life (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 Policy:** access to cellular therapy including social and economic barriers to care and influence of psychosocial factors on 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. During the initial appointment of CIBMTR chairs, some staggering of term durations was done to ensure future continuity as chair terms expire. Chairs 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, to be determined by the Chief Scientific Director in consultation with the Statistical Director and Program Leader for observational studies.

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 the event that no relevant or appropriate proposals addressing those areas are submitted.

CIBMTR **Steering Committees** provide an additional level of oversight use of certain resources. The two major programs requiring such oversight are the Clinical Trials Support Programs and the Immunobiology Program. The Steering Committee for the Immunobiology Program is the NMDP Histocompatibility Committee which has responsibility for reviewing requests for specimens from the NMDP repository. The Histocompatibility Committee includes at least one representative from CIBMTR for these deliberations. The structure for the Steering Committee that will make decisions about allocation of resources to conduct CIBMTR clinical trials has been drafted and this Committee will meet for the first time in February 2006. However, no NIH grant funds (U24-CA76518) targeted to the CIBMTR are used for this activity.

CIBMTR **Advisory Committee** members are elected by the CIBMTR Assembly. The Assembly is comprised of a single representative from each CIBMTR Research Center. The CIBMTR Advisory Committee also includes appointed members representing donor centers, patients and collection centers (Appendix 3). The CIBMTR Advisory Committee reviews, at least annually, scientific and other activities of the CIBMTR, providing input to the Executive Committee.

The CIBMTR **Executive Committee** is a subcommittee of the Advisory Committee that provides ongoing advice and counsel to the CIBMTR Statistical Center. It includes the Chair, Chair-elect or Immediate Past Chair, four Vice-Chairs (each representing a geographic region), and the four appointed members of the Advisory Committee. Additionally, the CIBMTR Senior Research Advisor, Chief Scientific Director 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;
- reviews and assists in preparation of the agenda for the annual meeting.

The Executive Committee meets at least annually at the Tandem BMT Meetings and by conference call at least quarterly.

The **Nominating Committee** 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.

The previous success of the IBMTR and NMDP-Research, as will the future success of the CIBMTR, results, in large part, from the voluntary efforts of hundreds of physicians, basic scientists and clinical research associates who participate in these committees and contribute data and expertise to CIBMTR studies.

Two new **subcommittees** of the Advisory Committee were approved in 2005; the Consumer Advocacy Committee (CAC) and the International Affairs Liaison Committee.

Consumer Advocacy Committee:

It was agreed prior to the inception of the CIBMTR that individuals with personal HCT experience would be a values resource and that such individuals should be encouraged to become actively involved in the new organization. This includes patients, family members, and donors as well as representatives from NMDP donor and collection centers. Individuals from these groups historically sat on multiple NMDP committees which have been restructured or eliminated with the re-organization.

The CAC committee was mandated to help provide the patient and donor perspective in developing the CIBMTR's research agenda. Three CIBMTR Working Committees were identified in which this committee has special interest. These are: the Late Effects, Donor Safety and Health Services and Psychosocial Issues Committees.

Eight core members chose two co-chairs in June 2005. J. Douglas Rizzo, M.D. is the Scientific Director. Several NMDP, HRSA and other CIBMTR members sit as *ex officio* members. Meetings are primarily by teleconference (approximately every 6-8 weeks). A second in-person meeting is scheduled for February 2006 and will become an annual event at the BMT Tandem meetings.

A primary mission of this committee is focused on translating BMT research materials for the general public. Additionally they will have increasing presence in an advisory capacity to the CIBMTR Clinical Trials Advisory Committee.

International Affairs Liaison Committee:

The proposal for this committee was first submitted to the Advisory Committee in February

2005. Its major charge will be to facilitate communication between non-U.S. centers and CIBMTR leadership (as well as other national, regional and international organizations) and to design, develop and conduct studies dealing with questions specific to each geographic region.

1.2 CIBMTR Statistical Center

Since 1972, the IBMTR Statistical Center at the Medical College of Wisconsin (MCW) in Milwaukee (now the Milwaukee Campus of the CIBMTR Statistical Center) 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 1.2); it continues to play an important coordinating role in the CIBMTR. The MCW Statistical Center is an academic division of the Health Policy Institute of MCW. The Health Policy Institute and MCW provide administrative support for the Statistical Center in grants and account management, personnel issues and development activities.

Mary M. Horowitz, M.D., M.S. is Chief Scientific Director of the CIBMTR Statistical Center and John P. Klein, Ph.D. is Statistical Director. Dr. Horowitz is the Robert A. Uihlein Professor of Hematologic Research at MCW and is an attending physician in the MCW HSCT program. She also holds an M.S. in Biostatistics. Dr. Klein is a Professor and Chief of the Division of Biostatistics at MCW and an internationally recognized expert in survival analysis.

There is one Associate Scientific Director (Dr. J. Douglas Rizzo) and four Assistant Scientific Directors (Drs. Mary Eapen, Hari Parameswaran, Marcello Pasquini and Seira Kurian) who provide scientific leadership at MCW 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 M.S. degree in Epidemiology from MCW. His responsibilities, in addition to developing a long-term follow-up program, include providing medical oversight for the Regimen Related Toxicity/Supportive Care, Late Effects/Quality of Life and the Health Services/Psychosocial Issues Working Committees. As Program Leader over the Observational Program, he also oversees the operational aspects of the Statistical Center and serves as an attending physician in MCW's adult HCT unit.

Dr. Eapen is a pediatric hematologist/oncologist who received her clinical training and an M.S. 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 (Bone Marrow Transplant Clinical Trials Network). Dr. Seira Kurian joined the Statistical Center as an Assistant Scientific Director in August 2004. She is a pediatrician and holds an MS in Physiology and Biophysics as well as a Masters degree in Public Health. Her primary focus is in health services research and she serves as the primary biostatistician for the Donor Safety. Health Services/Psychosocial Issues and the Immune Deficiencies Working Committees.

Dr. Parameswaran Hari completed his Hematology/Oncology fellowship at MCW after serving as a Specialist Registrar in Haematology at Leicester University Teaching Hospitals in the UK. He is board certified in Medical Oncology, Clinical and Laboratory Haematology and Internal Medicine. He has been an Assistant Professor since July, 2004. He serves as Scientific Director of the Lymphoma and Plasma Cell Disorders Working Committees. Dr. Marcello 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 MCW. He has been an Assistant Professor at the MCW since July, 2005.

He is the Scientific Director of the Autoimmune Working Committee and serves as a Protocol Officer for the BMT CTN. Recruitment is in progress for an additional Associate Scientific Director to the Clinical Trials program.

The MCW Statistical Center has three Ph.D. 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. Other Ph.D. members of the MCW Division of Biostatistics also participate in selected CIBMTR studies. Additionally, there are four M.S. biostatisticians contributing to CIBMTR research activities on the Milwaukee Campus: Kathleen Sobocinski (who is the Associate Statistical Director and who has worked with the Statistical Center since 1973), Waleska Pérez, Jeanette Carreras, and Manisha Kukreja.

The Minneapolis office of the CIBMTR (NMDP-Research) 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 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 and as a member of the IBMTR Executive Committee. Dr. Mukta Arora is an Assistant Professor in the Division of Hematology, Oncology and Transplantation, at the University of Minnesota. She also has an M.S. degree in Clinical Research from the University of Minnesota. She serves as Scientific Director of the CIBMTR Chronic Leukemia, Graft-versus-Host Disease (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 Hematopoietic Stem Cell Transplantation. She obtained an M.S. 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 developing the new CIBMTR Clinical Trials Support Program. Additionally, Mr. Stephen Spellman, Manager of NMDP Scientific Services, has joined the Immunobiology Working Committee as Scientific Director. He received his M.B.S. degree in 2000 from the University of Minnesota in Immunobiology and Molecular Biology. There are also two MS level statisticians at the CIBMTR Minneapolis Campus: Michael Haagenson and Sharavi Gandham.

Rebecca Drexler B.S. A.A.S serves as the Clinical Research Manager of the CIBMTR Minneapolis office. Becky has twenty 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 and has an important managerial role in the new CIBMTR Clinical Trials Program. Rebecca Drexler and Paula Watry, Associate Director/Operations, CIBMTR (Milwaukee campus) serve as liaisons between the two offices. Ms. Watry joined the CIBMTR organization in October 2004; she had 10 years clinical experience as a Physician's Assistant in the MCW marrow transplant program. See Figure 1.2.

Each CIBMTR Working Committee has an assigned Scientific Director, Ph.D. statistician and M.S. statistician. The Scientific Directors of the CIBMTR Statistical Center work closely with Working Committee chairs and members to evaluate proposals, plan studies and prepare reports and manuscripts. They help interpret CIBMTR data for users in and outside of

participating centers. They are frequently called upon to provide and present data for federal and non-federal health care agencies, transplant centers and national and international hematology meetings. They provide scientific and medical oversight and coordination to CIBMTR statisticians and data management staff. For some studies and Working Committees, they may also serve as the primary Biostatistician. Masters level statisticians at both the Milwaukee and Minneapolis offices, in addition to performing data analyses, serve as coordinators for CIBMTR Working Committees (See Appendix 2), ensuring frequent communication between the Statistical Center and Working Committee chairs and members. Ph.D. statisticians have primary responsibility for ensuring appropriate study designs and performing complex analyses.

The unique combination of statistical and clinical expertise afforded by the CIBMTR Scientific and Statistical Directors contributes greatly to the planning and execution of studies proposed and approved by the Working Committees. The Center makes this resource information accessible to many other users as well.

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 centers that must provide outcome data on all transplants facilitated by NMDP.

Table 2.1 shows annual accession of patients from CIBMTR centers from the IBMTR's inception in 1970, the ABMTR's inception in 1991 and the NMDP's inception in 1987. *Table 2.2A* shows 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 2.2B* shows similar information for transplants reported to NMDP.

Until 1995, the IBMTR collected comprehensive clinical data on <u>all</u> 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. Consequently, in 1995, the IBMTR switched to a system whereby basic data (*Transplant Essential Data and Preregistration Forms)* are *registered* for all cases and comprehensive data *(Report Forms)* are provided for a subset of these (see below). This is the same system used previously by the ABMTR since its inception. Registration and Report Forms may be viewed on the CIBMTR website, www.cibmtr.org. Numbers of patients in *Table 2.1A* reflect only those whose comprehensive data were reported (Research Data Base). 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 analysis 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.

Table 2.1 Accession of patients (Comprehensive Reports only) into the CIBMTR (IBMTR since 1970, ABMTR since 1991, NMDP since 1987) through June, 2005.

	Allogeneic - IBMTR		**Autologous - ABMTR**		**Unrelated - NMDP**	
Interval	**Annual**	**Cumulative**	**Annual**	**Cumulative**	**Annual**	**Cumulative**
7/70 - 6/80	699	699				
7/80 - 6/81	283	982				
7/81 - 6/82	206	1188				
7/82 - 6/83	861	2049				
7/83 - 6/84	715	2764				
7/84 - 6/85	1132	3896				
7/85 - 6/86	1026	4922				
7/86 - 6/87	1175	6097				
7/87 - 6/88	1745	7842			25	25
7/88 - 6/89	1859	9701			121	146
7/89 - 6/90	1936	11637			198	344
7/90 - 6/91	1894	13531			339	683
7/91 - 6/92	2172	15703	9	9	441	1124
7/92 - 6/93	2513	18216	874	883	499	1623
7/93 - 6/94	2589	20805	1588	2471	610	2233
7/94 - 6/95	2344	23149	1614	4085	799	3032
7/95 - 6/96	2174	25323	1994	6079	910	3942
7/96 - 6/97	3477	28800	2918	8997	1009	4951
7/97 - 6/98	3332	32132	2869	11866	1146	6097
7/98 - 6/99	2723	34855	3540	15406	1115	7212
7/99 - 6/00	2636	37491	2710	18116	1235	8447
7/00 - 6/01	2602	40093	1756	19872	1281	9728
7/01 - 6/02	2518	42611	1329	21201	1309	11037
7/02 - 6/03	2829	45440	1460	22661	1291	12328
7/03 - 6/04	2519	47959	829	23490	1778	14106
7/04 - 6/05	2725	50748	947	24443	1834	15940

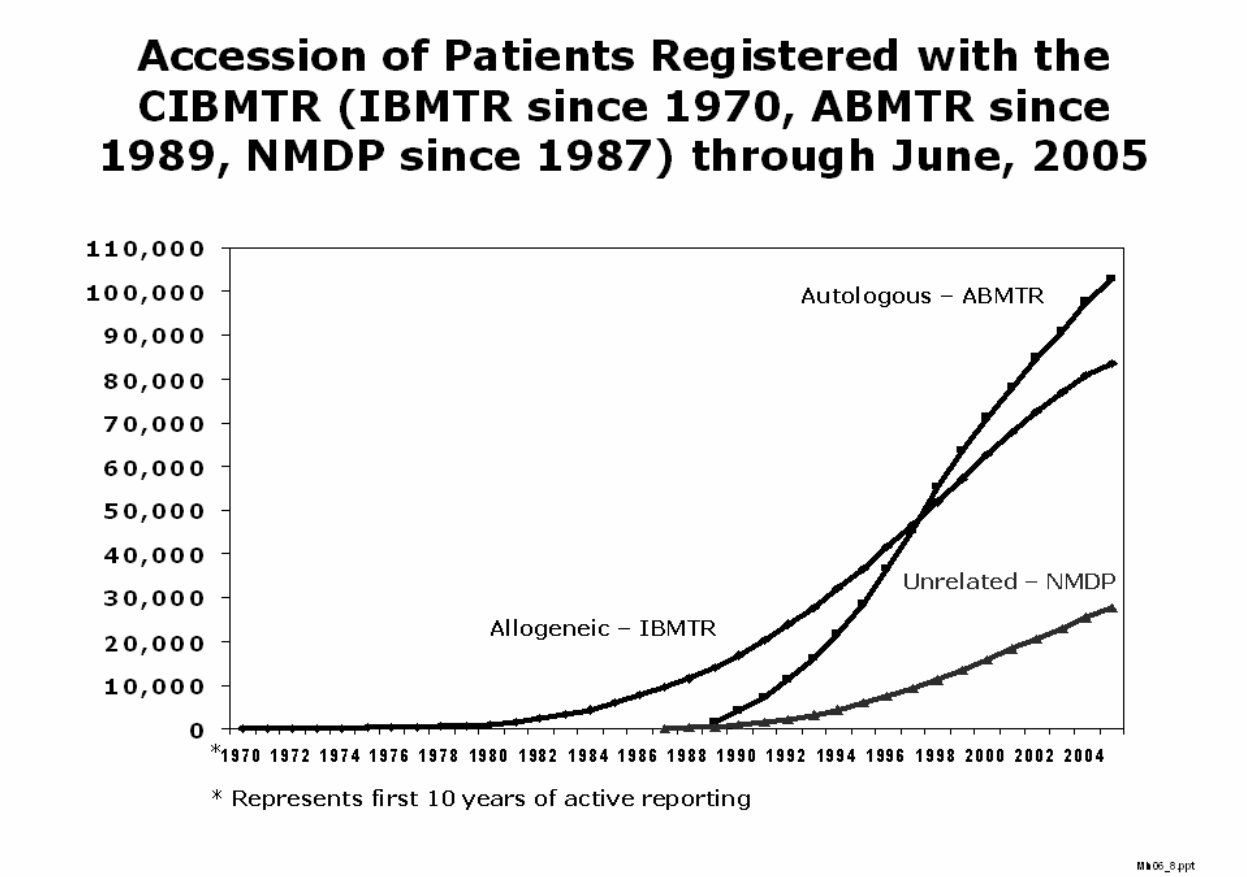

Figure 2.1

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 Form is adapted from the TED form but includes several additional data fields to allow rational selection of patients for comprehensive data reporting. Research centers submit the Preregistration Form early in the course of the transplant procedure. Information is entered in a randomization program that weights cases for selection on the basis of needs for current and future studies while ensuring 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, is 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 35% of allogeneic transplants done elsewhere and about 60% of autologous HCTs done in North and South America.

Significant efforts have been made throughout 2005 to harmonize all previous IBMTR and NMDP data collection forms and fields to simplify the workload of reporting centers and yet still be adaptable to both the Statistical Center and NMDP databases. This work is ongoing and

involves key staff members from both the Milwaukee and Minneapolis campuses. There is an expected release date of Summer 2006 for the major common forms with accompanying manuals. Several instructional sessions focused on these forms are planned during the 2006 BMT Tandem meetings.

Table 2.2A Distribution of diseases in CIBMTR database (IBMTR since 1970, ABMTR since 1989) through 2005.

	Allogeneic Transplants - IBMTR		**Autologous Transplants – ABMTR**	
Disease	**Registration Data**	**Comprehen-sive Data**	**Registration Data**	**Comprehen-sive Data**
Acute lymphoblastic leukemia	19820	9404	1382	419
Acute myelogenous leukemia	29285	12759	6150	1792
Chronic myelogenous leukemia	23345	10919	693	270
Chronic lymphocytic leukemia	1681	578	537	111
Hodgkin disease	903	322	11187	2073
Non-Hodgkin lymphoma	7403	2719	27419	5879
Plasma cell disorders	2770	1072	20423	3880
Breast cancer	174	91	23017	7687
Neuroblastoma	165	67	2429	701
Ovarian cancer	21	6	1653	691
Melanoma	44	15	58	2
Lung cancer	9	2	204	124
Sarcoma (soft tissue, bone, other)	47	14	760	241
Ewing sarcoma	53	24	670	222
Wilm tumor	7	2	232	41
Myelodysplastic syndromes	8224	3207	251	73
Other leukemia	1390	606	372	121
Medulloblastoma	4	3	451	100
PNET	2	2	114	33
Germ cell tumor	7	3	464	57
Brain tumors	5	3	976	224
Testicular cancer	7	4	1095	469
Other malignancies[b]	581	233	1239	131
Autoimmune diseases[c]	47	14	288	56
Severe aplastic anemia	7729	4732	-	-
Inherited erythrocyte abnormalities	4123	2699	-	-
SCID, other immunodeficiencies	2861	1340	-	-
Inherited disorders of metabolism	1400	736	-	-
Histiocytic disorders	467	220	-	-
Other non-malignancies	318	52	-	-
TOTAL	112892	51868	102064	25397

[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), other (n=72), ITP (N=8), Crohn's disease (n=11).

Table 2.2B. Distribution of diseases in NMDP database, 1987-2005 (comprehensive available for all patients).

Disease	Total
Acute myelogenous leukemia	4328
Chronic myelogenous leukemia	3557
Acute lymphoblastic leukemia	2963
Myelodysplastic disorders	1633
Non-Hodgkin lymphoma	1193
Severe aplastic anemia	724
Other leukemia	597
Plasma cell disorders	317
Inherited disorders of metabolism	269
SCID and other immunodeficiencies	261
Hodgkin lymphoma	296
Histiocytic disorders	128
Other malignancies	54
Inherited erythrocyte abnormalities	33
Inherited platelet disorders	18
Other	18
TOTAL	16389

3.0 SCIENTIFIC ACTIVITIES

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 2005. Preliminary Results sections describe 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. Members of the seventeen Working Committees have worked on a total of 173 studies in 2005.

3.1 Acute Leukemia Working Committee.

Co-Chair: Armand Keating, University of Toronto, Toronto, Ontario, Canada; Co-Chair: Martin Tallman, Northwestern University, Chicago, Illinois; Co-Chair: Jorge Sierra, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Statisticians: Waleska Pérez, MPH, Mei-Jie Zhang, Ph.D.; Scientific Director: Daniel J. Weisdorf

3.1.1 Publications

LK02-01: Baker KS, Loberiza FR, Jr., Yu H, Cairo MS, Bolwell BJ, Bujan-Boza WA, Camitta BM, Garcia JJ, Ho WG, Liesveld JL, Maharaj D, Marks DI, Schultz KR, Wiernik P, Zander AR, Horowitz MM, Keating A, Weisdorf DJ. **Outcome of ethnic minorities with acute or chronic leukemia treated with HCT in the United States.** *J Clin Oncol. 23:7032-7042, 2005.* We previously reported a higher risk of mortality among Hispanics after allogeneic HCT. However, it is not known how specific post-transplant events [acute or chronic GVHD, treatment-related mortality (TRM) and relapse] may explain mortality differences. The purpose of this study was to examine the relationship between ethnicity and post-transplant events, and determine their net

effect on survival. We identified 3028 patients with acute or chronic leukemia reported to the International Bone Marrow Transplant Registry between 1990-2000 who received an HLA (human leukocyte antigen) identical sibling HCT after a myeloablative conditioning regimen in the United States. There were 2418 (80%) Caucasians and 610 (20%) ethnic minorities: 251 (8%) Blacks, 122 (4%) Asians, and 237 (8%) Hispanics. Cox proportional hazards regression was used to compare outcomes between Caucasians and ethnic minorities while adjusting for other significant clinical factors. No statistically significant differences in the risk of acute or chronic GVHD, TRM or relapse were found between Caucasians and any ethnic minority group. However, Hispanics had higher risks of treatment failure (death or relapse) [relative risk (RR) 1.30, 95% confidence interval (CI) 1.08-1.54, p=0.004], and overall mortality (RR 1.23, 95% CI 1.03-1.47, p=0.02). The higher risks of treatment failure and mortality among Hispanics are the net result of modest, but not individually statistically significant, increases in both relapse and TRM and cannot be accounted for by any single transplant-related complication. Further studies should examine the role of social, economic, and cultural factors.

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.** *British Journal of Haematology, 2006. In press.* Most AML patients lack HLA-identical sibling donors for transplantation. Autotransplants and unrelated donor (URD) transplants are therapeutic options. To compare autologous versus URD transplantation for AML in first (CR1) or second complete remission (CR2), we studied the outcomes of 668 autotransplants and 476 URD transplants reported to the Center for International Blood and Marrow Transplant Research. Proportional hazards regression adjusted for differences in prognostic variables. In multivariate analyses TRM was significantly higher and relapse lower with URD transplantation. Adjusted 3-year survival probabilities were: in CR1 57 (53-61)% with autotransplants and 44 (37-51)% URD (p=0.002); in CR2 46% (39-53)% and 33 (28-38)%, respectively (p=0.006). Adjusted 3-year LFS probabilities were: CR1, 53% (48-57)% with autotransplants and 43 (36-50)% with URD (p=0.021); CR2 39 (32-46)% and 33 (27-38)%, respectively (p=0.169). We concluded that autologous and URD transplantation produce prolonged LFS in some patients. High TRM offsets the superior anti-leukemia effect of URD transplantation. This retrospective, observational database study shows that autotransplantation, in general, offers higher 3-year survival for AML patients in CR1 and CR2. Cytogenetics, however, were known in only two-thirds of patients and confounding by selection bias cannot be eliminated.

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. **Pretransplant consolidation chemotherapy decreases leukemia relapse after autologous blood and bone marrow transplants for acute myelogenous leukemia in first remission.** *BBMT, 2006. In press*. 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 CR1 we compared posttransplant outcomes of 146 patients receiving no consolidation with outcomes of 244 receiving standard-dose (<1 gm/m^2) and 249 receiving high-dose (1-3 gm/m^2) cytarabine, using proportional hazards regression to adjust for differences in prognostic variables. One-year TRM 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 LFS 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, 5-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). Although most patients received 1 or 2 cycles of consolidation, there was no detectable effect of the number of courses on transplant outcome. In multivariate analysis, 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 concluded that patients with AML in CR1 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 (Cy) 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.** *BBMT, 2006. In press*. 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) stratifying on TBI dose. 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, LFS and overall survival were done separately for CR1 and CR2 transplants. Transplant-related mortality did not differ by conditioning regimen. In CR1, there were also no significant differences in relapse, LFS or overall survival by conditioning regimen. In CR2, these outcomes differed among conditioning groups. In comparison with Cy-TBI<13 Gy, risks of relapse, treatment failure (inverse of LFS) 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 dose to ≥13 Gy.

3.1.2 Preliminary Results

LK03-02: Comparison of HLA-Identical sibling HCT versus chemotherapy as postremission therapy in t(8;21) AML: A collaborative study between the German AML Intergroup and the CIBMTR). *(Study Chairs: A. Ganser, Medical School of Hannover, Hannover, Germany, R Schlenk, University of Ulm,, Ulm, Denmark, J. Krauter, Medical School of Hannover, Hannover, Germany, Study Statistician: WS. Pérez)*. *Manuscript in preparation*. *Poster presentation at American Society of Hematology meetings, December 2005*. The t(8;21) is associated with high complete remission rates and high survival rates after cytarabine-containing postremission therapy for AML. However, patients with leukocytosis and additional cytogenetic abnormalities, such as loss of sex chromosome (LOS), have worse outcomes. We compared patients ages 16 to 60 years with t(8;21) AML in CR1, comparing 132 patients receiving postremission chemotherapy with 118 receiving HLA-identical sibling HCT. The chemotherapy cohort included patients treated with double induction followed by cytarabine-containing regimens in one of eight different German AML Intergroup clinical trials (SHG-Hannover-AML-2/95, SHG-Hannover-AML-1/99, SHG-Dresden-AML-96, AMLHD93, AMLHD98A, AMLCG92, AMLCG99, OSHO-AML-96) between 1993 and 2002. HCT recipients

were registered with the CIBMTR from 1990 to 2000. To adjust for potential bias caused by delayed entry into the transplant cohort, left-truncated univariate analysis and Cox multivariate models were used. The median age of patients receiving chemotherapy and HCT were 42 and 32 years of age, respectively (p<0.001). The table below shows five-year outcomes in months, including relapse rate, treatment related mortality (TRM), adjusted leukemia free survival and adjusted overall survival derived from multivariate analyses.

	TRM % (95% CI)	Relapse % (95% CI)	LFS % (95% CI)	OS % (95% CI)	
				LOS	No LOS
Chemotherapy	6 (2-11)	29 (21-37)	64 (55-73)	55 (41-69)	84 (74-92)
HCT	32 (22-44)	14 (8-21)	55 (45-65)	64 (50-77)	53 (39-67)
P-value*	<0.001	0.01	0.24	0.74	0.02

*From multivariate models

WBC (white blood cells) > 25.4×10^9/L at diagnosis was associated with higher relapse risk (RR=2.09, P=0.03), shorter LFS (RR=1.9, P=0.008) and shorter overall survival (RR=1.91, P=0.012), independent of post-remission treatment. Neither year of treatment nor specific chemotherapy protocols were significantly associated with outcomes. HCT and chemotherapy had similar overall survival in patients with LOS and leukocytosis; in those without LOS, survival was significantly higher with chemotherapy. In this cohort of patients with t(8;21) treated in the 1990s, high transplant related mortality offset the anti-leukemia benefit of HCT, suggesting that HCT be reserved for patients who fail post-remission chemotherapy.

D00-52: Impact of cytogenetics on outcome of HLA-mismatched unrelated donor HCT for adults with AML. *(Study Chair: M. Tallman, Northwestern University, Chicago, IL; Study Statistician: S. Gandham). Manuscript in preparation.* Matched unrelated donor HCT is a potentially curative treatment for patients with AML. Its graft-versus-leukemia (GVL) effect may be potent enough to overcome the otherwise poor prognosis associated with AML though efficacy for high risk cytogenetic subgroups is uncertain. This study analyzed outcomes by cytogenetic risk group in 324 patients transplanted in CR1, and 440 transplanted in CR2 using NMDP donors from 1988 to 2002. Using the SWOG (Southwest Oncology Group) / ECOG (Eastern Cooperative Oncology Group) classification of cytogenetic risk groups (Slovak et al. *Blood*, 2000), cytogenetics were classified as favorable in 14% of patients, intermediate in 71% and unfavorable in 16%. 56% of patients were male and 42% were older than 35 years at HCT. 76% of patients and donors were matched at HLA-A, -B and -DRB1, 17% were mismatched at one or more loci and 7% were potentially matched (serologically matched at HLA-A and -B and potentially allele matched at -DR). Outcomes are shown below.

Disease Status	N	Kaplan-Meier Estimate of Survival at 5 years	Kaplan-Meier Estimate of LFS at 5 years	Cumulative Incidence of 100 Day Transplant-Related Mortality	Cumulative Incidence of Relapse at 5 years
CR1	324	32 ± 6%	32 ± 5%	32 ± 5%	18 ± 4%
Intermediate	227	33 ± 7%	32 ± 7%	31 ± 6%	16 ± 5%*
Unfavorable	85	31 ± 11%	31 ± 10%	29 ± 10%	23 ± 9%*
CR2	440	36 ± 5%	35 ± 5%	25 ± 4%	16 ± 3%
Favorable	93	46 ± 10%	44 ± 10%	25 ± 9%	10 ± 6%**
Intermediate	313	33 ± 6%	32 ± 5%	27 ± 5%	16 ± 4%**
Unfavorable	34	37 ± 17%	38 ± 16%	15 ± 12%	32 ± 15%**

*p-value indeterminate; ** p=0.01

These data suggest that, with the exception of the 5-year relapse rate, cytogenetics have little influence on outcome for patients undergoing unrelated donor HCT for AML in CR1. In CR2, results in patients with favorable cytogenetics are somewhat better than in those with intermediate or unfavorable cytogenetics, but differences are not statistically significant. Effective GVL with protection against relapse is observed, even in high risk cytogenetic subgroups. In this retrospective study, other prognostic factors influenced outcome, but overall survival for patients with unfavorable cytogenetics appeared at least as good as previously reported with HLA-matched sibling HCT.

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 in AML and ALL patients relapsing after autologous transplant. *(Study Chairs: S. Pavletic, NIH Bethesda, MD, J Foran, University of Alabama, Birmingham, AL; Study Statistician: W. 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: W. Pérez).*

R02-14: Unrelated donor HCT in AML using reduced intensity and nonmyeloablative preparative regimens. *(Chair Chairs: M. Pulsipher, University of Utah School of Medicine, Salt Lake City, UT, B. Bolwell, Cleveland Clinic Foundation, Cleveland, OH; Study Statistician: W. Pérez).*

R03-50: Outcome and prognostic factors of adult patients with Philadelphia negative ALL who received allogeneic HCT from unrelated donors in CR1. *(Study Chair: D. Marks, Bristol Children's Hospital, Bristol, UK; Study Statistician: W. Pérez).*

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

LK04-01: Comparison of autologous HCT and allogeneic HCT for patients with acute promyelocytic leukemia (APL) 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: W. Pérez).*

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LK04-02: Transplant outcomes in patients older than 55 years with AML or myelodysplastic syndrome. (*Study Chair: S. Luger, Univ. of Pennsylvania Philadelphia, PA; Study Statistician: W. 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: W. Pérez).*

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

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

3.2 <u>Chronic Leukemia Working Committee.</u> Co-Chair: Sergio Giralt, Anderson Cancer Center, Houston, TX; Co-Chair: Jeffrey Szer, Royal Melbourne Hospital, Parkville, Australia; Co-Chair: Ann Woolfrey, Fred Hutchinson Cancer Research Center, Seattle, WA; Statisticians: Kathleen A. Sobocinski, M.S., Sergey Tarima, Ph.D.; Scientific Director: Mukta Arora, M.D.

3.2.1 Publications

CK98-03: Guilhot F, Sobocinski KA, Guilhot J, Zhang M-J, Antin JH, Bashey A, Gale RP, Litzow MR, Maharaj D, Marks DI, McCarthy PL, Schouten HC, Weiner RS, Harousseau J-L, Michallet M, Maloisel F, Blaise D, Guerci A, Giralt SA, Horowitz MM. **Comparison of HLA-identical sibling HCT versus interferon plus cytarabine (IFN/ARA-C) for chronic myelogenous leukemia (CML) in chronic phase.** *BBMT*, *In Press*. Treatment for CML evolved dramatically over the last 10 years. Three therapeutic strategies (allogeneic HCT, alpha-interferon-based therapy and imatinib) are demonstrated to produce durable cytogenetic remissions. Long-term

datas are available only for transplantation and alpha-interferon. The purpose of this study was to compare long-term outcomes of chronic phase CML patients treated with either alpha-interferon and cytarabine or HLA-identical sibling HCT, with the aim of determining subsets who may benefit from one strategy over the other. We performed a retrospective analysis of patients 15-55 years of age, with Philadelphia-positive CML, diagnosed in 1991-1996 and receiving either an HLA-identical sibling HCT or interferon combined with cytarabine for primary treatment. The transplant cohort included 373 patients transplanted within one year of diagnosis whose transplant outcomes were reported to the IBMTR. The non-transplant cohort included 186 patients treated with interferon combined with cytarabine on a French national protocol (CML 91). To adjust for differences in time to treatment and baseline patient characteristics, left-truncated multivariate Cox regression models were used. The probability of survival among patients receiving interferon and cytarabine depended on Sokal risk group: 77 (67-86)%, 67 (53-80)% and 35 (13-61)% at 6 years for low, intermediate, and high-risk patients, respectively. Transplant outcome was not associated with Sokal risk score but was associated with time to transplantation: 6-year survival was 73 (65-80)% for patients transplanted less than 6 months after diagnosis and 56 (44-67)% for those transplanted 6-12 months after diagnosis. There was a significant long-term survival advantage with transplantation for high risk CML, but not low or intermediate risk disease. We conclude that for patients with CML unable to receive imatinib therapy, a trial of interferon and cytarabine may be recommended for those with low or intermediate risk disease; those with high-risk disease should proceed to allografting as soon as an appropriate donor is identified.

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 CML.** *Submitted.* 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 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

CK00-02: Outcome of allogeneic transplantation for myelofibrosis. *(Study Chairs: K. Ballen, Massachusetts General Hospital, Boston, MA; Sergio Giralt, MD Anderson Cancer Center, Houston, TX; Study Statistician: K. Sobocinski). Analyses in progress. Oral Presentation at American Society of Hematology in December 2005.* 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 transplantation for myelofibrosis. Patients received a variety of conditioning and GVHD prophylaxis regimens. Most patients received ablative conditioning with either TBI (n=117) or busulfan (Bu) (n=150) and cyclophosphamide (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 5 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 (KPS) greater than or equal to 90%, younger age, more recent date of transplantation, and absence of blasts in peripheral blood prior to transplantation 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 transplantation 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 nonmyeloablative conditioning regimens for myelofibrosis.

CK00-05: Identical-Twin transplants for B-cell chronic lymphocytic leukemia (B-CLL). *(Study Chair: Steve 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 effect; (2) no leukemia cells in the graft; and (3) no graft exposure to therapy. 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. 11 were males; median age was 51 years (range, 37-68 years). 18 received total body radiation. None had Richter transformation. Interval from diagnosis to transplant was 27 months (5-171 months). At transplant, 8 had Rai stage 3/4 disease, 5 had >50x10^9/L lymphocytes, 10 had received $\geq$3 prior therapies, 8 had received prior fludarabine, and 5 had a prior CR, 18 engrafted and 13 achieved posttransplant CR; median time to CR was 3 months (1-5 months). Probability of 100 day survival was 89 (72-99)%. 10 subjects are alive (8 disease-free) at median follow-up of 63 months (9-116 months). Ten subjects either never achieved CR (N=6) or relapsed posttransplant (N=4). 5-year cumulative incidence of relapse was 52 (27-77)%. Estimated 5-year overall and leukemia-free survivals were 59 (34-81)% and 43 (20-67)%, respectively. Causes of death were interstitial pneumonitis (N=1) and leukemia (N=8). 5-year cumulative incidence of TRM was 5% (0-20%). We used a highly sensitive PCR (polymerase chain reaction) 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 PCR 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 month 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 pt, who relapsed with B-CLL 6 y 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 TRM and with a high-rate of durable clinical and molecular remissions. The 5-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 IV versus oral busulfan as a conditioning agent prior to transplantation. *(Study Chair: M. Horowitz; Study Statistician: K. Sobocinski). Manuscript in preparation.* Using CIBMTR data on outcome of transplants performed using oral busulfan (Bu) as part of the pretransplant conditioning regimen, a matched pairs analysis was conducted comparing these data against clinical data obtained from patients receiving intravenous (IV) busulfan in four clinical studies and two clinical amendments. The primary objective of the analysis was to compare two key clinically important outcomes in patients receiving IV Bu or oral Bu, i.e., overall survival to day 100, and the incidence of hepatic veno-occlusive disease (HVOD) and mortality through post-transplant day +28 (HVOD28). Primary matching criteria included disease, disease stage/status, stem cell source, and performance score at time of transplant; a goal of three oral-Bu matches per each IV Bu recipient was sought. A total of 216 patients (161 allo, 55 auto) were identified in the CIBMTR database that matched criteria for 101 of the 138 IV Bu patients. No matches could be found for 37 IV Bu patients. Of the 101 IV Bu patients (70 allo, 31 auto), 47 had three, 21 had two, and 33 had one CIBMTR oral Bu match(es). There were no graft failures among the patients receiving IV Bu; six (2.9%) oral Bu patients failed to engraft (p=0.19). Overall incidence of HVOD28 was 4.6% (4/83) with IV Bu and 20.3% (38/149) with oral Bu (p<0.001). Among autotransplant recipients, 100-day mortality was 0% for those receiving IV Bu and 9.3% for those receiving oral Bu (p=0.16). Among allotransplant recipients, 100-day mortality was 8.7% with IV Bu and 22.5% with oral Bu patients (p=0.015). Logistic regression analysis showed that only the mode of Bu administration was a significant factor for the risk of HVOD28, with IV Bu associated with a greatly reduced risk (p=0.004) compared to oral Bu. Bayesian analyses provided the same conclusion, and indicated that there was a >99% probability that IV Bu was superior to oral Bu with regard to the probability of HVOD28 and 100-day mortality. Logistic regression analyses by treatment group indicated that IV Bu was associated with a lower probability of 100-day mortality compared to oral Bu 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 these analyses of controlled case-matched data, there appears to be a beneficial effect of IV Bu compared to oral Bu on the outcome of HCT, with lower early mortality associated with IV Bu administration. These findings are consistent with results of other controlled and uncontrolled studies comparing IV Bu to oral Bu when either is given as a component of an HCT regimen.

CK03-02: Late relapse in long-term CML survivors. *(Study Chair: J. Douglas Rizzo, IBMTR/ABMTR, Medical College of Wisconsin, Milwaukee, WI and J. Goldman, Hammersmith, London, UK; Study Statistician: K. Sobocinski).* A*nalyses in progress.* 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 5 or more years post-HCT. Of these, the median age at HCT was 34 yrs, 60% had received TBI as part of their conditioning; 67% had received cyclosporine (CSA) and methotrexate (MTX) for GVHD prophylaxis. Among patients alive and in remission 5 yrs after HCT, the cumulative incidences of subsequent relapse at 15 yrs post-HCT were 17%, 15%, 12% and 7% for recipients of sibling transplants in first chronic phase (CP), recipients of sibling transplants not in first CP, recipients of alternative donor transplants in first CP and recipients of alternative donor transplants not in first CP respectively. The latest relapse occurred at 16 yr post HCT. Corresponding survival rates at 15 years in the patients were 85%, 83%, 80% and 75%. 174 of the 2234 patients surviving in remission at 5 years post HCT subsequently died; the causes of death were CML (2% of 5 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

CK00-03: Effect of TBI on allogeneic HCT outcome. *(Study Chair: JY Cahn, Hôpital Jean Minjo, Besancon, France; Study statistician: K. Sobocinski).*

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

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; Michael Haagenson)*.

R02-03: Comparative analysis of unrelated versus partially matched related donors for allogeneic HCT for CML. *(Study Chair: D. Porter, University of Pennsylvania Medical Center, Philadelphia, PA; Study Statistician: G. Nelson).*

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: K. Sobocinski).*

CK 04-01: 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: K. Sobocinski).*

3.3 <u>Lymphoma Working Committee.</u> Co-chair: Hillard M. Lazarus, Case Western Reserve University, Cleveland, OH; Co-Chair: Julie M. Vose, University of Nebraska, Omaha, NE; Co-Chair: Koen van Besien, University of Illinois, Chicago, IL; Statisticians: Mei-Jie Zhang, Ph.D., Jeanette Carreras, M.P.H.; Scientific Director: Parameswaran Hari, M.D.

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 HCT.** *BBMT, 2006. In press*. 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 as underweight (BMI<18), 1,725 as overweight (BMI>25-30), and 926 as obese (BMI>30) at time of HCT. Outcomes evaluated include overall survival, relapse, and lymphoma-free survival. Treatment-related mortality was similar among the normal, overweight

and obese groups; the underweight group had a higher risk of TRM (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.

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 purpose of this study was to compare the clinical outcomes of elderly (age ≥ 55 years) NHL patients with younger NHL patients (< 55 years) receiving autologous transplantation while adjusting for patient-, disease-, and treatment-related variables. 1,004 NHL patients age ≥ 55 years receiving an autotransplant between 1990 through 2000 were reviewed and compared to 2,331 NHL patients < 55 years receiving autotransplants within the same time period. Younger patients were more likely to have follicular lymphoma, have B symptoms at diagnosis, have primary refractory disease, receive marrow rather than blood as the graft source, and undergo a TBI-containing regimen. Karnofsky performance score at transplantation was similar in the two groups. Median follow-up was 40 (range 1-136) months. In multivariate analysis, older patients were more likely than younger patients to experience TRM and more likely to relapse. The risk of treatment failure and death were higher in older patients (≥ 55 years) with chemo-sensitive and unknown chemo-sensitivity to salvage therapy prior to transplant; no such differences were observed for patients with resistant chemo-sensitivity. We conclude that autologous HCT in NHL patients ≥ 55 years of age is feasible but disease-related outcome and treatment-related toxicity is statistically inferior to patients < 55 years. Further studies addressing supportive care particular to older patients and further work to identify elderly patients most likely to benefit from this approach is recommended.

LY02-01: Reduced intensity vs myeloablative conditioning for HLA matched sibling transplantation in follicular lymphoma. *(Study Chair: K. Van Biesen, University of Chicago, Chicago, IL; Study Statistician: J. Carreras). Manuscript in preparation.* ***Oral presentation at the American Society of Hematology in December 2005.*** Several new reduced intensity conditioning regimens are being investigated for allogeneic transplantation. To evaluate their effects in follicular lymphoma, we studied outcome of HLA-identical sibling transplants in 205 recipients reported to the CIBMTR between 1997 and 2002. Only patients without prior allogeneic or autologous transplantation were included. Twenty-seven patients (13%) had follicular large cell (grade III) lymphoma; the remaining had grade I or II disease. 27% had chemotherapy-resistant disease and 32% had poor performance status prior to transplantation. Conditioning regimens were categorized as myeloablative (n=120) or reduced intensity (n=85). Ablative conditioning was defined as TBI containing regimens with single fraction of ≥500 cGy, fractionated doses of ≥ 800 cGy, BU doses >9 mg/kg or melphalan doses >150 mg/m^2. We defined reduced intensity conditioning as TBI doses <500 cGy, BU doses <9 mg/kg, melphalan doses ≤150 mg/m^2 and fludarabine regimens without busulfan or melphalan. 70% of ablative conditioning was TBI based; 24% was BUCy. Melphalan based regimens were used in 23% of reduced intensity regimens, reduced dose BU in 21%, fludarabine Cy in 41% and low dose TBI in 7%. Fewer than 10% of transplants reported in 1997 used reduced intensity conditioning, about 50% in 2000 and 80% in 2002. Median recipient age was 45 (28-70) y for myeloablative

transplants vs. 50 (27-67)y for reduced intensity conditioning (p<0.001). Median time from diagnosis to transplant was 24 mo vs. 34 mo, respectively (p=0.001). Blood cells were used for 65% of ablative but 92% of reduced intensity transplants (p<0.001). GVHD prophylaxis included a calcineurin antagonist in all patients, but was combined with MTX in 86% of ablative compared to 54% of reduced intensity transplants (p<0.001). Median follow-up of survivors was 49 mo for ablative vs. 36 mo for reduced intensity HCT (p=0.004). In univariate analysis, there were no differences in acute or chronic GVHD, TRM, progression-free survival or overall survival between the two groups. The median hospital stay was slightly shorter with reduced intensity vs. ablative (25 vs. 28 days, p=0.05).There was a trend toward an increased risk of disease recurrence with reduced intensity conditioning (p=0.09). Eleven of 40 deaths with ablative conditioning vs 2 of 30 with reduced intensity conditioning were attributed to organ failure (p=0.03); 5 and 4 deaths, respectively, were attributed to GVHD (p=NS), and 8 and 11 deaths, respectively, to relapse (p=NS).

Outcomes	**Ablative (%)**	**Reduced Intensity (%)**	**P-value**
30 day mortality	8 (3-13)	6 (2-12)	0.64
100 day mortality	19 (13 - 27)	15 (8 - 24)	0.46
Acute GVHD @ 100 days, grades (2-4)	37 (28 - 46)	40 (30 - 51)	0.62
Chronic GVHD @ 1 year	44 (34 - 53)	53 (42 - 64)	0.20
TRM @ 1 year	23 (16 - 31)	20 (12 - 29)	0.57
TRM @ 3 years	25 (18-24)	24 (16-24)	0.83
Progression/Relapse @ 1 year	8 (4 - 14)	17 (9 - 25)	0.09
Progression/Relapse @ 3 years	9 (5-15)	21 (13-31)	0.03
PFS @ 1 year	68 (60 - 76)	63 (53 - 73)	0.47
PFS @ 3 years	65 (56-74)	55 (44-66)	0.14
OS @ 1year	72 (64 - 80)	72 (62 - 81)	0.90
OS @ 3 years	70 (61-77)	64 (53-74)	0.40

GVHD = graft vs host disease; TRM = treatment related mortality; PFS = progression-free survival; OS = overall survival.

In multivariate analysis, performance score and chemotherapy sensitivity were independently associated with TRM, OS and PFS, but conditioning regimen was not. There was a trend for increased risk of recurrence after RIC (RR=1.91; p=0.09). In summary, RIC is now, by far, the most common approach for allotransplantation in follicular lymphoma. In this analysis, TRM, GVHD, OS and PFS after RIC are similar to ABLAT.

3.3.3 Planned Studies

D98-10: Unrelated bone marrow transplantation 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 patients with NHL. *(Study Chair: G. Hale, St. Jude Children's Research Hospital, Memphis, TN; Study Statistician: J. Carreras).*

LY04-02: Autologous vs HLA-identical sibling transplantation for diffuse large cell lymphoma. *(Study Chair: B. Hayes-Lattin, Oregon Health Science University, Portland, OR; Study Statistician: J. Carreras).*

LY04-03: Outcomes of autologous versus allogeneic transplantation for patients with NHL with pre-existing central nervous system (CNS) 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 lymphoma after allogeneic HCT. *(Study Chair: M. Tomblyn, University of Minnesota, Minneapolis, MN; Study Statistician: J. Carreras).*

LY05-02: Clinical outcome of a second autologous HCT for patients with NHL or hodgkin disease relapsing after a first autologous HCT. *(Study Chair: S. Smith, University of Chicago, Chicago, IL; Study Statistician: J. Carreras).*

LY05-03: Allogeneic HCT with non-myeloablative or reduced intensity conditioning for relapsed and refractory hodgkin disease. *(Study Chairs: M. Devetten, University of Nebraska Medical Center, Omaha, NE; P. Anderlini, University of Texas M.D. Anderson Cancer Center, Houston, TX; Study. Statistician: J. Carreras).*

3.4 Plasma Cell Disorder Working Committee. Co-Chair: Donna Reece, Princess Margaret Hospital, Toronto, Ontario, Canada; Co-Chair: David H. Vesole, St. Vincent's Comprehensive Cancer Center, NY, NY; Co-Chair: Hartmut Goldschmidt, University of Heidelberg, Heidelberg, Germany; Statisticians: Mei-Jie Zhang, Ph.D, Waleska S. Pérez, M.P.H.; Scientific Director: Parameswaran Hari, M.D.

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**. *Submitted.* The purpose of this study was to determine the outcome of high dose therapy with autologous HCT in patients with primary systemic amyloidosis. 107 recipients of autologous HCT for amyloidosis from 48 transplant centers were reported to the CIBMTR between 1995 and 2001. Hematologic and organ responses were assessed at 100 days and 1 year. Transplant-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 affected site (bone marrow, kidney, liver, heart) in 28 of 77 patients (36%); the 1 year responses included complete response (CR)(16%), partial response (PR) (16%), stable disease (SD) (31%) and disease progression (11%). With a median follow up of 30 months, the 1 and 3-year survival rates were 66% (95% CI 56 - 75) and 56% (95% CI 45 - 66), respectively. Day + 30 TRM was 18 (CI 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, 3-year survival was comparable to single center results. Of note, TRM was higher than that reported by single centers which may reflect differences in patient selection and/or experience in treating this

challenging disease. A better understanding of the recently recognized prognostic factors and more stringent patient selection will hopefully result in lower TRM and improved survival.

3.4.2 Preliminary Results

MM01-01: Autologous or allogeneic stem cell transplantation in patients with Waldenstrom macroglobulinemia. *(Study Chair: A. Anagnostopoulos, Alexandra Hospital, Athens, Greece; Study Statistician: WS. Pérez). Manuscript in preparation.* The role of HCT in Waldenstrom macroglobulinemia (WM) has not been extensively studied. We performed a retrospective analysis of 36 patients with WM who received autologous (N=10) or allogeneic (N=26) HCT. Diagnostic and response criteria for WM were based on the Second International Workshop definitions. The following outcomes were analyzed: non-relapse mortality, relapse, progression-free survival and overall survival. Median age at the time of HCT was 51 years and median time from initial treatment to HCT was 29 months. 78% of the patients had $\geq$2 prior chemotherapy regimens and 52% had disease resistant to salvage chemotherapy. 58% of patients in the allogeneic HCT group received myeloablative conditioning regimens containing TBI. Only 5 of 26 allogeneic HCT recipients received non-myeloablative/reduced intensity conditioning. After a median follow-up of 65 months, 21 of 36 (58%) patients have died. Primary disease accounted for 29% and 25% of the deaths in the allogeneic and autologous HCT groups, respectively. Relapse rates at 3 years were 29% and 24% for the allogeneic and autologous HCT groups, respectively. Progression-free survival rates at 3 years were 31% and 65%, and overall survivals were 46% and 70% for the allogeneic and autologous HCT group, respectively. We conclude that autologous HCT is a safe (non-relapse mortality of 11%) and feasible treatment option for patients with WM, especially for those who present with adverse prognostic factors. Nucleoside analogues and alkylators that may affect stem cell mobilization should be avoided in patients who may be candidates for autologous HCT. Allogeneic HCT carries a much higher non-relapse mortality risk (40%) and should not be considered outside the context of a clinical trial.

3.4.3 Planned Studies

MM00-02: Outcomes following syngeneic HCT for multiple myeloma: A matched comparison to autologous transplantation. (*Study Chair: A. Bashey, University of California-San Diego, La Jolla, CA; Study Statistician: WS. Pérez*).

MM02-01/D01-117: Comparison of second autologous transplant versus related or unrelated non-myeloablative 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 vs 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, WI; 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 Statistician: WS. Pérez).*

3.5 Solid Tumors Working Committee. Co-Chair: Patrick J. Stiff, Loyola University Medical Center, Maywood, IL; Co-Chair: Richard Childs, National Heart, Lung and Blood Institute, Bethesda, MD; Co-Chair: Didier Blaise, Institut Paoli Calmettes, Marseille, France; Statistician: Brent Logan, Ph.D., Kathleen A. Sobocinski, M.S.; Scientific Director: Mukta Arora, M.D.

3.5.1 Preliminary Results

BC99-01: C**IBMTR/EBMT review of allogeneic HCT in metastatic breast cancer**. (*Study Chairs: N.T. Ueno, M.D. Anderson Cancer Center, Houston, TX; D. Niederwieser, University of Leipzig, Leipzig, Germany; Study Statistician: J. Douglas Rizzo; Collaborators: EBMT). Manuscript in preparation.* To determine the feasibility and efficacy of allogeneic HCT for metastatic breast cancer, we reviewed data from 18 IBMTR/EBMT centers on 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 (PD). 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 (PBSC) 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 2 years was 22%. Median survival time and median time to progression were both 8 months; 15% remained free of progression at 2 years. Progression-free survival at 2 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: Utility of single versus tandem autotransplants for advanced testes/germ cell cancer. *(Study Chair: H. Lazarus, Case Western Reserve University, Cleveland, OH; Study Statistician: W. Perez/J. Carreras) Manuscript in preparation.* While tandem autografts are commonly used to treat patients with advanced testis cancer, their value compared to a single transplant is unknown. To evaluate the results of high-dose chemotherapy and autologous stem cell re-infusion in relapsed testicular/germ cell tumor patients. Data were evaluated from 300 patients who underwent autologous transplantation between 1989-2002 in 76 centers worldwide. We compared results for those patients intended to undergo tandem autograft procedures (N=102) versus patients in whom a second autograft was not planned (N=198). The probability of 5-year survival was 35 (CI: 25–46)% in the planned tandem transplant group compared to 42 (35-49)% in the group not planned to have a second transplant (p=0.29). The probability at 5 years of progression-free survival for these two groups was 34 (25-44)% and 38 (31–45)%, respectively (p=0.50). In univariate analysis, despite the planned tandem autograft

group having significantly more advanced disease at diagnosis and greater likelihood of exhibiting cisplatin-resistance, patients intended to receive tandem transplants had lower TRM at one year (3% versus 10%, p=0.02). In multivariate analysis, adverse risk factors for all patients for relapse included at least one salvage attempt before autografting, residual disease using serum tumor markers or imaging studies at time of transplant or autograft performed beyond 12 months from initial diagnosis. Although in multivariate analysis the planned tandem autograft group had significantly lower TRM (p=0.031), these patients had a significantly increased risk of relapse beyond 9 months after first transplant compared to the planned single transplant population (p=0.030). Tandem autotransplants do not appear to be superior to planned single transplants. Testicular/germ cell tumor patients at highest risk for poor outcome, however, may be chosen specifically to receive tandem transplants introducing an inherent selection bias. Given these findings, routine use of tandem autografts in relapsed/refractory testis/germ cell tumors does not appear justified until transplant regimens are developed that incorporate active agents, specific for this tumor type, in escalated dose.

3.5.2 Planned Studies

ST99-03: Transplants for soft tissue sarcoma. *(Study Chair: K. Antman, Columbia University, New York, NY; Study Statistician: W. Perez)*..

ST00-02: Allografts for renal cell cancer. *(Study Chair: A John Barrett, NHLBI(National Heart, Lung, and Blood Institute)/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*

3.6 <u>Pediatric Cancers Working Committee.</u> Co-Chair: Bruce M. Camitta, Midwest Children's Cancer Center, Medical College of Wisconsin, Milwaukee, WI; Co-Chair: Stephan Grupp, Children's Hospital of Philadelphia, Abramson Pediatric Research Center, Philadelphia, PA; Co-Chair: Stella Davies, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH; Statisticians: TBD, Mei-Jie Zhang, Ph.D.; Scientific Director: Mary Eapen

3.6.1 Publications

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 transplants for acute leukemia in children less than 18 months.** *J Clin Oncol, 2006. In press.* Outcomes in children (<18 months at diagnosis) 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 was 6%, 15% and 31% after HLA-matched sibling, unrelated donor bone marrow and unrelated donor cord blood transplantation, respectively. Risks of relapse, overall and LFS 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 LFS 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 AML in CR1 using the same eligibility criteria as is currently used for those with HLA-matched sibling donors.

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 S. **Outcomes after HLA-matched sibling transplants 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.** *Submitted.* ***Oral presentation at the American Society of Hematology in December 2005.*** 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 vs. 8 years) and less likely to have combined marrow and extra-medullary relapse (12% vs. 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 repalse and the transplant conditioning regimen used. For children with early first relapse (<36 months), risk of a second relapse was significantly lower with TBI containing transplant regimens (RR 0.50, 95% CI 0.34-0.73, p=0.0004) than with chemotherapy regimens. For children with a late relapse, risk of second relapse were similar after TBI-containing regimens and chemotherapy but significantly higher after HCT with non-TBI containing 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.

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: C. Muehlenbein). 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 (UCB) 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, TRM, relapse, LFS) and overall survival. Cumulative incidence rates were calculated for neutrophil recovery, grades 2 – 4 acute GVHD, chronic GVHD, TRM and relapse. Probabilities of LFS and overall survival were calculated using the Kaplan-Meier estimator. 95% confidence intervals were calculated using standard techniques. Variables were tested using a time-varying covariate method to determine whether the proportional hazards assumption was met. All variables met this assumption except the variable for cytogenetic risk group such that there was an early and late effect on overall mortality. 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 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 in primary induction failure or in relapse at transplantation. There were no significant differences in risks of relapse among those transplanted in CR1 and CR2. Treatment failure (relapse or death; inverse of LFS) was

significantly higher in older recipients, those transplanted in primary induction failure or relapse and poor risk cytogenetics. There were no significant differences in risks of treatment failure among those transplanted in CR1 and CR2. Overall mortality was significantly higher in older recipients, those transplanted in primary induction failure or relapse and those with intermediate or poor risk cytogenetics. There were no significant differences in risks of treatment failure among those transplanted in CR1 and CR2. The effect of cytogenetics on overall mortality was time dependent such that there was an early and late effect dependent on risk group. For patients with poor risk cytogenetics, the effect was early, mortality was significantly higher at 2 months and thereafter. For patients with intermediate risk cytogenetics this effect was later, mortality was higher at 6 months and thereafter. 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: C. Muehlenbein).*

R02-34: Unrelated bone marrow transplantation in children with Philadelphia chromosome positive ALL. *(Study Chair: H Frangoul, Vanderbilt University Medical Center, Nashville, TN; Study Statistician: C. Muehlenbein*).

PC03-05: Optimal therapy for patients (<18) with ALL and isolated central nervous system relapse: comparison of overall and leukemia free survival after chemotherapy and HCT. *(Study Chair: Mary Eapen, CIBMTR, BM Camitta, Childrens Hospital of Wisconsin, Milwaukee, WI; Study Statistician: C. Muehlenbein).*

PC04-02: Comparison of outcomes after reduced intensity and standard dose conditioning transplants in children with ALL and AML. *(Study Chair*: *M. Pulsipher, University of Utah Medical Center, Salt Lake City UT; R. Kadota, Children's Hospital of San Diego, San Diego, CA, M. Kletzel, Northwestern University Children's Memorial Hospital, Chicago IL; Study Statistician: C. Muehlenbein)*.

PC05-01: HCT for children with non-hodgkin lymphoma. *(Study Chair: G. Hale, St. Jude Children's Research Hospital, Memphis, TN, T. Gross, Children's Hospital of Columbus, Columbus, OH; Study Statistician: C. Muehlenbein).*

PC05-02: Outcome of unrelated HCT for children with advanced ALL. *(Study Chair: E. Nemecek, Oregon Health & Science University; Study Statistician: C. Muehlenbein).*

3.7 <u>Non-Malignant Marrow Disorders Working Committee.</u> Co-Chair: Judith C.W. Marsh, St. George's Hospital Medical School, London, UK; Co-Chair: Ricardo Pasquini, Hospital de Clinicas, Curitiba, Brazil; Co-Chair: Mark Walters, Children's Hospital-Oakland, Oakland, CA; Statisticians: Jeanette Carreras, M.P.H., Sergey Tarima, Ph.D; Scientific Director: Mary Eapen, M.D.

3.7.1 Publications

AA00-02: Roy V, Pérez WS, Eapen M, Marsh JC, Pasquini M, Pasquini R, Mustafa MM, Bredeson CN; Non-Malignant Marrow Disorders Working Committee of the International Bone

Marrow Transplant Registry. **Bone marrow transplantation for Diamond-Blackfan anemia.** *BBMT 11: 600-608, 2005.* Patients with Diamond-Blackfan anemia who are unresponsive to or intolerant of corticosteroids, experience treatment failure with other treatments, develop additional cytopenias or clonal disease, or opt for curative therapy are often treated with allogeneic HCT. We studied 61 patients receiving transplants for Diamond-Blackfan anemia between 1984 and 2000. The median age was 7 years (range, 1-32 years). Among 55 patients with available transfusion information, 35 (64%) had received 20 or more units of blood before transplantation. Donors for most patients (67%) were HLA-matched relatives. The median time to neutrophil recovery was 17 days (range, 10-119 days) and to platelet recovery was 23 days (range, 9-119 days). Five patients did not achieve neutrophil engraftment. The 100-day mortality rate was 18 (10-29)%. Grades II to IV acute GVHD occurred in 28% and chronic GVHD in 26%. The 3-year probability of overall survival was 64 (50-74)%. In univariate analysis, a Karnofsky score ≥90% and transplantation from an HLA-identical sibling donor were associated with better survival. These data suggest that allogeneic bone marrow transplantation is effective for the treatment of Diamond-Blackfan anemia. Transplantation before deterioration of performance status may improve survival.

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 donors for severe aplastic anemia.** *Submitted*. For patients with acquired severe aplastic anemia without an HLA-matched sibling donor and not responding to immunosuppressive treatment, bone marrow transplantation 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, mortality rates transplant-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.

3.7.2 Preliminary Results

AA98-03: HLA-identical sibling bone marrow transplantation for severe aplastic anemia: Results of a randomized controlled trial. *(Study Chair: R. Champlin, MD Anderson Cancer Center, University of Texas, Houston, TX; Study Statistician: WS. Pérez). Manuscript in preparation.* Addition of antithymocyte globulin (ATG) to a preparative regimen of high dose CY has been advocated to enhance engraftment after allogeneic HCT for treatment of aplastic anemia. 134 patients with aplastic anemia were randomized to receive CY alone or in combination with ATG as a preparative regimen for allogeneic bone marrow transplantation from an HLA-identical sibling donor. Patients received cyclosporine and methotrexate as post transplant immunosuppressive therapy. The bone marrow was not T-cell depleted and there was no planned treatment with hematopoietic growth factors. Patients were treated between October 1994 and October 2001. Median age (range) was 25 (1-51) years and median time from diagnosis to transplant was 2 (<1-109) months. Sixty-seven (52%) patients had received

no prior therapy. There were no significant differences between the two groups for age, sex, donor-recipient sex-match, interval from diagnosis to transplant, prior treatment, CMV (cytomegalovirus) seropositivity, year of transplant, performance status or nucleated cell dose. Patients in the Cy+ATG were more heavily transfused prior to transplant. Univariate outcomes, with a median follow-up of 60 (5-103) months were as follows:

Outcomes	Cy (N=62)	Cy+ATG (N=72)	P-value
ANC>0.5x10^9/L @ 28 days	79 (64 - 91)%	81 (66 – 92)%	0.85
ANC>0.5x10^9/L @ 100 days	95 (71 - 100)%	97 (69 - 100)%	0.86
Acute GVHD @ 100 days, grades (2-4)	18 (9 - 28)%	13 (6 - 22)%	0.46
Chronic GVHD @ 1 year	15 (7 - 25)%	22 (12 – 33)%	0.32
Chronic GVHD @ 3 years	17 (9 - 28)%	29 (19 – 41)%	0.12
Overall survival @ 1year	84 (74 - 92)%	90 (82 – 96)%	0.31
Overall survival @ 3years	76 (64 - 86)%	81 (70 – 90)%	0.51

Among 1-year survivors, 48 of 51 (94%) patients and 55 of 61 (90%) patients in the Cy and Cy+ATG groups, respectively, achieved transfusion independence. Twelve patients received second transplants, all for graft failure: 8 in the Cy alone group and 4 in the Cy+ATG group (p=0.2). Two patients prepared with Cy alone died of graft failure vs. none of the patients receiving Cy + ATG. In conclusion, this study did not detect a significant benefit from the addition of ATG to Cy as a preparative regimen for patients with severe aplastic anemia; however, the sample size was relatively small, limiting power to detect small differences.

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: J. Carreras). Additional analyses in progress.* The use of peripheral blood stem cells (PBSC) as an alternative stem cell source to bone marrow (BM) for allogeneic transplantation is increasing. Most studies of PBSC transplantation have included patients with malignancies. Limited data exist regarding the relative merits of PB versus BM as a graft source in transplantation for non-malignant marrow disorders. We compared results of 151 HLA-identical sibling PBSC transplants with results of 722 HLA-identical sibling bone marrow transplants for acquired aplastic anemia. Transplants were performed between 1995 and 2000 in 240 centers. The two patient groups were similar in age at transplantation, sex, Karnofsky performance score, use of growth factors post-transplant, and type of GVHD prophylaxis. PBSC recipients were more likely than BM recipients to receive TBI-based conditioning (12% versus 5%) and tended to have a longer interval between diagnosis and transplantation (median 4 versus 2 months). Recovery of neutrophils and platelets was significantly faster with PBSC than with bone marrow transplants (median time to ≥0.5x10^9/L neutrophils 13 versus 19 days, p<0.001; median time to ≥20x10^9/L platelets 25 versus 15 days, p<0.001). The cumulative incidences of acute GVHD at 100 days post-transplant were 22 (15-30)% versus 17 (14-21)% with PBSC and BM, respectively (p=0.22). The 2-year cumulative incidences of chronic GVHD were 29 (20-38)% versus 16 (13-19)% with PBSC and BM, respectively (p < 0.01). The 2-year probabilities of survival were 67 (58-74)% and 80 (76-82)%, with PBSC and BM, respectively (p < 0.05). In conclusion, other than early hematopoietic recovery, our study suggests no advantage of PBSC over BM in HLA-identical sibling transplantation for acquired aplastic anemia and raises concern about possibly poorer long-term outcomes with PBSC. Further evaluation of PBSC transplantation for aplastic anemia should be done in the context of controlled clinical trials.

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.

D01-04: Unrelated donor transplantation for Fanconi Anemia: Analysis of prognostic factors impacting engraftment and survival. *(Study Chair: J. Wagner, University of Minnesota, Minneapolis, MN; Study Statistician: M. Eapen). Manuscript in preparation.* 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 vs. 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% vs. 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.

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.

AA01-01: Matched related donor HCT for sickle cell disease. *(Study Chair: J. Panepinto, Medical College of Wisconsin, Milwaukee, WI; Study Statistician: J. Carreras). Manuscript in preparation.* ***Poster presentation at the American Society of Hematology in December 2005.*** Allogeneic HCT is the only known therapy to cure sickle cell disease though few patients receive this therapy. We report 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 predominant genotype. Indications for HCT were predominantly 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 $\geq$ 10 red blood cell transfusions prior to HCT. Twenty patients (26%) had poor performance scores prior to transplantation. BuCy 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 $\geq$20,000/ul at day 100 was 93% (95% confidence interval [CI], 86-98)%. The probabilities of grades 2-4 acute GVHD at day 100 and chronic GVHD at 5 years were 10% (95% CI, 4-19%) and 22% (95% CI, 12-33%), respectively. Sixty-five of 68 patients are alive after HCT with a median follow up of 5 years. The 5-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 predominant 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 (MRI) of the brain pre- and post-transplant, 8 showed stable disease post transplant, one showed improvement and one had a worsening MRI. 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.

3.7.3 Planned Studies

AA02-01: Allogeneic HCT with fludarabine-based conditioning for severe and very severe aplastic anemia. *(Study Chair: M. Sabloff, Ottawa Hospital, Ottawa, Ontario, Canada; Study Statistician: J. Carreras).*

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).*

3.8 <u>Immune Deficiencies/Inborn Errors Working Committee (previously Immune Deficiency and Metabolic Disorders Working Committee).</u> Co-Chair: A. Filipovich, Children's Hospital Medical Center; Cincinnati, OH; Co-Chair: Mitchell Horwitz, Medicine/Cellular Therapeutics, Duke University Medical Center, Durham, NC; Co-Chair: Carmem Maria Sales-Bonfim, Federal University of Parana, Rua General Carneiro, Curitiba, Brazil; Statisticians: Seira Kurian. M.D., M.S., M.P.H., Sergey Tarima, Ph.D.; Scientific Director: Mary Eapen

3.8.1 Preliminary Results

ID98-05: HCT for infantile osteopetrosis. *(Study Chair: A. Fasth, Queen Silvia Children's Hospital, Goeteberg, PJ Orchard, University of Minnesota, Minneapolis, MD.; 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. BuCy (77%) was the most frequently used preparative regimen; 18% 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: R.M. Egeler, Leiden University Medical Center, Leiden, The Netherlands; Study Statistician: M. Eapen). Manuscript in preparation.* Langerhans cell histiocytosis (LCH) is a poorly understood and occasionally aggressive disorder that features lesional cells akin to Langerhans cells. We studied the results of HCT for LCH through the collaborative use of three large observational databases. The study included 22 allogeneic transplantations (HLA-identical and non-identical related as unrelated donors) for LCH reported to the CIBMTR, the EBMT and the general 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 for LCH, 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 1 and 2 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 in LCH is feasible for patients who fail conventional therapy, TRM is high. It is uncertain whether newer approaches in transplantation such as reduced-intensity conditioning regimens may lower TRM.

3.8.2 Planned Studies

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

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 Nat'l Medical Center, Washington, DC; Study Statistician: S. Kurian).*

ID02-02: Descriptive study of outcomes after HCT for leukocyte adhesion deficiency. *(Study Chair: N. Farinha, Portugal; Study Statsitician: S. Kurian).*

ID04-01: HCT for X-linked lymphoproliferative syndrome. *(Study Chair: T. Gross, M.D., Columbus Hospital, Columbus, OH, G. Hale MD, St. Jude's Children's Research Hospital, Memphis, TN; Study Statistician: S. Kurian).*

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: S. Kurian).*

ID05-01: Unrelated HCT for life-threatening hemophagocytic disorders *(Study Chair: Scott Baker, University of Minnesota, Minneapolis M; Study Statistician: S. Kurian).*

3.9 Autoimmune Disorders Working Committee. Co-Chair: Richard Nash, Dept. of Transplantation Biology, Fred Hutchinson Cancer Research Center, Seattle, WA; Co-Chair: Harold Atkins, Ottawa General Hospital, Ottawa, Ontario, Canada; Statisticians: Brent Logan, PhD, Manisha Kukreja, M.B.B.S., M.P.H.; Scientific Director: Marcello Pasquini, M.D.

3.9.1 Planned Studies

AI05-02: The Effect of allogeneic HCT on the activity and pProgression of multiple sclerosis: A cross-sectional study. *(Study Chair: Richard Nash, MD, Fred Hutchinson Cancer Research Center, Seattle, WA).*

3.10 GVHD Working Committee. Co-Chair: A. John Barrett, National Heart, Lung and Blood Institute, Bethesda, MD; Co-Chair: Olle Ringdén, Huddinge University, Huddinge, Sweden; Co-Chair: Claudio Anasetti, H. Lee Moffitt Cancer Center and Research Institute, Moffitt Cancer Center, Tampa FL; Co-Chair: Steven Pavletic, National Cancer Institute, Bethesda, MD; Statisticians: Sharavi Gandham, M.S., Tao Wang, Ph.D.; Scientific Director: Mukta Arora, M.D, M.S.

3.10.1 Publications

GV98-07: Hakumei Oh, Fausto R. Loberiza, Jr, Mei-Jie Zhang, Olle Ringden, Hideki Akiyama, Takayoshi Asai, Shuichi Miyawaki, Shinichiro Okamoto, Mary M. Horowitz, Joseph H. Antin, Asad Bashey, Jennifer M. Bird, Matthew H. Carabasi, Joseph W. Fay, Robert Peter Gale, Roger H. Giller, John M. Goldman, Gregory A. Hale, Richard E. Harris, Jean Henslee-Downey, Hans-Jochem Kolb, Mark R. Litzow, Philip L. McCarthy, Steven M. Neudorf, Derek S. Serna, Gerard Socie, Pierre Tiberghien, and A. John Barrett. **Comparison of GVHD and survival after HLA-identical sibling HCT in ethnic populations**. *Blood 2005;105 1408-1416.* The association between ethnicity and the incidence of GVHD and other clinical outcomes is controversial. We compared results of HLA-identical sibling bone marrow transplants for leukemia among different ethnic populations, including 562 Japanese, 829 Caucasian Americans, 71 African Americans, 195 Scandinavians and 95 Irish, performed between 1990 and 1999. Results in adults and children were analyzed separately. Multivariate analyses of adult patients showed that Caucasian, African Americans and Irish had significantly higher risks of acute GVHD than Japanese or Scandinavians (RR 1.77, $p<0.0001$, RR 1.84, $p<0.006$, RR 2.22, $p<0.001$, respectively). Caucasian Americans, African Americans and Irish, but not Scandinavian patients had a significantly higher risk of early (1^{st} 3 months after transplant) TRM compared with Japanese (RR 2.99, $p<0.0001$, RR 5.88, $p<0.0001$, RR 2.66, $p<0.009$, respectively). No differences in the risk of chronic GVHD, relapse, and overall survival were noted. In the pediatric cohort (limited to Japanese and Caucasian Americans), Caucasian Americans had a significantly higher risk of acute (RR 1.93, $p=0.04$) and chronic (RR 3.16, $p=0.002$) GVHD. No differences in other clinical outcomes were noted. Our findings suggest that ethnicity may influence the risk of GVHD, although overall survival after transplantation remains similar.

GV98-09: Jean-Yves Cahn, John P. Klein, Stephanie J. Lee, Noe¨ l Milpied, Didier Blaise, Joseph H. Antin, Ve´ronique Leblond, Norbert Ifrah, Jean-Pierre Jouet, Fausto Loberiza, Olle Ringden, A. John Barrett, Mary M. Horowitz, and Gerard Socie. **Prospective evaluation of 2 acute GVHD grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire, Dana Farber Cancer Institute, and International Bone Marrow Transplant Registry (IBMTR) prospective study**. *Blood. 2005; 106:1495-1500.* The most commonly used grading system for acute GVHD was introduced 30 years ago by Glucksberg; a revised system was developed by the International Bone Marrow Transplant Registry (IBMTR) in 1997. To prospectively compare the 2 classifications and to evaluate the effect of duration and severity of acute GVHD on survival, we conducted a multicenter study of 607 patients receiving T-cell replete allografts, scored weekly for acute GVHD in 18 transplantation centers. Sixty-nine percent of donors were HLA-identical siblings and 28% were unrelated donors. The conditioning

regimen included total body irradiation in 442 (73%) patients. The 2 classifications performed similarly in explaining variability in survival by acute GVHD grade, although the Glucksberg classification predicted early survival better. There was less physician bias or error in assigning grades with the IBMTR scoring system. With either system, only the maximum observed grade had prognostic significance for survival; neither time of onset nor progression from an initially lower grade of acute GVHD was associated with survival once maximum grade was considered. Regardless of scoring system, acute GVHD severity accounted for only a small percentage of observed variation in survival. Validity of these results in populations receiving peripheral blood transplants or non-myeloablative conditioning regimens remains to be tested.

GV00-01: Jörg D. Seebach, Georg Stussi, Jakob R. Passweg, Fausto R Loberiza Jr, James L. Gajewski, Armand Keating, Martin Goerner, Philip A. Rowlings, Pierre Tiberghien, Gerald J. Elfenbein, Robert Peter Gale, Jon J. van Rood, Vijay Reddy, Eliane Gluckman, Brian J. Bolwell, Thomas R. Klumpp, Mary M. Horowitz, Olle Ringdén, A. John Barrett. **ABO Blood group carrier in allogeneic HCT revisited.** *BBMT, 2005; 11: 1006-1013.* Some reports show a worse HCT outcomes when outcome donor and recipient are mismatched for ABO-blood groups. These studies, however, included small and heterogenous study populations and did not consider bidirectional ABO-incompatibility separately. Since the issue remains controversial, we analyzed the impact of ABO-mismatch on the overall survival, TRM, and occurrence of acute and chronic GvHD in a large homogenous group of patients undergoing allogeneic HCT. 3103 patients with early disease stage leukemia, transplanted between 1990 and 1998 with bone marrow from an HLA-identical sibling were studied. Median follow-up was 54 months. 2108 (68%) donor-recipient pairs were ABO identical, 451 (15%) had a minor, 430 (14%) a major and 114 (4%) a bidirectional ABO-mismatch. The groups did not differ significantly in patient or donor characteristics from one another except for more female-to-male gender mismatch in the bidirectional ABO mismatch group (p=0.017). In multivariate models of overall survival, TRM, and grade II-IV acute GVHD, there were no significant differences among the 4 groups. Bi-directional ABO mismatch was associated with a significantly higher risk of grade III-IV acute GVHD (hazards ratio 1.869, 95% CI, 1.192-2.93, p=0.006). Patients with major ABO mismatch received RBC (red blood cell) transfusions (p=0.001) for a longer time post-transplant and had a slightly slower neutrophil recovery (p<0.001). There is no evidence of a substantial effect of ABO blood group incompatibility on the outcome of conventional HCT among patients with leukemia.

GV02-01: Hanna J. Khoury, MD, Fausto R. Loberiza Jr, MD, MS, Olle Ringdén, MD, PhD, A. John Barrett, MD, FRCP, Brian J. Bolwell, MD, Jean-Yves Cahn, MD, Richard E. Champlin, MD, Robert Peter Gale, MD, PhD, Gregory A Hale, MD, Alvaro Urbano-Ispizua, MD, Rodrigo Martino, MD, Philip L. McCarthy, MD, Pierre Tiberghien, MD, PhD, Leo F. Verdonck, MD, PhD, Mary M. Horowitz, MD, MS. **Impact of post transplant G-CSF on outcomes of allogeneic HCT.** *Blood, First Edition Paper, prepublished online October 20, 2005.* 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 BM, 609 recipients of HLA-identical PBSC, and 675 recipients of unrelated donor BM transplants. 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 mo (range, 2-87) months. G-CSF shortened the post-transplant neutropenic period, but did not affect TRM 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, TRM, LFS, 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: S. Gandham). 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 CNS involvement. Six of the cytogenetic only relapses occurred in children with CML. Two patients had isolated extramedullary relapse, one testicular and one CNS. 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; P.L. McCarthy, Roswell Park Cancer Institute, Buffalo, NY; Study Statisticians: K. Sobocinski, M.J. Zhang). Manuscript in preparation.* Related HLA-matched 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 $\geq$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 BuCy+/-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 $\geq$40 yrs p<0.0001 and RR=1.55 for 20-39 yrs p=0.018 versus age <20 yrs) and conditioning regimen (RR=1.6 for CyTBI+/-other versus BuCy+/-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 pretransplant 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: S. Gandham).*

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

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

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

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

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

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

GV05-01: Grade and duration of acute GVHD and relapse rate. *(Study Chair, Shin Mineishi, M.D., University of Michigan, Ann Arbor; Study Statistician: S. Gandham).*

GV05-05: DLI after non-myeloablative HCT. *(Study Chair, Ronald Sobecks, M.D., Cleveland Clinic Foundation, Ohio; Study Statistician: S. Gandham).*

3.11 <u>Graft Sources and Manipulation Working Committee.</u> Co-Chair: John E. Wagner, University of Minnesota, Minneapolis, MN; Co-Chair: Hans Johnsen, Dept. of Hematology, Herlev Hospital, University of Copenhagen, DK; Co-Chair: Adrian Gee, Baylor College of Medicine, Houston, TX; Statisticians: Mei-Jie Zhang, Ph.D., M.S. Statistician, TBD; Scientific Director: Mary Eapen, M.D.

3.11.1 Publications

HC98-02: Schmitz N, Eapen M, Horowitz MM, Loberiza FR, Zhang M-J, Klein JP, Rizzo JD, Gratwohl A, and Champlin RE. **Long term outcome of patients transplanted with mobilized blood or bone marrow: A report from the CIBMTR and the EBMT.** *Submitted.* We previously compared outcomes after allogeneic PB and BM transplantation in 824 patients with leukemia, age $\geq$ 20 years and transplanted in 1995-1996. As the late consequences of PB transplantation are largely unknown, we report follow-up information obtained on 483 surviving patients from the initial cohort, 173 recipients of PB and 310 recipients of BM grafts. With longer follow up,

chronic GVHD remained more frequent after PB transplantation compared to BM (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 PB transplants for patients with advanced CML but survival was lower after PB 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 PB and BM transplantation in acute leukemia. These data suggest cautious use of PB grafts for allogeneic transplantation in good risk patients as higher risks of chronic GVHD may increase late mortality.

3.11.2 Preliminary Results

HC98-05 (updated analysis): Unrelated donor HCT in children with acute leukemia: Risks and benefits of umbilical cord blood (CB) versus bone marrow (BM). *(Study Chairs: Pablo Rubinstein, New York Blood Center, New York, NY and John Wagner, University of Minnesota, Minneapolis, MN). Manuscript in preparation.* ***Oral presentation at the American Society of Hematology in December 2005.*** Though CB is an accepted alternative to BM for HSCT in children, the selection of CB over BM remains controversial. Therefore, we compared the results of 492 unrelated donor BM and 508 CB transplants in patients younger than 16 years of age and transplanted in 1995-2003. Median follow up was 45 and 59 months for CB and BM recipients, respectively. Compared to BM recipients, CB recipients were younger, less likely to be Caucasian, more likely to have advanced disease at HCT, less likely to receive irradiation for conditioning and more likely to receive cyclosporine for GVHD prophylaxis. 7% of CB recipients were matched at HLA A, B (low resolution) and DRB1, 40% were mismatched at a single locus and 53% were mismatched at 2 loci. 75% of BM recipients were matched and 25% were mismatched at a single locus. Neutrophil recovery (≥500/ul) at day 42 depended on graft type and cell dose: 97% with BM, 86% with matched CB, 79% with high cell dose (>0.3 x 10^8/kg) CB graft mismatched at 1 or 2 loci and 64% with low cell dose (≤0.3 x 10^8/kg) CB grafts. Rates of grades 2-4 acute GVHD were 70% with mismatched BM, 50% with matched BM, 40% with mismatched CB and 20% with matched CB. Corresponding rates of chronic GVHD were 35%, 33%, 17% and 27%. The relative efficacy of CB and BM transplantation depended on HLA disparity and CB cell dose as shown in the Table below. Children receiving matched CB had significantly lower risks of treatment failure and overall mortality than those receiving matched BM; children receiving high cell dose CB mismatched at 1 locus had risks similar to those receiving matched BM. Children receiving low cell dose CB mismatched at 1 locus and CB mismatched at 2 loci (any cell dose) had higher risks of treatment failure and mortality than matched BM recipients during the first 3 months after transplantation; among children surviving the first 3 months, subsequent risks were similar to children receiving BM. The 3-year probability of LFS was highest after matched CB transplants (60%); LFS probabilities were similar with matched BM and high cell dose CB mismatched at 1 locus (40% and 41%, respectively). Probabilities were lower after mismatched BM, low cell dose CB mismatched at 1 locus and CB mismatched at 2 loci (30%, 36% and 33%, respectively). These data support use of matched CB grafts or CB mismatched at 1 locus with a high cell dose for children needing HCT, whether or not a matched BM donor is available; low cell dose or 2-loci mismatched CB grafts may provide a reasonable alternative when a matched BM donor is not available or for those whose disease requires immediate transplantation.

	Treatment failure			Overall mortality		
	N	**Relative Risk (95% confidence interval)**	**P-value**	**N**	**Relative Risk (95% confidence interval)**	**P-value**
BM matched	368	1.00		368	1.00	
BM 1-Ag mismatched	123	1.26 (0.98 – 1.62)	0.07	123	1.22 (0.93 – 1.59)	0.15
CB matched	35	0.52 (0.30 – 0.92)	0.02	36	0.54 (0.30 – 0.97)	0.04
CB 1-Ag mismatched, high dose	157	0.95 (0.75 – 1.22)	0.71	157	0.96 (0.75 – 1.25)	0.78
CB 1-Ag mismatched, low dose	44			44		
First 3 months		1.85 (1.14 – 2.99)	0.01		2.35 (1.44 – 3.83)	0.001
After the first 3 months		0.69 (0.35 – 1.35)	0.71		0.73 (0.37 – 1.42)	0.35
CB 2-Ag mismatched, any dose	266			266		
First 3 months		1.75 (1.36 – 2.60)	<0.001		2.06 (1.57 – 2.71)	<0.001
After the first 3 months		0.87 (0.65 – 1.16)	0.66		0.94 (0.70 – 1.25)	0.66

D00-65: Outcomes after unrelated donor peripheral blood stem cell and bone marrow transplants. *(Study Chair: C. Anasetti, H. Lee Moffitt Cancer Center and Research Institute, Tampa FL; Study Statistician: M. Haagenson). Manuscript preparation.* ***Oral presentation at the American Society of Hematology in December 2005.*** Data from the CIBMTR indicate that approximately 70% of unrelated donor HCT in the U.S. utilize peripheral blood (PB) rather than bone marrow (BM) as a graft source. Comparative studies verifying its benefit, however, are lacking. We, therefore, performed a retrospective analysis comparing the results of 275 unrelated PB and 620 unrelated BM transplants in adults 18-60 years of age with ALL, AML, MDS (myelodysplastic syndrome) or CML, transplanted in 2000-2002. 73% of PB grafts were matched at HLA A, B, C (low resolution) and DRB1, 21% were mismatched at a single locus and 6% were mismatched at ≥ 2 loci. 69% of BM grafts were matched, 26% were mismatched at a single locus and 5% were mismatched at ≥ 2 loci. Median follow-up was 24 (range, 6-48) and 34 (range, 6-54) months for PB and BM recipients, respectively. Groups were similar except PB recipients were less likely to have CML, were more likely to have MDS and were transplanted more recently. Incidences of neutrophil recovery (95% vs. 90% at day 100, p=0.01) and platelets ≥20,000/ul (81% vs. 66%, at 1-year, p <0.0001) were significantly higher after PB than BM transplants. Incidences of grades 2-4 but not grades 3-4 acute GVHD were significantly higher after PB than BM transplants (56% vs.45%, at day 100, p=0.003). Chronic GVHD was also significantly higher after PB transplants (54% vs. 39%, at 3 years, p<0.0001). Despite higher rates of grade 2-4 acute and chronic GVHD after PB transplantation, incidence of relapse was similar in the two groups for both early and advanced leukemia. In multivariate analysis, risks of TRM, treatment failure (relapse or death) and overall mortality during the first 9 months after transplantation were similar. However, among patients surviving the first 9 months, subsequent risks of TRM (relative risk [RR] 1.90, 95% confidence interval [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 PB cohort. Three-year adjusted (from multivariate models) probabilities of LFS were 29% and 31%, p=0.5, after PB and BM 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, PB 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 PB in the setting of unrelated donor HCT.

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: H. Tang). 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 hematopoietic stem cell products. We surveyed a total of 2972 patients 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 vs 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% (95% Confidence Interval [CI] 72-93%) versus 81% (95% CI 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: D. Wall, Texas Transplant Institute, San Antonio, TX; Study Statistician: John 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 UCB banks, search coordinating center and transplant programs with prospective collection of outcome data coordinated by the NMDP. Critical to UCB 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 UCB units to 144 patients at 44 NMDP transplant programs included in this analysis (median f/u 217 days, 26–1204 days). The median recipient age was 8.2 years (0.2–63.1 years, 38 were $\geq$ 15 years) and median weight was 27 kg (3–158 kg: 26% > 57 kg). Transplant indications included malignancy in 113 (ALL 36, AML 43, MDS 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 malignancy patients had advanced disease (60 patients [53%] were beyond CR2 or in relapse).

The median pre-freeze TNC was 4.4 x 10^7/kg (0.3–433 x 10^7/kg) and CD34+ cells 7.9 x 10^5/kg (1.1–68.5 x 10^5/kg) in units selected for transplantation. Thus, the median UCB TNC was 142 x 10^7 cells (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 (8–62 days) and platelet count > 20,000 x 10^9/L of 64 days (12–473) respectively. 1-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 TRM rate was 26% ± 7%. For patients ≥ 15 yrs, TRM was 42% ± 16% vs. 21% ± 8% for patients < 15 years. Higher cell dose was associated with faster neutrophil and platelet engraftment. Units with both high TNC/kg and high CD34+/kg were associated with more rapid engraftment vs. those with only high TNC 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 UCB is a valuable alternative unrelated donor histocompatible stem cell source. Since transplantation using UCB units containing both high TNC and CD34+ content resulted in more rapid engraftment, optimal CB 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: S. Gandham).*

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 TBD).*

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

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

GS05-03: Comparison of outcomes after unrelated cord blood vs. bone marrow grafts in children with severe aplastic anemia. *(Study Chair: J Wagner, University of Minnesota, Minneapolis, MN; Study Statistician TBD).*

3.12 Late Effects and Quality of Life Working Committee. Co-Chair: Gerard Socie, Hopital St. Louis, Paris, France; Co-Chair: John Wingard, University of Florida, Gainesville, FL; Co-Chair: Brian Bolwell, Cleveland Clinic Foundation, Cleveland OH; Statistician: John Klein, PhD; M.S. Statistician: Kathleen A. Sobocinski, M.S.; Scientific Director: J. Douglas Rizzo, M.D., M.S.

3.12.1 Publications

LE99-01: Andrykowski MA, Bishop M, Hahn EA, Cella D, Beaumont JL, Brady M, Horowitz M, Sobocinski K, Rizzo JD, Wingard JR. **Health-related quality of life and psychological growth**

following HCT: a multi-center, comparative study. *J Clin Oncol, 23:599-608, 2005.* The purpose of this study was to examine health-related quality of life (HRQOL) and psychological growth in long-term, adult survivors of HCT for a malignant disease. HCT survivors (n=662) were recruited through the CIBMTR from 40 HCT centers. Survivors completed a telephone interview and a set of questionnaires a mean of 7.0 (range 1.8-22.6) years post-HCT. Study measures included a variety of standardized measures of HRQOL and psychological growth. An age-and gender-matched healthy comparison group (n=158) was recruited using a peer nomination method. The comparison group completed a parallel telephone interview and set of questionnaires. MANCOVA analyses indicated the survivor group reported poorer status relative to the comparison group for all HRQOL outcome clusters including Physical Health, Physical Functioning, Social Functioning, Psychological Adjustment, and Dyadic Adjustment. In contrast, the survivor group reported better status relative to the comparison group for a Psychological Growth outcome cluster. Mean effect size for the 24 specific outcome indices examined was 0.36 standard deviation with the largest differences between the survivor and comparison groups apparent on measures of general health, physical function and well-being, depression, cognitive function, and fatigue. We conclude that the experience of HCT for a malignant disease has a wide-ranging, longstanding, and profound impact upon adult recipients. Relative to healthy controls, HCT survivors report poorer physical, psychological, and social functioning but, conversely, enhanced psychological growth. (This study supported, in part, by RO1-CA81320)

LE98-07: Curtis RE, Metayer C, Rizzo JD, Socié G, Sobocinski KA, Flowers MED, Travis WD, Travis LB, Horowitz MM, Deeg HJ. **Impact of chronic GVHD therapy on the development of squamous cell cancers after HCT: An international case-control study.** *Blood 105:3802-3811, 2005.* Previous studies of HCT recipients suggest that GVHD and its therapy may increase the risk of solid cancers, particularly squamous cell carcinomas (SCC) of the buccal cavity and skin. However, the importance and magnitude of these associations are not well characterized. We conducted a case-control study of 183 patients with post-transplant solid cancers (58 SCC, 125 non-SCC) and 501 matched controls within a cohort of 24,011 patients who received HCT at 215 centers worldwide. Our results showed that chronic GVHD and its therapy were strongly related to the risk of SCC, whereas no increase in risk was found for non-SCC cancers. Long duration of chronic GVHD therapy (p=0.0001), the use of azathioprine, particularly when combined with cyclosporine and steroids (p= 0.0002), and severe chronic GVHD (p=0.004) were identified as major risk factors for the development of SCC. Since most patients who received prolonged immunosuppressive therapy and those with severe chronic GVHD were also treated with azathioprine, the independent effects of these risk factors could not be evaluated. Additional analyses determined that prolonged immunosuppressive therapy and the use of azathioprine were also significant risk factors for both SCC of the skin and of the oral mucosa. These data regarding risk of SCC provide further encouragement to strategies to prevent chronic GVHD, and for those patients with moderate/severe chronic GVHD, the development of more effective and less carcinogenic regimens for treatment. Our results also suggest that clinical screening for SCC in patients exposed to prolonged chronic GVHD and/or immunosuppressive therapy is appropriate.

Santo-Tomas L, Loberiza FR, Klein JP, Layde PM, Lipchik RJ, Rizzo JD, Bredeson CN, Horowitz MM. **Risk factors for bronchiolitis obliterans in allogeneic bone marrow transplant for leukemia.** *Chest 128:153-161, 2005.* Reported risk factors for bronchiolitis obliterans in allogeneic hematopoietic stem cell transplant recipients come from modest-sized studies and are limited to experiences of single institutions. This study sought to identify risk factors for BO using multicenter data from the CIBMTR. Data on 6,275 adult patients with leukemia who received HLA-identical sibling transplants from 1989-97 and survived at least 100

days post-transplant were evaluated. Risk factors were analyzed using proportional hazards regression. Seventy-six patients were found to have bronchiolitis obliterans, with an incidence rate of 1.7% at 2 years post-transplant. The Kaplan-Meier estimate of median time to onset was 431 days. Histologic evaluation was performed in 36 patients (47%). In 28 patients (37%), diagnosis was based on pulmonary function tests (PFT's), CT scan (Computerized Tomography) of the chest, or a combination of both. On multivariate analysis, the factors that were associated with an increased risk for developing bronchiolitis obliterans included: peripheral blood-derived stem cells, a busulfan-based conditioning regimen, interval from diagnosis to transplant $\geq$ 14 months, female donor to male recipient sex-match, prior interstitial pneumonitis, and an episode of moderate to severe acute GVHD. In addition to corroborating previously reported risk factors, such as acute GVHD and a busulfan-based conditioning regimen, we found that PBSC transplantation, long duration to transplant, female donor to male recipient, and a prior episode of interstitial pneumonitis are associated with an increased risk for bronchiolitis obliterans.

J. Douglas Rizzo, MD, John R. Wingard, MD, Andre Tichelli, MD, PhD, Stephanie J. Lee, MD, Maria Teresa Van Lint, MD, Linda J. Burns, MD, Stella M. Davies, MD, James L.M. Ferrara, MD, Gérard Socié, 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.*** *BMT, BBMT, 2006. In Press.* 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.

LE99-01: Bishop MM, Beaumont JL, Hahn EA, Cella D, Andrykowski MA, Brady MJ, Horowitz MM, Sobocinski KA, Rizzo JD, Wingard JR. **"For Better and for worse": The long-term impact of cancer and HCT on the quality of life and posttraumatic growth of partners.** *Submitted.* Little is known about the long-term effects of cancer and HCT on the partners of cancer survivors. This study examined the HRQOL and posttraumatic growth (PTG) of adult partners of long-term HCT survivors compared to survivors and controls. HCT survivor/partner pairs (n=177), coupled continuously since HCT, were drawn from 40 North American transplant centers. Married peer-nominated acquaintances served as controls (n=133). Outcomes were measured a mean of 6.7 (range, 1.9-19.4) years post-HCT. Self-reported physical health of partners was comparable to that of controls and *better* than that of survivors. Self-reported fatigue and cognitive dysfunction were worse compared to controls, although not as bad as the survivors. Partners and survivors reported *equal* levels of depressive symptoms, sleep and sexual problems; both groups were worse than controls. The odds of partner depression were nearly 3.5 times that of controls. Partners reported *worse* outcomes than both survivors and controls on social support, loneliness, dyadic satisfaction, social constraint at HCT, and spiritual

well-being. In contrast to survivors, partners reported little PTG, no more than controls. Predictors of poorer outcomes included having chronic health problems, experiencing multiple life changes, reporting social constraint, and survivor depression. Predictors of better outcomes included optimism, social support, and active coping. Partners experience many of the emotional and social costs of HCT that the patient does without the compensatory benefits of PTG that survivors report. Predictors of poor outcomes may be 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). Analyses in progress.* 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 29,737 allogeneic transplant recipients and studied whether specific patient and transplant characteristics were associated with increased risk. 6,873 patients had survived for 5 or more years post-transplant and 2,063 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 71% 20 years after transplantation. Univariate analyses of transplant-related variables suggest that conditioning with TBI may increase the risk of subsequent cancers of the salivary, brain, thyroid, breast and bone/connective tissue and melanoma. 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 HCT survivors. *(Study Chairs: S. Lee, Dana-Farber Cancer Institute, Boston, MA; M. Bishop, University of Florida, Gainesville, FL; Study statistician: K. Sobocinski). Manuscript in preparation.* HCT is curative for many patients with acute leukemia, CML and lymphoma. However, having survived their diseases and transplants, it is not known how many patients participate in healthy behaviors and currently recommended preventive services to avoid future health problems. We collected self-reported information on health-preserving behaviors as part of a large, cross-sectional study of HCT patients, spouses and acquaintances. Results were compared to screening recommendations from the U.S. Preventive Services Task Force infectious disease recommendations from the Center for Disease Control, according to age, sex, and presence or absence of chronic GVHD. Self-reported information was classified as health provider independent (if medical contact not required, i.e., tobacco avoidance, exercise, and seat belt use, reported on a 0-3 summary scale) or health provider dependent (e.g., cholesterol tests, stool guaiacs, sigmoidoscopy, blood pressure check, dental exam, breast exam, mammograms, immunizations, colon cancer screening, reported as % compliance since screening and preventive health recommendations vary depending on age, sex and health status). Access to the medical system was graded on a 0-3 scale reflecting insurance coverage, having a physician, and being seen in the clinic or hospital within the past year; average scores were 1.9 for men and 2.1 for women. 212 pts have been studied so far, 83 (39%) allogeneic and 129 (61%) autologous transplant recipients. 42% had acute leukemia, 19% CML, 18% lymphoma and 20% breast cancer. The sample is predominantly Caucasian (89%), married (70%), female (64%), and well educated (74% had

post high school education). Median age was 50 (range 22-75) years and median time since HCT was 7 (range, 2.7-19.5) years. Only 28% of patients practiced all 3 healthy provider-independent behaviors: 86% do not smoke, 81% always use seatbelts and 33% often or always get the recommended amount of exercise. Despite good access to medical care, overall compliance with provider-dependent behaviors was only 63%. Screening rates were highest for breast and cervical cancer (77-82% of women) and lowest for colon cancer (22-32% of patients ≥50 years). In multivariate analysis, provider-independent behaviors were associated with higher education (p=0.001) while greater compliance with provider-dependent behaviors was associated with female gender (p=0.03), higher education (p=0.04) and autologous HCT (p=0.01). Age, disease type, time since HCT, income, marital status and intensity of pre-HCT chemotherapy were not associated with compliance. In conclusion, self-reported compliance with recommended health behaviors in survivors of HCT procedures is reasonably good, but there is considerable room for improvement. Efforts to improve general preventive screening and promote healthy behaviors may be able to exploit HCT patients' frequent contact with the medical system and past experience with illness. (This study supported, in part, by R01-CA81320)

LE99-01: Relationship quality and quality of life for HCT survivors and their partners. *(Study Chair: J.R. 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

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).*

LE03-02: Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome after HCT. *(Study Chair: E. Cohen, Medical College of Wisconsin, Milwaukee, WI; Study Statistician: K. Sobocinski).* [Deferred, pending funding]

LE05-01: Incidence of bronchiolitis obliterans after reduced-intensity HCT. *(S. Mineishi, Vanderbilt University, Nashville, TN; Study Statistician: K. Sobocinski).*

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

3.13 Immunobiology Working Committee. Co-Chair: Effie Petersdorf, Fred Hutchinson Cancer Research Center, Seattle, WA; Co-Chair: Carolyn Hurley, Georgetown University School of Medicine, Washington, DC; Co-Chair: Machteld Oudshoorn, Europdonor Foundation; Statistician: Michael Haagenson, M.S., Tao Wang, Ph.D.; Scientific Director: Mary M Horowitz, M.D.; Assistant Scientific Director: Stephen Spellman, M.S.

This is a new Working Committee which met for the first time in February 2005 to plan its Scientific Agenda and prioritize the following studies. Many of these studies make use of biologic specimens from the NMDP's donor-recipient repository (indicated by an "s" after the study number).

3.13.1 Publications

R02-40s: Cooley S, McCullar V, Wangen R, Bergemann TL, Spellman S, Weisdorf DJ, and Miller JS. **KIR reconstitution is altered by T cells in the graft and correlates with clinical outcomes after unrelated donor transplantation.** *Blood.106:4370-4376, 2005.* Although unrelated HCT is curative for many hematologic malignancies, complications and relapse remain challenging obstacles. Natural killer (NK) cells, which recover quickly after transplant, produce cytokines and express killer immunoglobulin-like receptors (KIR) that regulate their cytotoxicity. Some clinical trials based on a KIR ligand mismatch strategy are associated with less relapse and increased survival, but results are mixed. We hypothesized that T cells in the graft may affect NK cell function and KIR expression after unrelated transplantation, and that these differences correlate with clinical outcomes. NK cell function was evaluated using 77 paired samples from the NMDP Research Repository. Recipient NK cells at 100 days after both unmanipulated and T cell depleted transplants were compared with NK cells from their normal donors. NK cells expressed less KIR and produced more interferon (IFN)-α after unmanipulated compared to T-cell depleted transplants. Multivariate models showed that increased NK cell IFN-α production correlated with more acute GVHD, and decreased KIR expression correlated with inferior survival. These results support the notion that T cells in the graft affect NK cell reconstitution in vivo. Understanding these mechanisms may inform strategies to improve clinical outcomes from unrelated HCT.

SC02-01: Loren A, Bunin GR, Boudreau C, Champlin RE, Cnaan A, Horowitz MM, Loberiza FR, Porter, DL. **Impact of prior pregnancy on outcomes of allogeneic HCT.** *Submitted.* Allogeneic HCT can cure adults with hematologic malignancies, but results in significant morbidity and mortality. GVHD is a major complication; attempts to reduce the risk of GVHD include selecting donors based on several characteristics, including parity, a criterion which has been controversial. This retrospective cohort study using data from the CIBMTR is the first multi-center analysis of the effects of donor and recipient parity on outcomes of HCT in the modern transplant era. We studied patients at least 18 years old who received a non-T-cell-depleted, myeloablative HLA-identical sibling HCT between 1995 and 1999, for ALL, AML or CML. The study endpoints included acute and chronic GVHD, overall survival, and relapse. There were 2,626 patients who met inclusion criteria and had complete information on both donor and recipient pregnancy status. Donors and recipients were categorized as: males, nulliparous females, or parous (one or more pregnancies) females. We compared all possible combinations of donor and recipient pregnancy status (9 groups in total); the reference group was male donor/male recipient pairs. Multivariate Cox proportional hazards regression was used to adjust for other prognostic factors. Because multiple groups were compared, significant p-values were considered to be less than or equal to 0.006. Results: After controlling for important patient-, disease-, and transplant-related covariates, the risk of chronic GVHD was significantly increased in parous female donor/male recipient pairs (HR 1.56, 95% CI 1.23 –

1.94, p < 0.0001). Neither donor nor recipient parity had an impact on overall survival, acute GVHD, or relapse risk. In summary, this multi-center study showed that use of parous female donors resulted in a significantly increased risk of chronic GVHD in male recipients, but without concomitant reduction in relapse. Thus, H-Y antigens may be important targets of GVHD, but not of a graft-versus-leukemia effect. As when selecting unrelated donors, avoidance of parous female donors, particularly for male patients, in HLA-identical sibling transplants is recommended when possible.

3.13.2 Preliminary Results

R02-33s: Interleukin-1 genotype and outcome of unrelated donor HCT for CML. *(Study Chairs: M. MacMillan, University of Minnesota, Minneapolis, MN, S. Davies, Cincinnati's Children's Hospital Medical Center, Cincinnati, OH; Study Statistician: S. Gandham). Manuscript in preparation. .**Poster presentation at the American Society of Hematology in December, 2005.*** 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 1 year 40% C/C donor, 68% T/C donor, 75% T/T donor, p <0.01). Multiple regression analysis showed reduced TRM 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.

Table 1

Endpoint	Recipient has T-allele	Donor has T-allele	Both have T-allele	Neither have T-allele	p-value
TRM @ 1 yr	41%	43%	43%	43%	0.99
Acute GVHD	64%	67%	68%	72%	0.80
Chronic GVHD	50%	57%	52%	52%	0.81
Relapse@1yr	7%	<1%	3%	1%	0.14
Relapse@2yrs	7%	4%	3%	3%	0.63
LFS @ 2yrs	46%	51%	47%	47%	0.90
Survival@2yrs	49%	52%	48%	48%	0.95

The data show no impact of IL-1 genotype on survival or TRM. 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, LFS, GVHD or TRM. Survival (and LFS) 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 TRM 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 transplant for CML.

R03-57s: Survey of diversity of immune response genes in unrelated HCT. *(Study Chair: C. Hurley, Georgetown University Hospital, Washington, DC; Study Statistician: M. Haagenson). Manuscript in preparation.* 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.

R02-07: The effect of KIR ligand incompatibility on the outcome of unrelated donor transplants by the NMDP, the EBMT and the Dutch Registry. *(Study Chair: S. Farag, The Ohio State University, Columbus, OH; Study Statistician: G. Nelson, Christian Boudreau, John Klein). Manuscript in preparation.* While matching for HLA class I alleles, including HLA-C, is an important criterion for unrelated donor transplantation, results in related haplotype-mismatched transplantations for myeloid malignancies suggest lower rates of GVHD, relapse and mortality when donor-recipient pairs are mismatched for KIR ligands. We hypothesized that outcomes after unrelated donor transplants may be similarly improved in KIR ligand mismatched donor-recipient pairs through the effect of alloreactive natural killer cells. Outcomes after 1571 unrelated donor transplantations for myeloid malignancies where donor-recipient pairs were HLA-A, -B, -C, -DRB1 matched (n=1,004), 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. TRM, 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 KIR ligand matched had similar rates of TRM, 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 of KIR ligand mismatch determined from HLA typing.

3.13.3 Planned Studies

3.13.3.1 HLA Genes

D98-125: Cross-reactive group matching and outcome in HCT. *(Study Chairs: J. Wade, University of Toronto, Toronto, ON, Canada; C. Hurley, Georgetown University Hospital, Washington, DC; Study Statistician: M. Haagenson).*

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).*

R02-27: HLA matchmaker analysis of HCT outcome. *(Study Chair, R. Duquesnoy, University of Pittsburgh, Pittsburgh, PA; Study Statistician: M. Haagenson).*

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).*

R04-97: Degree of HLA class I and II matching and outcomes after unrelated donor HCT. *(Study Chairs: S. Lee, Dana-Farber Cancer Institute, Boston MA, C. Anasetti, H. Lee Moffitt Cancer and Research Institute, Tampa FL; Study Statistician: M. Haagenson).*

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: E. Abdi, University of Queensland Toowoomba Hospital, Toowoomba, Queensland, Australia; Study Statistician: S.Gandham).*

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

3.13.3.3 NK/KIR

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, C. Hsu, Memorial Sloan-Kettering Cancer Center, New York, NY; Study Statistician: M. Haagenson).*

R04-91s: KIR-ligand absence and outcome of unrelated donor HCT. *(Study Chair: J. Miller, University of Minnesota Minneapolis, MN; 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).*

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

3.13.3.5 Sensitization and Tolerance

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: S. Gandham).*

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

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: S. Gandham).*

3.13.3.6 Minor Histocompatibility Antigens

IB05-01: Multiplexed genotyping of human minor histocompatibility antigens (mHAgs): Clinical relevance of mHAg disparity in HCT. *(Study Chair: T. Ellis, Blood Center of Wisconsin, Milwaukee, WI; Study Statistician: M. Haagenson)..*

3.14 <u>Regimen-related Toxicity/Supportive Care Working Committee</u>. Co-Chairs: Karen Ballen, Massachusetts General Hospital, Boston, MA; Co-Chair: Andrea Bacigalupo, Ospedale S. Martino, Genova, Italy; Statistician: Sharavi Gandham, MS, Brent Logan, PhD; Scientific Director: J. Douglas Rizzo, M.D.

This is a new Working Committee that met in February 2005 for the first time to plan its Scientific Agenda, including setting priorities for the planned studies (some reassigned from other committees) listed below.

3.14.1 Preliminary Results

D01-08: Reduced intensity conditioning regimens with volunteer unrelated donor progenitor cell transplantation: Lessons learned from the first 286 patients reported to the NMDP. *(Study Chairs: S. Giralt, M.D. Anderson Cancer Center, Houston, TX; Study Statisticians: B. Logan, O. McGaha).* We performed a retrospective analysis of adult patients

with hematologic malignancies undergoing allogeneic HCT with an unrelated donor after a reduced intensity conditioning regimen. Patients were included for this analysis if they were older than 18 years and had undergone an unrelated donor transplant from 1/1/96 until 05/31/01 with a reduced intensity regimen 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. Recipients receiving reduced intensity conditioning were older (53 vs 33 years) and had a higher likelihood of having advanced disease (81% vs 51%) when compared to myeloablative conditioning recipients. The 2 year survival rate is 34% (95%CI; 28,39). Prognostic factors for survival in univariate analysis were: disease stage, time to transplant from diagnosis, degree of HLA match, and source of stem cells. Unrelated donor transplantation with reduced intensity conditioning was rapidly adopted by the transplant community. These transplants are being performed more frequently in older patients, and can result in long term disease control in some patients. Unrelated donor transplantation with reduced intensity conditioning should continue to be explored in the context of clinical trials.

3.14.2 Planned Studies

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

SC03-01/R02-26: A retrospective study of the impact of oObesity on toxicity and outcomes in HCT for AML: *(Study Chair: W. Navarro, UCSF, San Francisco, CA, StudyStatistician: S. Gandham*

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

RT05-02: The effect of low body mass index on aloogeneic transplant outcome in children aged 2-10 years receiving HCT for aplastic anemia and myelodysplasia. *(Study Chair: C. Barker, BC Childrens Hospital, Vancouver, Canada; Study Statistician: S. Gandham).*

RT05-03: Second matched unrelated donor transplant as a rescue strategy for patients who fail to engraft after initial transplantation: An analysis of risk factors and treatment outcomes *(Study Chair: J. Schriber, City of Hope Samaritan BMT Unit, Phoenix, AZ; Study Statistician: S. Gandham).*

RT05-01: Role of gemtuzumab ozogamicin in the development of hepatic veno-occlusive disease *(Study Chair: Scott I. Bearman, University of Colorado Health Sciences Center, Denver, CO; Study Statistician: S. Gandham).*

3.15 Infection and Immune Reconstitution Working Committee. Co-Chair: Jan Storek, University of Calgary, Calgary, Alberta, Canada; Co-Chair: Jo-Anne van Burik, University of Minnesota, Minneapolis, MN; Co-Chair: Ronald Gress, National Institutes of Health, Bethesda, Maryland; Statistician: Manisha Kukreja, M.B.B.S., M.P.H., Seregey Tarima, Ph.D.; Scientific Director: Marcie Tomblyn, MD, MS.

This is a new Working Committee which met for the first time in February 2005 to plan its Scientific Agenda for this year, including setting priorities for the planned studies some of which were reassigned from other committees.

3.15.1 Planned Studies

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: WS. Pérez).*

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: K. Sobocinski).*

LE04-01: CMV infection and mortality after HCT. *(Study Chair: Michael Boeckh, Fred Hutchinson Cancer Research Center, Seattle, WA; Study statistician: WS. Pérez).*

LE04-02: Outcome of HCT in HIV- positive patients with hematological malignancies. *(Study Chair: V. Gupta, Princess Margaret Hospital, Toronto, Ontario, Canada; Study Statistician: K. Sobocinski).*

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: WS. Pérez).*

II05-01: 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: WS. Pérez).*

II05-02: Atypical mold infections in HCT patients. *(Study Chairs: M. Tomblyn,* University of Minnesota, Minneapolis, MN; Steven Trifilio, RPh, Northwestern University, Chicago, IL*; Study Statistician: WS. Pérez)*

II05-03: Tranferability and curability of atopy (allergies) with allogeneic HCT. *(Study Chair: J. Storek, University of Calgary, Calgary,* Alberta, Canada*; Study Statistician: WS. Pérez)*.

3.16 <u>Donor Health and Safety Working Committee.</u> Co-Chairs: Michael Pulsipher, University of Utah School of Medicine, Salt Lake City, UT; Co-chair: Paolo Anderlini, M D Anderson Cancer Center, Houston, TX; Co-Chair: Susan Leitman, NIH Clinical Center Blood Bank, Bethesda, MD; Statistician: Seira, Kurian M.D. M.S., M.P.H., Brent Logan, PhD; Scientific Director: Dennis Confer

3.16.1 Preliminary Results

D01-84a: Unrelated-donor PBSC collection facilitated by the NMDP, 1999-2005: efficacy and toxicities, serious unexpected events, and outcomes of standard vs. large volume collections. *(Study Chair: M. Pulsipher, University of Utah School of Medicine, Salt Lake City, UT; Study Statistician: S. Kurian).* ***Poster presentation at the American Society of Hematology in December, 2005.*** Between 1999 and 2005 the NMDP conducted a prospective trial assessing the safety and efficacy of PBSC collection in >5000 healthy unrelated donors. Donors ranged in age from 18-60 and were mobilized with 10 ug/kg/d G-CSF on days 1-5 with collection on day 5 alone or days 5 and 6. 2400 donor collections (1999-2003) were analyzed in detail for efficacy and toxicity and 5334 collections (1999-June 2005) were reviewed for serious unexpected events. 90% of subjects underwent collection using peripheral access, with 10% requiring central catheter placement. Female donors required central access more frequently

than males (20% vs 4%, p<0.001). G-CSF induced bone pain peaked on days 4-5 and was present in greater than 80% of donors, although severe bone pain occurred in at most 5% (Table 1). Grade 3-4 CALGB (Cancer and Leukemia Group B) toxicities occurred in 136 donors (6%) and unexpected serious adverse events (SAE) occurred in 30 (0.6%, Table 2). Median yield of CD34+ cells for the cohort was 27 x 106 cells/L processed (n=1776, range 0.7-236) on day +5 of G-CSF and 24 x 106 cells/L processed (n=1285, range 1-133) on day +6. Median CD34+ cell dose/kg recipient weight collected was 5 x 10^6/kg (n=1040, range 0.1-110) on day +5 of G-CSF and 3 x 10^6/kg (n=751, range 0.1-29) on day +6. Inadequate collections were rare with 5% and 6% of donors yielding <2 or 2 but <3 x 10^6 CD34+ cells/kg recipient weight, respectively (n=1001). The risk of toxicity was the same for standard (12L), intermediate (>12≤16L), and large (>16L) volume collections. Importantly, as volumes of apheresis in a single day increased, the yield of CD34+ cells/L processed was unchanged (median yield 27, 26, 28, and 29 x 10^6/L processed for <12L, ≥12<16L, ≥16<20L, 20L); day 5 collection, p =0.4). This resulted in similar outcomes measured in CD34 cells/kg recipient weight for large volume single day collections compared to standard volume 2 day collections. Platelet counts fell more with large compared to standard volume apheresis (change in platelets -83 vs -105 x 10^9/L, p<0.001), however, the drop in platelets over the course of 2 standard volume procedures was greater than a single large volume procedure (-131 vs -107 x 10^9/L, p<0.001). In summary, this large prospective trial shows that unrelated donor PBSC collection yields adequate CD34+ cell numbers with low, but measurable rates of significant toxicity. Single-day large vs two-day standard volume procedures resulted in similar cell yields without evidence of increased toxicity. With this data, centers can now more appropriately counsel unrelated adult donors regarding risks of PBSC donation. Large volume, single day collection is a safe and effective resource-sparing alternative to standard volume procedures.

3.16.2 Planned Studies

D01-84: Experience of NMDP bone marrow donors. *(Study Chair: Susan Leitman, NIH Clinical Center Blood Bank, Bethesda, MD; Study Statistician: S. Kurian)*

DS05-02: Pediatric and older related donor outcomes. *(Study Chair: M. Pulsipher, University of Utah School of Medicine, Salt Lake City, UT; Study Statistician: S. Kurian)*

DS05-03: Long term donor follow-up. *(Study Chair: M. Pulsipher, University of Utah School of Medicine, Salt Lake City, UT; Study Statistician: S. Kurian)*

3.17 Health Policy and Psychosocial Issues Working Committee.

Co-Chair: Stephanie Lee, Dana Farber Cancer Institute, Boston, MA; Co-Chair: Galen Switzer, University of Pittsburg Medical Center, Pittsburg, PA; Statistician: Seira Kurian M.D., M.S., M.P.H., John Klein, PhD; Scientific Director: J. Douglas Rizzo

3.17.1 Preliminary Results

HS 05-06: The likelihood of HCT in the United States: Implications for umbilical cord blood storage. (*Study Chair: Marcelo C. Pasquini Medical College of Wisconsin ; Frances Verter , University Medical Center Utrecht (UMCU), Utrecht, Netherlands; Mary Horowitz, Medical College of Wisconsin; Study Statistician Brent Logan).* ***Poster presentation at the American Society of Hematology in December, 2005****.* The likelihood of utilizing stored cells depends, in part, on the likelihood of developing a condition for which HCT is indicated. This study estimates the latter likelihood based on data for current HCT use as reported to the CIBMTR from 2001 through 2003.

First, age-related incidences of HCT were calculated; then, using the cumulative incidence function, we calculated the lifetime likelihood under two scenarios. In scenario 1, we calculated the likelihood of receiving an autologous HCT by age, in decades, from birth to 70 years. In scenario 2, we calculated the likelihood of being a candidate for either an autologous or an allogeneic HCT. This likelihood was derived from the number of HLA-identical sibling HCTs multiplied by three (to account for patients considered acceptable candidates but lacking an HLA-matched sibling donor) in addition to the number of autologous HCT. The number of HCT performed represented fewer than 20% of the malignant diagnoses most commonly treated with HCT, according to Surveillance, Epidemiology and End Results (SEER) data. After the second decade of life, the age-related incidences of HCT under both scenarios steadily increased with age. The cumulative incidences for scenario 1 ranged from 0.02% (at age 20) to 0.23% (at age 70); for scenario 2 they ranged from 0.06% (at age 20) to 0.46% (at age 70). Given the current indications for HCT, the lifetime likelihood of undergoing an autologous HCT or being a candidate for HCT is about 1 in 400 and 1 in 200, respectively. How closely these estimates correspond to the likelihood that a stored cord blood unit is used depends upon several conditions including a) sufficient number of stem cells; b) satisfactory stem cell quality after the storage period; and, c) relative attractiveness, in particular clinical situations, of cord blood cells compared to other graft sources (e.g. peripheral blood or bone marrow).

3.17.2 Planned Studies

HS05-01: Ethnicity and unrelated donor transplant outcomes. *(Study Chairs: Stella Davies, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH; K. Scott 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: S. Kurian)*

SC01-01: Quality of clinical trials in the HCT literature, *(Study Chair: S. Kurian, Medical College of Wisconsin, Milwaukee, WI; Study Statistician: S. Kurian).*

HS 05-02: **The volume effect for matched unrelated donor bone marrow transplants for three kinds of leukemia (ALL, AML, CML)- Learning by doing vs. selective referral.** (*Study Chair: Frank Schneider, Harvard University Cambridge, MA; Study Statistician: S. Kurian*).

HS 05-03: Outcomes of allogeneic HCT in patients with variable income sources. *(Study Chair: Richard Maziarz, Oregon Health and Science University Portland, OR, Study Statistician: S. Kurian).*

HS 05-04: Access to unrelated HCT. *(Study Chair: J. Doug Rizzo, Medical College of Wisconsin, Milwaukee, WI; Study Statistician: S. Kurian).*

HS 05-05: Cost-effectiveness of alternative graft sources in allogeneic HCT. *(Study Chair: S. Kurian Medical College of Wisconsin Milwaukee, WI, J. Doug Rizzo Medical College of Wisconsin Milwaukee, WI; Study Statistician: S. Kurian).*

HS 05-07: **Feasibility of collecting social, economic, health insurance, cultural, spiritual well-being and social support data among different ethnic groups receiving allogeneic HCT.** *(Study Chair: S. Kurian Medical College of Wisconsin, Milwaukee, WI; Study Statistician: S. Kurian).*

3.18 Statistical Center Methodologic Studies

A critical scientific activity of the CIBMTR Statistical Center is the development and adaptation of statistical metholdology for optimal analysis of CIBMTR and other transplant-related data. Under the leadership of Dr. John Klein, CIBMTR statisticians are addressing several areas of statistical research.

3.18.1 Multistate Models

Several papers were written on multistate models for HCT data:

Shu Y and Klein JP. **Additive hazards Markov regression models illustrated with bone marrow transplant data.** *Biometrika 2005. In Press*. This work develops alternatives to the Cox proportional hazards modeling for the multistate models. It shows how additive hazards regression models can be used for the transition rates and then how these regression models can be synthesized to obtain estimates of the probability a patient is 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.** *Mathematical Biosciences, 2005*. *In Press.* In this paper, a random effect is added to the usual Cox Markov model for multistate data. The developed method was applied to a bone marrow transplantation data analysis.

Shu Y, Klein JP, Zhang MJ. **Asymptotic theory for the Cox semi-Markov illness-death model.** *Submitted.* This paper describes asymptotic variance estimations for the transition hazards under a semi-Markov multi-state model.

Anderson PK and Klein JP. **Regression analysis for multistate models based on a pseudo-value approach, with applications to bone marrow transplantation studies.** *Scandinavian Journal of Statistics, 2006. In Press.* Drs. Klein and Anderson have continued their study of the use of regression models for the current leukemia free survival function based on pseudo-values in a paper cited below. This work was presented at the workshop on Statistical Analysis of Complex Event History Data in Oslo, Norway in September 2005.

Zhang MJ and Scheike TH **Directly modeling the regression effects in multistate models.** *Scandinavian Journal of Statisticis, 2006. In Press.* Drs. Zhang and Scheike have proposed some flexible regression models using an inverse censoring weighting technique to model the multi-state time-to-event data. This work was also presented at the workshop on Statistical Analysis of Complex Event History Data in Oslo, Norway in September 2005 and is cited below.

3.18.2 Competing Risks

CIBMTR faculty are investigating methods for making inferences from competing risks data. Competing risks arise in a variety of situations in HCT studies including analyses of relapse, GVHD and TRM. 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,** *Journal of Planning and Inference,* 2005. *In Press.* In this paper, we focused on

testing for the equality of two or more cumulative incidence functions. New tests were proposed and various tests were investigated.

Klein JP. **Modeling competing risks in cancer studies.** *Statistics in Medicine* 2005. *In Press*. In this paper, we argued that Aalen's additive hazards model is more appropriate and internally consistent than the usual Cox Regression model.

KleinJP and Andersen PK. **Regression modeling of competing risks data based on pseudo-values of the cumulative incidence function**. *Biometrics 61: 223-229, 2005.* We applied novel regression technique for censored lifetime data based on pseudo-values to the competing risks data. We model the cumulative incidence functions directly and use pseudo-values in a generalized estimating equation to obtain estimates of model parameters.

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 in this paper.

Sun LQ, Liu JX, SunJG, Zhang MJ. **Modeling the subdistribution of a competing risk.** *Statistica Sinica 2005. In Press.* In the paper, we model the subdistribution hazard through a general model. Robust variance estimates were presented. The model-fitting problem was 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.

3.18.3 Regression Models for Censored Data

Bhattacharyya M and Klein JP. **A Note on testing in Aalen's additive hazards regression model.** *Statistics in Medicine 2005. In Press.* In this paper appropriate weights, which lead to consistent tests based on Aalen's additive hazards model, were considered and proposed.

3.18.4 Techniques for Censored and Truncated Data

Andersen PK, Ekstrom C, Klein JP**,** Shu Y, Zhang M-J. **Simulation based goodness of fit tests for a copula based on bivariate right-censored data.** *Biomed J. Published online Nov. 22, 2005.* Simulation based goodness of fit tests were proposed and evaluated through a simulation study.

Boudreau C and Lawless JF. **Survival analysis based on the proportional hazards model and survey data,** *Submitted.* 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, Harhoff M, Andersen PK. **Analyzing survival curves at a fixed point in time.** *Submitted.* Here we focused on testing for the equality of survival curves at a fixed point in time.

Logan BR, Wang H, Zhang M-J. **Pairwise multiple comparison adjustment in survival analysis.** *Statistics in Medicine, 24: 2509-2523, 2005.* This paper described methods for controlling the family wise error rate when performing pairwise comparisons among several groups and when the outcome is the time to an event of interest.

Logan BR. **Optimal two-stage randomized phase II clinical trials.** *Clinical Trials 2: 5-12, 2005.* Designs were proposed for randomized phase II clinical trials, in which one is interested in evaluating several potential new treatments prior to a comparative phase III clinical trial.

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 personnel, 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 has made this type of information available to several investigators including those at Baylor College of Medicine, the International Working Group on Non-myeloablative Stem Cell Transplant (IwNST), the University of Florida, the Fred Hutchinson Cancer Research Center, several pharmaceutical companies and others. We formalized the process for trial planning support for our work with the BMT Clinical Trials Network (BMT CTN). CIBMTR data are routinely used to evaluate proposals for BMT CTN trials and to facilitate/simulate study designs and accrual projections.

- *Data collection instruments*: CIBMTR data collection forms have been the basis for data collection forms for several clinical trials including the NHLBI-sponsored cord blood transplantation study (COBLT) and a Phase II multicenter study of non-myeloablative stem cell transplants being conducted in 16 U.S. transplant centers. CIBMTR provided its database structure and schema to the Pediatric Blood and Marrow Transplant Consortium (PBMTC) to aid them in building a clinical information system for PBMTC trials. They serve as the basis for data collection forms in the BMT Clinical Trials Network. The CIBMTR has an open policy for sharing 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 also formed the basis for the development of the Canadian BMT Group’s National Registry developed over the past several years. The forms are freely available on our website.

- *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. These include Phase II trials of donor lymphocyte infusion for relapse and a

recently concluded clinical trial of nonmyeloablative stem cell transplants coordinated with Texas Southwestern University.

- *Trial interpretation:* The CIBMTR Registry database is a valuable tool for evaluating results of clinical trials, especially single arm studies. The Statistical Center has made the Registry 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 Study CK02-03 in section 3.2.2 is a good example of this.

3.19.2 Statistical Education/CONSULTATION

Dr. J.P. Klein, Statistical Director of the CIBMTR, has authored, or contributed to, chapters in critical texts on Bone Marrow Transplantation as well as numerous Journal publications. He and Mei-Jie Zhang, PhD collaborate 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 team members, in the role of appointed consultants. 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.

All CIBMTR PhD statisticians are members of The Division of Biostatistics (Health Policy Institute/MCW) and function as consultants for CIBMTR research activity including the BMT CTN program. All have teaching responsibilities as well. Mei-Jie Zhang made presentations at our 2005 BMT Tandem meeting and Brent Logan presented at the combined CIBMTR Data Managers/NMDP Council meetings in November, 2005.

Drs. Logan, Klein and Zhang have continued their statistical education work as evidenced in the following paper: Logan BR, Zhang MJ and Klein, JP. **Regression models for hazard rates versus cumulative incidence probabilities in bone marrow transplant data.** *BBMT, 2006. In Press.*

4.0 OTHER ACTIVITIES

4.1 Presentations

In 2005, there were 147 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 2005, the CIBMTR, through its Information Resource Program, provided information in response to more than 1150 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 where answers to the most frequently asked questions can be found. During 2005, there were an estimated 12,000 visits to the ibmtr.org website. In December this site was dismantled and transferred to cibmtr.org, housed at NMDP and developed by their web team. Visits to these websites are from physicians, patients, and other individuals interested in blood and marrow transplantation.

Table 4.2.1 Requests for information received by the CIBMTR Statistical Center, November 30, 2004 to November 30, 2005.

TYPE OF ORGANIZATION	**TOTAL**
Physician	795
Medical Society	21
Patient or Relative	53
Federal Government Agency	16
State Government	0
Insurance Company	24
Pharmaceutical Company	187
Consulting Firm	14
Market Research Firm	24
Law Firm	0
Donor Registry/Blood Bank	7
Student	10
News media	3
TOTAL	**1154**

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 ~1650 participants attending the BMT Tandem Meetings in 2005. 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. All were included in the participant profile. Continuing Medical Education (CME) and Continuing Education (CE) credits are issued for attending the BMT Tandem Meetings for physicians and allied health professionals from the United States.

Disease- and technology-specific Working Committees guide scientific research for the CIBMTR; Executive and Advisory Committees consider issues of policy (see Section 1.1 above). Meetings of Working, Advisory and Executive Committees, and new subcommittees (such as the Consumer Advocacy Committee) are held during the Tandem BMT Meetings, as well as by telephone or in conjunction with meetings of the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO).

The second in person meeting of the CIBMTR Transitional Advisory Committee was held at the BMT Tandem meetings in Keystone, Colorado in February 2005. The Executive Committee of

the CIBMTR met at the BMT Tandem meetings and quarterly by phone as well as at the ASH sessions in December 2005. Additionally, conference calls of Working Committee chairs with their assigned Biostatistician were implemented to provide further guidance to the Statistical Center for scientific studies.

To further enhance communication between the Statistical Center and CIBMTR participants, the CIBMTR Statistical Center publishes a biannual newsletter summarizing activities. The first newsletter since the affiliation was published in January 2005

4.4 External Review Committee Recommendations

In October 2002, the IBMTR convened a panel of experts in hematology, oncology, immunology, histocompatibility, transplantation, epidemiology and other related fields for a one-day forum to review past, current and planned IBMTR activities. Forum participants included many Executive Committee and Working Committee members, external scientific reviewers, representatives from NIH and key Statistical Center staff. In advance of the one-day meeting, participants received written background materials and were asked to prepare a short written critique, focusing on ways in which the IBMTR might better serve the HCT community. Participants were asked to be candid with their feedback, comments and critiques.

The 2002 reviewers cited primary strengths of the IBMTR as the size and quality of its database and interactions among highly skilled and committed investigators. They noted the increasing number of peer-reviewed publications and the Statistical Center's leadership in the field of survival analyses. Also noted was the influence of the IBMTR upon the field of transplantation since its resources were increasingly being utilized by scientists, patients, regulatory agencies, pharmaceuticals and third-party payers.

Uniformly, the group agreed that the IBMTR should continue its important role as a repository of data and of well-designed retrospective analysis. Forum participants also provided many suggestions for both improving current operations and productivity and for expanding into new areas. These included the following major recommendations:

- The IBMTR should initiate and promote a national and international effort to simplify data reporting for transplant centers. *A major initiative took place throughout 2005 utilizing both CIBMTR and NMDP expert staff in the total re-design and re-structuring of most data collection forms. Additionally, the IBMTR and NMDP were successful in applying for a grant in response to the National Institute of Health's Broad Agency Announcement BAA-RM-04-2 3 to fund software and systems development to allow communication of transplant outcome data between networks. This project builds on the expertise and resources developed through U24-CA76518. Both of the above are also influenced by CIBMTR efforts in the design of Common Data Elements – a work in progress - which also impacts the idea of an Information Systems based data management oversight team. A first meeting occurred in November 2005 with plans for a January 2006 second session to maintain forward motion in this critical initiative for our organization. Lastly, several Statistical Center staff members met with members of the EBMT Data Centre in London to address common data reporting problems.*

- The IBMTR should explore establishing a tissue repository (DNA and RNA) that could be linked to clinical data. *The affiliation of NMDP and IBMTR greatly facilitates addressing this recommendation. We plan to build on the NMDP's expertise in establishing and maintaining an unrelated donor-recipient repository to begin a similar effort for related*

donor-recipient pairs. This will allow more sophisticated immunologic and observational studies and provide much needed biologic samples for addressing issues such as the impact of cytokine genes in the setting of genotypic identity for HLA. A record of available unrelated donor-recipient samples has been developed and is available to basic scientists in this field. The CIBMTR Immunobiology Working Committee is closely aligned with the NMDP Histocompatibility Committee which oversees this respository. See below.

- The IBMTR should expand its activity in providing descriptive analyses of HCT outcomes in rare diseases, principally genetic disorders of childhood, e.g. congenital anemias and neutropenias, immunodeficiencies and other inborn errors of metabolism. *See Section 3.8.*

- The IBMTR should devote additional effort to studying late effects of HCT during the prolonged period of survival afforded to patients who, otherwise, would have died at an earlier age. *See Section 3.12.*

- IBMTR studies should increase their emphasis on issues related to the immunology of HCT, i.e., the interplay of GVHD, graft versus malignancy, and immune reconstitution. *The new CIBMTR Working Committee structure includes a Committee devoted to Immunobiology, chaired by C. Hurley, M. Oudshoorn and E. Petersdorf, who are leaders in this area (see Section 3.13). The availability of biologic specimens through the NMDP Repository and the anticipated establishment of a related donor-recipient repository will facilitate development of this program.*

The terms of the CIBMTR affiliation call for periodic External Reviews to be held every three years.

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. These activities, including data collection, entry, and auditing, for NMDP transplants do not fall under the purview of NMDP-Research and do not involve CIBMTR personnel.

5.1 Data Collection

CIBMTR data collection forms are continually reviewed to assess needs for revision and are updated accordingly. Form revisions and additions are done in collaboration with the NMDP in order to achieve uniformity in content and format. *TED on the Web* has been available since early 2004 to provide an additional alternative for HCT centers to submit Registration data. Pre-registration, MTED, TED and TEDFU forms now can be directly submitted via the Internet, in lieu of the paper version of these forms or use of StemSoft.

As noted previously, harmonization of NMDP and IBMTR forms is in progress, under the auspices of a combined NMDP/CIBMTR Forms Committee that will complete its first major task with release of the first harmonized forms in Spring 2006. The work of this combined committee will persist due to scheduled form reviews. The participated in successful application for a grant to develop a public system for electronic exchange of clinical network data (*AGNIS, A Growable Network Information System*, PI: Dennis Confer, co-PI: Mary Horowitz). This three-year project, which includes representation from the international HCT community, has the potential to greatly facilitate both submission of data to the CIBMTR and sharing data for collaborative

projects with other organizations. There is also an ongoing initiative to incorporate the CaDSR common data elements into all future data collection efforts.

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 2005, in conjunction with the Annual Meeting in Keystone, CO. 149 data managers attended. Participants indicated a high level of satisfaction with topics covered and training provided. Another two day training session was conducted by CIBMTR personnel in November 2005 in Minneapolis in conjunction with the NMDP annual Council meeting. 125 data managers attended. The intention was to facilitate greater attendance and a more in-depth program.

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 Executive Committee.

Thirty one allogeneic and thirteen autologous HCT programs were audited in 2005; an additional seven programs will be audited by February 28, 2006, the end of the current U24 funding period. Audits at six centers were deferred for various reasons. To date, overall accuracy is 98.5% 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.

5.4 Computer Capabilities

Computer resources for the CIBMTR Statistical Center are shared with the other 6 divisions of the Health Policy Institute (HPI) of 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 and Dell Pentium workstations for each staff member. Both networks reside on the MCW network infrastructure The Intel server purchased this year has 4G of RAM, dual processors with RAID and tape backup capabilities. We also implemented MS Outlook Exchange server on this new network server, giving us a departmental mail server and capability to synchronize documents on and off line.

The intra-departmental networks are separated from other college departments on the Unix side by a dedicated sentry SUN workstation as described below in the HIPAA security section 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.

The CIBMTR Statistical Center continued a relationship with the Bioinformatics Research Center (BRC), a department at MCW created to promote the development and integration of emerging informatics technology into MCW's clinical research and basic science environment (funds provided, in part, by MCW). The BRC is an invaluable resource to the CIBMTR for developing software systems using standard relational database methodology, configuring the system for essential security requirements and defining operating methods that ensure 24/7 database availability needed for entry, editing and tracking of data. The contract with the BRC also increased programmer resources needed to continue to revise and enhance the components of the data system.

Specific projects in 2005 include the following:

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

- A system was developed to automate reconciliation of CTN study accrual and reporting between EMMES and CIBMTR Statistical Center.

- We have developed a detailed database dictionary for documenting relationships between IBMTR forms and NMDP forms for work on the Forms Harmonization between the two organizations.

- We have contributed actively to the AGNIS technical committee in its 3 year funding period. The dictionary mentioned above allows us to extract lists of terms and value domains to use in the CaDSR metadata repository recommended by the NCIB. Other elements of our database structure have been extracted to the Universal Modeling Language (UML) that is used as input to the CaDSR system.

- No new forms or form revisions were released in 2005. All efforts involving forms revision were focused on the Forms Harmonization project involving IBMTR and NMDP forms. This major effort has resulted in agreement on the content of the Harmonized 120, 130, 140,150, and 190.

- Development is underway for the software necessary to handle the entry, editing and viewing of the Harmonized 120 and Harmonized 130 inserts. Modifications were needed to database structures to handle new items collected. An operational pilot of a browser-based application has been developed using Microsoft ASP.net technology. With the forms finalization, we will begin rolling out the pages of the harmonized forms set.

- 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 the NIH grant (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 MCW IRC and the MCW 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 2005, all Statistical Center personnel are required to also complete the more complex training tool, Collaborative IRB (Institutional Review Board) Training Initiative Program (CITI). All certificates are on file in the CIBMTR administrative office or in the Department of Medicine, Division of Neoplastic and Related Diseases office. In January 2006, the Minneapolis CIBMTR staff will begin taking the more extensive CITI course as well.

6.1 Health Insurance Portability and Accountability Act (HIPAA)

The NMDP (including NMDP-Research, the Minneapolis campus of the CIBMTR) is exempt from the HIPAA requirements. NMDP has been designated a "public health authority" 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 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 the Health Insurance Portability and Accountability Act, which went into effect April 14, 2003. These measures are documented below.

6.1.1 HIPAA Security Measures

On the Milwaukee campus, security requirements contained in the HIPAA legislation are satisfied by current CIBMTR policies as documented in our SOP for security procedures (IS110-1). Our security measures fall into two categories as defined in the HIPAA code: physical and technical.

Physical security measures include:

- consoles and processing units for the UNIX file-server and the UNIX database server are housed in a locked, temperature controlled room;
- disks used for database storage are mirrored for fault tolerance;
- database backup tapes are taken off-site daily;
- daily review of backup logs to ensure that problems do not go undetected;
- standard procedures for exiting applications and terminating session when workstations are unattended.

Technical security measures include:

- UNIX database server (known as mort) has a separate file system from the departmental UNIX network;
- a very limited number of users have UNIX login accounts on mort;
- unnecessary communication services (mail services, internet services) have been removed from the database server;
- TCP/IP wrapper rules narrow remaining services (ftp, telnet) to accesses from specific locations (IP addresses);
- all software applications accessing the ORACLE database require use of username and passwords, which are changed regularly;
- ORACLE data access Roles to associate particular user name/password pairs with access privileges appropriate for job description;
- a dedicated UNIX workstation is configured as a gatekeeper, applying TCP/IP wrapper rules to limit access to the department UNIX network from outside the Statistical Center;
- the gatekeeper machine has a file system separate from the rest of the departmental network, requires a separate UNIX account login and encrypts the incoming session using Secure Shell;
- access to the gatekeeper machine, thus access to the departmental network from outside, is limited to a few senior staff members with responsibility for system management.

Many of the full system back-up procedures are implemented weekly using DAT (digital audio tape) for all user files and system files; database files are backed up nightly. Back-up tapes are maintained in a fireproof, magnetic field-proof storage cabinet in a secured area outside the computer room and retained for six months. To assure ease of recovery in the event of an inadvertent loss of data, the Statistical Center performs an additional weekly back-up of all databases and a biweekly back-up of all Registry files. Weekly back-up tapes are kept for one month and the bi-weekly tapes for two years. Study files are archived indefinitely. Report forms are kept in locked files in a secure area.

6.1.2 HIPAA Confidentiality Measures

HIPAA regulations also specify requirements to maintain confidentiality of Protected Health Information (PHI). 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 PHI, 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 PHI 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 MCW and as well as 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 91% of our participating centers in the United States. Data use agreements have been executed with 81% of our 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 is not entered in the database, and is 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 <u>all</u> 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.

7.0 SIGNIFICANCE

CIBMTR activities funded under U24-CA76518 continue to provide a unique resource of information and expertise to the medical and scientific community. The affiliation with NMDP 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 transplant-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.

List of Appendices

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Appendix 1

CIBMTR – Participating Centers

Fundaleu Dr Mainetti	Buenos Aires	Argentina	CIBMTR Registration
Fundaleu “Angelica Ocampo”	Buenos Aires	Argentina	CIBMTR Research
ITMO Instituto de Trasplante de Medula Osea	Buenos Aires	Argentina	CIBMTR Research
Hospital de Pediatria, S.A.M.I.C.	Buenos Aires	Argentina	CIBMTR Registration
Hospital Universitario Austral	Buenos Aires	Argentina	CIBMTR Research
Institutos Medicos Antartidica	Buenos Aires	Argentina	CIBMTR Registration
Alexander Fleming Institute	Buenos Aires	Argentina	NMDP/CIBMTR Research
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 Prince 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	Waratah, Newcastle	Australia	CIBMTR Research
Westmead Hospital	Westmead	Australia	CIBMTR Research
University of Graz	Graz	Austria	CIBMTR Research
Medical University of Vienna	Vienna	Austria	CIBMTR Registration
Ludwig Blotzmann Institute	Vienna	Austria	CIBMTR Registration
St. Anna Child Hospital	Vienna	Austria	CIBMTR Registration
A.Z. Sint-Jan	Brugge	Belgium	CIBMTR Registration
Children Reine Fabiola Hospital	Brussels	Belgium	CIBMTR Registration
Cliniques Universitaires Saint Luc	Brussels	Belgium	CIBMTR Research
University Hospital Antwerp	Edegem	Belgium	CIBMTR Research
University Ziekenhuis Gasthuisberg	Leuven	Belgium	CIBMTR Research
University de Liege	Liege	Belgium	CIBMTR Registration
Hospital de Barretos	Barretos	Brazil	CIBMTR Registration
Univ. Estadual de Campinas/TMP/UNICAMP	Campinas	Brazil	CIBMTR Research
Universidade Federal De Parana	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
Real Institute de Medula Ossea	Recifo	Brazil	CIBMTR Research
University Sao Paulo	Ribeirao Preto	Brazil	CIBMTR Registration
Hemorio	Rio de Janeiro	Brazil	CIBMTR Registration
Instituto Nacional de Cancer	Rio de Janeiro	Brazil	NMDP/CIBMTR Research
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

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CIBMTR – Participating Centers

Instituto de Oncologia Pediatrica	Sao Paulo	Brazil	CIBMTR Registration
University Sao Paulo - INCOR	Sao Paulo	Brazil	CIBMTR Research
Alberta Children's Hospital	Calgary-Alberta	Canada	CIBMTR Research
T. Baker Cancer Center	Calgary-Alberta	Canada	CIBMTR Registration
Victoria Gen. Hosp.-QEII H&S Ctr.	Halifax	Canada	CIBMTR Research
McMaster University Medical Center	Hamilton-Ontario	Canada	CIBMTR Research
Queen's University	Kingston Ontario	Canada	CIBMTR Registration
London Health Science Center-Ontario	London-Ontario	Canada	CIBMTR Research
Hopital 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-Ontario	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
Vancouver Hospital & Health Sciences Center	Vancouver-BC	Canada	CIBMTR Research
Cancer Care Manitoba	Winnipeg-Manitoba	Canada	CIBMTR Research
Peking University People's Hospital	Beijing	China	NMDP/CIBMTR Research
Medical College of Zhejiang University	Hangzhou	China	NMDP/CIBMTR Research
Instituto de Cancerologia	Medellin	Columbia	CIBMTR Registration
Institute de Transplant de Medula Osea	Barranquilla	Columbia	CIBMTR Registration
Fundacion Clinica Valle Del Lili	Bogota	Columbia	CIBMTR Registration
University Hospital	Bratislava	Czech.	CIBMTR Registration
Charles University Hospital	Pilsen	Czech.	CIBMTR Research
Institute of Hem. and Blood Transfusion	Prague	Czech.	CIBMTR Registration
University Hospital Motol	Prague	Czech.	CIBMTR Registration
University Hospital	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 for Children	London	England	CIBMTR Research
Imperial College School of Medicine	London	England	CIBMTR Research
London Clinic	London	England	CIBMTR Registration
Royal Free Hospital	London	England	CIBMTR Registration
Royal London Hospital, Whitechapel	London	England	CIBMTR Research
St. George's Hospital	London	England	CIBMTR Research
Royal Victoria Hospital, Newcastle	Newcastle	England	CIBMTR Research
Royal Marsden Hospital	Sutton	England	CIBMTR Research
Helsinki University Central Hospital	Helsinki	Finland	NMDP/CIBMTR Research
Turku University	Turku	Finland	CIBMTR Research
Centre Hospitalier Régional Univ. d'Angers	Angers	France	CIBMTR Registration
Hopital Jean Minjoz	Besancon	France	CIBMTR Research
Hopital Claude Huriez, Lille	Lille	France	CIBMTR Registration
Hospital Edouard Herriot	Lyon	France	CIBMTR Registration

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CIBMTR – Participating Centers

Institute J. Calmettes	Marseille	France	CIBMTR Research
Hopital Saint Louis	Paris	France	CIBMTR Research
Hospital Jean Bernard	Poitiers	France	CIBMTR Research
Charite - Campus Virchow Klinikum (Adults)	Berlin	Germany	NMDP/CIBMTR Research
University Hospital Charite, Virchow	Berlin	Germany	NMDP/CIBMTR Research
Universitatsklinik Dresden	Dresden	Germany	NMDP/CIBMTR Research
University Medical Center Dusseldorf	Dusseldorf	Germany	NMDP/CIBMTR Research
University Hospital of Essen	Essen	Germany	NMDP/CIBMTR Research
Freiburg University Medical Center	Freiburg	Germany	NMDP/CIBMTR Research
Martin Luther University, Halle-Witt	Halle	Germany	CIBMTR Registration
Universitaetsklinikum Hamburg-Eppendorf	Hamburg	Germany	NMDP/CIBMTR Research
Medical School of Hannover	Hannover	Germany	CIBMTR Registration
Universitat Heidelberg	Heidelberg	Germany	NMDP/CIBMTR Research
Clinic of Bone Marrow Transpl. & Hem./Onc.	Idar-Oberstein	Germany	NMDP/CIBMTR Research
Christian Albrechts University	Kiel	Germany	CIBMTR Research
Leipzig University BMT Center	Leipzig	Germany	NMDP/CIBMTR Research
University Hospital, Mainz	Mainz	Germany	NMDP/CIBMTR Research
Blinik Grosshadern, Munich	Munich	Germany	CIBMTR Research
University of Munich	Munich	Germany	NMDP/CIBMTR Research
Children's Hospital	Tuebingen	Germany	CIBMTR Registration
University of Tuebingen	Tuebingen	Germany	NMDP/CIBMTR Research
Universitatsklinik Ulm	Ulm	Germany	NMDP/CIBMTR Research
Deutsche Klinik für Diagnostik	Wiesbaden	Germany	NMDP/CIBMTR Research
Univ. of Hong Kong & Queen Mary Hospital	Hong Kong	Hong Kong	NMDP/CIBMTR Research
National Institute of Haematology & Blood	Budapest	Hungary	CIBMTR Registration
Tata Memorial Hospital	Mumbai	India	CIBMTR Research
Institute Rotary Cancer Hospital	New Delhi	India	CIBMTR Research
Christian Medical College Hospital	Tamil Nadu	India	CIBMTR Research
Dr. Shariati General Hospital	Tehran	Iran	CIBMTR Research
St. James Hospital	Dublin	Ireland	CIBMTR Research
Rambam Medical Center	Haifa	Israel	NMDP/CIBMTR Research
Haddasah University	Jerusalem	Israel	NMDP/CIBMTR Research
Schneider Children's Medical Center of Israel	Petach Tikva	Israel	NMDP/CIBMTR Research
Chaim Sheba Medical Center (Pediatric)	Tel-Hashomer	Israel	NMDP/CIBMTR Research
Chaim Sheba Medical Center (Adult)	Tel-Hashomer	Israel	NMDP/CIBMTR Research
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	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

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CIBMTR – Participating Centers

Ajou University Medical Center	Suwon	Korea	CIBMTR Research
Catholic Hem. Stem Cell Transpl Center	Seoul	Korea	NMDP/CIBMTR Research
Hamid Al-Essa Transp. Ctr., Kuwait U.	Safat	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 Raza IMSS	Mexico D.F.	Mexico	CIBMTR Research
University Hospital	Monterrey	Mexico	CIBMTR Registration
Hospital San Jose - Tec de Monterrey	Monterrey, Nuevo Leon	Mexico	NMDP/CIBMTR Research
Clinica Ruiz de PuebLA	Puebla	Mexico	CIBMTR Registration
Leiden University Medical Centre	Leiden	Netherlands	NMDP/CIBMTR Research
Academy Hospital Maastricht	Maastricht	Netherlands	CIBMTR Registration
University Medical Center	Nijmegen	Netherlands	NMDP/CIBMTR Research
Dr. Daniel Den Hoed Cancer Center	Rotterdam	Netherlands	NMDP/CIBMTR Research
Auckland Hospital	Auckland	New Zealand	CIBMTR Research
Starship Children's Health	Auckland	New Zealand	CIBMTR Research
ChristchurcHospital Hospital	Christchurch	New Zealand	CIBMTR Research
Wellington Hospital	Wellington	New Zealand	CIBMTR Research
RiksHospitalet - The National Hospital	Oslo	Norway	NMDP/CIBMTR Research
Institute Oncologica Nacional	Panama City	Panama	CIBMTR Research
Bismillah Taqee Institute of Health Sciences	Karachi	Pakistan	CIBMTR Research
Bone Marrow Transplant Center	Rawai Pindi	Pakistan	CIBMTR Registration
Med University of Gdansk	Gdansk	Poland	CIBMTR Research
Silesian Medical Academy	Katowice	Poland	NMDP/CIBMTR Research
Lower Silesian Center for Cellular Transplant	Wroclaw	Poland	NMDP/CIBMTR Research
Inst. Portugues de Oncologia do Lisbon	Lisbon	Portugal	CIBMTR Research
Inst. Portugues de Oncologia Centro do Porto	Porto	Portugal	CIBMTR Registration
Petrov Medical University	St. Petersburg	Russia	CIBMTR Research
King Faisal Specialist Hosp. & Research Center	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'l University Hospital	Singapore	Singapore	CIBMTR Research
Singapore General Hospital	Singapore	Singapore	CIBMTR Research
University of Cape Town Leukemia Center	Cape Town	South Africa	CIBMTR Research
Constantiaberg Medi-Clinic	Cape Town	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	CIBMTR Research

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CIBMTR – Participating Centers

Lund University Hospital	Lund		Sweden	NMDP/CIBMTR Research
Karolinska University Hospital	Stockholm		Sweden	NMDP/CIBMTR Research
University Hospital Uppsala	Uppsala		Sweden	NMDP/CIBMTR Research
Basel Kantonsspital	Basel		Switzerland	CIBMTR Research
University Hospital Bern	Bern		Switzerland	CIBMTR Registration
University Hospital-Zurich	Zurich		Switzerland	CIBMTR Registration
National Taiwan-Pediatric	Taipei		Taiwan	CIBMTR Research
Veterans General Hospital	Taipei		Taiwan	CIBMTR Research
Ankara University	Ankara		Turkey	CIBMTR Registration
Gulhane Military Medical Academy	Ankara		Turkey	CIBMTR Research
Hacettepe Univ. Inst. of Hematology/Oncology	Ankara		Turkey	CIBMTR Registration
Asoc. Espanola Primera de Socorros Mutuos	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
Children's Hospital Medical Center	Akron	OH	USA	CIBMTR Research
New York Hematology/Oncology PC	Albany	NY	USA	CIBMTR Registration
Phoebe Cancer Center	Albany	GA	USA	CIBMTR Registration
Harrington Cancer Center	Amarillo	TX	USA	CIBMTR Research
University of Michigan Medical Center	Ann Arbor	Mi	USA	NMDP/CIBMTR Research
Arlington Cancer Center	Arlington	TX	USA	CIBMTR Registration
Children's Healthcare of Atlanta at Egleston	Atlanta	GA	USA	NMDP/CIBMTR Research
Northside Hospital	Atlanta	GA	USA	NMDP/CIBMTR Research
Emory University Hospital	Atlanta	GA	USA	NMDP/CIBMTR Research
Medical College of Georgia	Augusta	GA	USA	CIBMTR Research
Greenbaum Cancer Center, U. of Maryland	Baltimore	MD	USA	NMDP/CIBMTR Research
Johns Hopkins University	Baltimore	MD	USA	NMDP/CIBMTR Research
Our Lady of the Lake Regional Center	Baton Rouge	LA	USA	CIBMTR Registration
St. Francis Hospital & Health Centers	Beech Grove	IN	USA	NMDP/CIBMTR Research
Alta Bates Medical Center	Berkeley	CA	USA	CIBMTR Registration
National Heart, Lung and Blood Institute	Bethesda	MD	USA	CIBMTR Registration
National Institute of Health	Bethesda	MD	USA	CIBMTR Registration
National Cancer Institute	Bethesda	MD	USA	CIBMTR Research
Deaconess Billings Clinic	Billings	MT	USA	CIBMTR Registration
University of Alabama at Birmingham	Birmingham	AL	USA	NMDP/CIBMTR Research
St. Luke’s Regional Medical Center	Boise	ID	USA	CIBMTR Research
Massachusetts General Hospital	Boston	MA	USA	CIBMTR Registration
Beth Israel Deaconess Medical Center	Boston	MA	USA	NMDP/CIBMTR Research
Dana Farber/Partners Cancer Care	Boston	MA	USA	NMDP/CIBMTR Research
Tufts-New England Medical Center	Boston	MA	USA	NMDP/CIBMTR Research
BMT Stem Cell Transplant Inst. at Bethesda	Boynton Beach	FL	USA	CIBMTR Research
Our Lady of Mercy Medical Center	Bronx	NY	USA	CIBMTR Research
Roswell Park Cancer Institute	Buffalo	NY	USA	NMDP/CIBMTR Research
Fletcher Allen Health Center	Burlington	VT	USA	CIBMTR Registration
UNC Hospitals	Chapel Hill	NC	USA	NMDP/CIBMTR Research
Roper Hospital	Charleston	SC	USA	NMDP/CIBMTR Research
Medical University of South Carolina	Charleston	SC	USA	NMDP/CIBMTR Research
Carolinas Medical Center	Charlotte	NC	USA	CIBMTR Research
University of Chicago-Child	Chicago	IL	USA	CIBMTR Registration

Appendix 1

CIBMTR – Participating Centers

The Children's Memorial Medical Center	Chicago	IL	USA	NMDP/CIBMTR Research
Univ. of Illinois at Chicago Med. Center.	Chicago	IL	USA	NMDP/CIBMTR Research
Northwestern Memorial Hospital	Chicago	IL	USA	NMDP/CIBMTR Research
Univ. of Chicago Stem Cell Transplant Prog.	Chicago	IL	USA	NMDP/CIBMTR Research
Rush-Presbyterian - St. Luke's Medical Center	Chicago	IL	USA	NMDP/CIBMTR Research
The Jewish Hospital	Cincinnati	OH	USA	NMDP/CIBMTR Research
Cincinnati Children's Hospital Medical Center	Cincinnati	OH	USA	NMDP/CIBMTR Research
Rainbow Babies-Case Western University	Cleveland	OH	USA	CIBMTR Research
Cleveland Clinic Foundation	Cleveland	OH	USA	NMDP/CIBMTR Research
University Hospitals of Cleveland	Cleveland	OH	USA	NMDP/CIBMTR Research
Columbus Children's Hospital	Columbus	OH	USA	NMDP/CIBMTR Research
Arthur James Cancer Research Institute	Columbus	OH	USA	NMDP/CIBMTR Research
Spohn Hospital	Corpus Christi	TX	USA	CIBMTR Registration
Children's Medical Center of Dallas	Dallas	TX	USA	NMDP/CIBMTR Research
Medical City Dallas Hospital	Dallas	TX	USA	NMDP/CIBMTR Research
Univ. of Texas SW Medical Center at Dallas	Dallas	TX	USA	NMDP/CIBMTR Research
Baylor University Medical Center	Dallas	TX	USA	NMDP/CIBMTR Research
Penn State Geisinger Medical Center	Danville	PA	USA	CIBMTR Research
Miami Valley Hospital	Dayton	OH	USA	CIBMTR Research
Oakwood Hospital and Medical Center	Dearborn	MI	USA	NMDP/CIBMTR Research
Dekalb Medical Center - Transplant Unit	Decatur	GA	USA	CIBMTR Registration
University of Colorado - Children's Hospital	Denver	CO	USA	NMDP/CIBMTR Research
Presbyterian/St. Luke’s Medical Center	Denver	CO	USA	NMDP/CIBMTR Research
Henry Ford Health System	Detroit	MI	USA	NMDP/CIBMTR Research
Karmanos Can Inst/Wayne St. Univ. Hosp.	Detroit	MI	USA	NMDP/CIBMTR Research
City of Hope National Medical Center	Duarte	CA	USA	NMDP/CIBMTR Research
Duke University Medical Center	Durham	NC	USA	NMDP/CIBMTR Research
El Paso Cancer Treatment Center	El Paso	TX	USA	CIBMTR Registration
Inova Fairfax Hospital	Fairfax	VA	USA	NMDP/CIBMTR Research
Cook Children's Medical Center	Fort Worth	TX	USA	NMDP/CIBMTR Research
Shands Hospital - University of Florida	Gainesville	FL	USA	NMDP/CIBMTR Research
Devos Children's Hospital, Spectrum Health	Grand Rapids	Mi	USA	NMDP/CIBMTR Research
Cancer Center of Carolinas	Greenville	SC	USA	CIBMTR Research
Hackensack University Medical Center	Hackensack	NJ	USA	NMDP/CIBMTR Research
Penn State, Milton S. Hershey Medical Center	Hershey	PA	USA	NMDP/CIBMTR Research
Hawaii BMT Program/St. Francis Medical Ctr.	Honolulu	HI	USA	NMDP/CIBMTR Research
The Methodist Hospital	Houston	TX	USA	CIBMTR Research
Texas Children's Hospital	Houston	TX	USA	NMDP/CIBMTR Research
M.D. Anderson Cancer Center	Houston	TX	USA	NMDP/CIBMTR Research
Comprehensive Cancer Institute	Huntsville	AL	USA	CIBMTR Research
Methodist Hospital Indiana	Indianapolis	IN	USA	CIBMTR Research
Oncology Hematology Associates	Indianapolis	IN	USA	CIBMTR Research
Riley Hospital for Children	Indianapolis	IN	USA	CIBMTR Registration
St. Vincent Hospital Indianapolis	Indianapolis	IN	USA	CIBMTR Research
Indiana University Transplant Program	Indianapolis	IN	USA	NMDP/CIBMTR Research
University of Iowa Hospitals and Clinics	Iowa City	IA	USA	NMDP/CIBMTR Research
University of Mississippi Medical Center	Jackson	MS	USA	NMDP/CIBMTR Research
Nemours Child Clinic	Jacksonville	FL	USA	CIBMTR Registration
Mayo Clinic Jacksonville/St. Luke's Hospital	Jacksonville	FL	USA	NMDP/CIBMTR Research
Mayo Clinic Jacksonville (Pediatrics)	Jacksonville	FL	USA	NMDP/CIBMTR Research
Children's Mercy Hospital	Kansas City	MO	USA	CIBMTR Research

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St. Luke's Hospital	Kansas City	MO	USA	NMDP/CIBMTR Research
University of Kansas Medical Center	Kansas City	KS	USA	NMDP/CIBMTR Research
Thompson Cancer Survival Center	Knoxville	TN	USA	CIBMTR Registration
UCSD Medical Center	La Jolla	CA	USA	NMDP/CIBMTR Research
Scripps Green Hospital	La Jolla	CA	USA	NMDP/CIBMTR Research
Wilford Hall USAF Medical Center	Lackland	TX	USA	CIBMTR Research
Southwest Cancer Center	Las Vegas	NV	USA	CIBMTR Registration
Dartmouth-Hitchcock	Lebanon	NH	USA	CIBMTR Research
University of Kentucky Medical Center	Lexington	KY	USA	NMDP/CIBMTR Research
University of Arkansas for Medical Sciences	Little Rock	AR	USA	NMDP/CIBMTR Research
Loma Linda University Medical Center	Loma Linda	CA	USA	NMDP/CIBMTR Research
UCLS-Pediatrics	Los Angeles	CA	USA	CIBMTR Research
Cedars-Sinai Medical Center	Los Angeles	CA	USA	NMDP/CIBMTR Research
University Of California (UCLA)	Los Angeles	CA	USA	NMDP/CIBMTR Research
Children's Hospital of Los Angeles	Los Angeles	CA	USA	NMDP/CIBMTR Research
Univ. Med. Center, Univ. of Louisville Hosp.	Louisville	KY	USA	NMDP/CIBMTR Research
Texas Tech University Health Sciences Center	Lubbock	TX	USA	NMDP/CIBMTR Research
University of Wisconsin Hospital and Clinics	Madison	WI	USA	NMDP/CIBMTR Research
North Shore University Hospital	Manhasset	NY	USA	NMDP/CIBMTR Research
Marshfield Clinic	Marshfield	WI	USA	CIBMTR Research
Loyola University Medical Center	Maywood	IL	USA	NMDP/CIBMTR Research
Baptist Centers for Cancer Care	Memphis	TN	USA	CIBMTR Registration
UT Blood & Marrow Transplant Center	Memphis	TN	USA	NMDP/CIBMTR Research
St. Jude Children's Research Hospital	Memphis	TN	USA	NMDP/CIBMTR Research
Miami Children's Hospital	Miami	FL	USA	NMDP/CIBMTR Research
University of Miami	Miami	FL	USA	NMDP/CIBMTR Research
St. Luke Medical Center, Milwaukee	Milwaukee	WI	USA	CIBMTR Research
Froedtert Mem. Lutheran Hospital Cancer Ctr.	Milwaukee	WI	USA	NMDP/CIBMTR Research
Children's Hospital of Wisconsin	Milwaukee	WI	USA	NMDP/CIBMTR Research
Abbott Northwest Hospital	Minneapolis	MN	USA	CIBMTR Registration
Children's Hospital and Clinics	Minneapolis	MN	USA	CIBMTR Research
NMDP SCU Center	Minneapolis	MN	USA	NMDP/CIBMTR Research
Univ. of MN BMT Program/Fairview UMC	Minneapolis	MN	USA	NMDP/CIBMTR Research
Montana Cancer Center	Missoula	MT	USA	CIBMTR Registration
West Virginia University Hospitals, Inc.	Morgantown	WV	USA	NMDP/CIBMTR Research
Vanderbilt University Medical Center	Nashville	TN	USA	NMDP/CIBMTR Research
The Cancer Institute of New Jersey	New Brunswick	NJ	USA	NMDP/CIBMTR Research
Yale University/Yale New Haven Hospital	New Haven	CT	USA	NMDP/CIBMTR Research
Schneider Children's Hospital	New Hyde Park	NY	USA	NMDP/CIBMTR Research
Memorial Medical Center	New Orleans	LA	USA	NMDP/CIBMTR Research
Children's Hospital/LSUHSC	New Orleans	LA	USA	NMDP/CIBMTR Research
Tulane University Hospital and Clinic	New Orleans	LA	USA	NMDP/CIBMTR Research
Columbia Presbyterian Hospital	New York	NY	USA	CIBMTR Research
NYU Med. Ctr. Hassenfield Children's Ctr.	New York	NY	USA	CIBMTR Research
St. Vincent's Hospital, Manhattan	New York	NY	USA	CIBMTR Registration
New York Presbyterian Hospital at Cornell	New York	NY	USA	NMDP/CIBMTR Research
The Children's Hospital of New York	New York	NY	USA	NMDP/CIBMTR Research
Memorial Sloan-Kettering Cancer Center	New York	NY	USA	NMDP/CIBMTR Research
Mount Sinai Hospital	New York	NY	USA	NMDP/CIBMTR Research
Christiana Care Health Services	Newark	DE	USA	NMDP/CIBMTR Research
Hoag Cancer Center	Newport Beach	CA	USA	CIBMTR Registration

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Virginia Oncology Associates	Norfolk	VA	USA	CIBMTR Registration
Children's Hosp. & Research Center Oakland	Oakland	CA	USA	NMDP/CIBMTR Research
Cancer Care Associates, Oklahoma City	Oklahoma City	OK	USA	CIBMTR Research
University of Oklahoma	Oklahoma City	OK	USA	NMDP/CIBMTR Research
The Nebraska Medical Center	Omaha	NE	USA	NMDP/CIBMTR Research
St. Joseph's Hospital Irvine	Orange	CA	USA	CIBMTR Research
UCI Medical Center	Orange	CA	USA	CIBMTR Research
Children's Hospital of Orange County (Choc)	Orange	CA	USA	NMDP/CIBMTR Research
Lutheran General Hospital	Parkridge	IL	USA	CIBMTR Registration
Methodist Medical Center Peoria	Peoria	IL	USA	CIBMTR Research
Temple University	Philadelphia	PA	USA	NMDP/CIBMTR Research
Thomas Jefferson University Hospital, Inc.	Philadelphia	PA	USA	NMDP/CIBMTR Research
University of Pennsylvania Medical Center	Philadelphia	PA	USA	NMDP/CIBMTR Research
Hahnemann University Hospitals	Philadelphia	PA	USA	NMDP/CIBMTR Research
Children's Hospital of Philadelphia	Philadelphia	PA	USA	NMDP/CIBMTR Research
Phoenix Children's Hospital	Phoenix	AZ	USA	NMDP/CIBMTR Research
City of Hope Samaritan	Phoenix	AZ	USA	NMDP/CIBMTR Research
Children's Hospital	Pittsburgh	PA	USA	CIBMTR Research
University of Pittsburgh Cancer Center	Pittsburgh	PA	USA	NMDP/CIBMTR Research
Western Pennsylvania Cancer Institute	Pittsburgh	PA	USA	NMDP/CIBMTR Research
Legacy Good Samaritan Hospital	Portland	OR	USA	CIBMTR Research
Providence Portland Medical Center	Portland	OR	USA	CIBMTR Research
Oregon Health & Science University	Portland	OR	USA	NMDP/CIBMTR Research
R. Williams Medical Center	Providence	RI	USA	CIBMTR Registration
Medical College of Virginia	Richmond	VA	USA	NMDP/CIBMTR Research
Strong Memorial Hospital	Rochester	NY	USA	NMDP/CIBMTR Research
Mayo Clinic Rochester	Rochester	MN	USA	NMDP/CIBMTR Research
Sutter Cancer Center	Sacramento	CA	USA	CIBMTR Registration
University of California-Davis	Sacramento	CA	USA	NMDP/CIBMTR Research
Latter Day Saints Hospital	Salt Lake City	UT	USA	CIBMTR Registration
University of Utah	Salt Lake City	UT	USA	NMDP/CIBMTR Research
Santa Rosa Children's Hospital	San Antonio	TX	USA	CIBMTR Registration
University of Texas-HSCSA	San Antonio	TX	USA	CIBMTR Research
Texas Transplant Institute	San Antonio	TX	USA	NMDP/CIBMTR Research
Children's Hospital and Health Center	San Diego	CA	USA	NMDP/CIBMTR Research
University of California	San Francisco	CA	USA	CIBMTR Registration
UCSF Medical Center	San Francisco	CA	USA	NMDP/CIBMTR Research
Guthrie Clinic, Ltd.	Sayre	PA	USA	CIBMTR Research
Maine Medical Center	Scarborough	ME	USA	CIBMTR Registration
Mayo Clinic	Scottsdale	AZ	USA	CIBMTR Research
Fred Hutchinson Cancer Center	Seattle	WA	USA	NMDP/CIBMTR Research
VA Puget Sound Health Care System	Seattle	WA	USA	NMDP/CIBMTR Research
LSU Medical Center	Shreveport	LA	USA	CIBMTR Research
Avera Mckennan Transplant Institute	Sioux Falls	SD	USA	NMDP/CIBMTR Research
Spartanburg Regional Medical Center	Spartanburg	SC	USA	CIBMTR Registration
St. Louis Children's Hospital	St. Louis	MO	USA	CIBMTR Research
Cardinal Glennon Children's Hospital	St. Louis	MO	USA	NMDP/CIBMTR Research
Barnes-Jewish Hosp./Wash. U School of Med	St. Louis	MO	USA	NMDP/CIBMTR Research
St. Louis University Medical Center	St. Louis	MO	USA	NMDP/CIBMTR Research
All Children's Hospital	St. Petersburg	FL	USA	NMDP/CIBMTR Research
Minnesota Oncology/Hematology, St. Paul	St. Paul	MN	USA	CIBMTR Registration

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CIBMTR – Participating Centers

Bennett Cancer Center	Stamford	CT	USA	CIBMTR Research
Stanford Hospital and Clinics	Stanford	CA	USA	NMDP/CIBMTR Research
Suny Stony Brook	Stony Brook	NY	USA	CIBMTR Research
Suny-Health Center	Syracuse	NY	USA	CIBMTR Research
H. Lee Moffitt Cancer Center & Research Inst.	Tampa	FL	USA	NMDP/CIBMTR Research
St. Vincent Mercy Medical Center Toledo	Toledo	OH	USA	CIBMTR Research
Arizona Oncology Associates	Tucson	AZ	USA	CIBMTR Research
University of Arizona Cancer Center	Tucson	AZ	USA	NMDP/CIBMTR Research
Cancer Care Associates	Tulsa	OK	USA	CIBMTR Research
St. Francis Hospital	Tulsa	OK	USA	CIBMTR Registration
Zalmen A. Arlin Cancer Institute	Valhalla	NY	USA	NMDP/CIBMTR Research
John Muir Medical Center	Walnut Creek	CA	USA	CIBMTR Research
Georgetown University Hospital	Washington	DC	USA	NMDP/CIBMTR Research
Children's National Medical Center	Washington	DC	USA	NMDP/CIBMTR Research
Waukesha Memorial Hospital	Waukesha	WI	USA	CIBMTR Research
Good Samaritan Medical Center	W Palm Beach	FL	USA	CIBMTR Registration
Via Christi/St. Francis	Wichita	KS	USA	CIBMTR Research
Alfred I DuPont Hospital for Children	Wilmington	DE	USA	CIBMTR Research
Medical Center of Delaware	Wilmington	DE	USA	CIBMTR Registration
Piedmont Hematology/Oncology Associates	Winston Salem	NC	USA	CIBMTR Registration
Wake Forest Univ.Baptist Medical Center	Winston-Salem	NC	USA	NMDP/CIBMTR Research
UMASS Memorial HealthCare	Worcester	MA	USA	NMDP/CIBMTR Research
Midwestern Regional Medical Center	Zion	IL	USA	CIBMTR Research

Appendix 2

CIBMTR™
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

CURRENT CIBMTR TRANSITIONAL ADVISORY COMMITTEE

Former IBMTR Executive Committee	Former ABMTR Executive	Former NMDP Research and Publications Committee	NMDP Histocompatibility Committee
Name	**Name**	**Name**	**Name**
O Ringden	RE Champlin	NR Kamani	C Anasetti
S Giralt	MR Litzow	A Flatau	RA Bray
A Filipovich	JM Vose	S Bearman	M Oudshoorn
M Bishop	PJ Stiff	J Casper	FO Smith
H Lazarus	E Stadtmauer	J Gajewski	SY Yang
MR Litzow	E Copelan	A Nademanee	SJ Mack
AJ Barrett	JF DiPersio	R Strauss	S Rosen-Bronson
J Apperley	ED Ball	A Feldmar	*(ex officio-ASHI)*
JR Passweg	D Vesole	N Collins	R Hartzman
J Szer	BJ Bolwell	K Ballen	*(ex officio-Navy)*
R Pasquini	DE Reece	S Giralt	R Baitty
		R Hartzman	*(ex officio-HRSA)*
		(ex officio-Navy)	R Ashton
		R Baitty	*(ex officio-HRSA)*
		(ex officio-HRSA)	D Confer
		R Ashton	*(ex officio)*
		(ex officio-HRSA)	M Setterholm
		D Confer	*(ex officio)*
		(ex officio)	P Coppo
			(ex officio)
			C Hurley
			(ex officio)

Other ex-officio members: J Chell, M Horowitz, J Klein.

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

CIBMTR (INTERIM*) EXECUTIVE COMMITTEE

Chair*: Richard E. Champlin, MD, MD Anderson Cancer Center, Houston, TX
Vice-Chair North America*: Sergio Giralt, MD, MD Anderson Cancer Center, Houston, TX
Vice-Chair South America*: Ricardo Pasquini, MD, Hospital de Clinicas, Federal University of Parana, Curitiba, Brazil
Vice-Chair Europe*: Olle Ringden, MD, PhD, Huddinge University Hospital, Huddinge, Sweden
Vice-Chair Asia/Australia/Africa*: Jeffrey Szer, MD, Royal Melbourne Hospital, Parkville, Victoria, Australia
Previous Chair/NMDP RAP Committee*: Naynesh R. Kamani, MD, Children's National Medical Center, Washington, DC
Previous Chair/NMDP Histocompatibility Committee*: Claudio Anasetti, MD, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL
CIBMTR Executive Director^:** Jeffrey Chell, NMDP
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 Program Leader/Statistical Methodology:** John Klein, PhD, Medical College of Wisconsin, Milwaukee, WI
CIBMTR Program Leader/Clinical Trials:** TBD
C**IBMTR Program Leader/Observational Studies**:** J. Douglas Rizzo, MD, Medical College of Wisconsin, Milwaukee, WI
Three appointed members of the Advisory Committee: Arthur Flatau, PhD and 2- TBN

* **terms expire 2/06** Assembly elections were held in November 2005 for terms starting March 1, 2006.

** ***ex officio***

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

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

CIBMTR Working Committees

Acute Leukemia Working Committee
Chairs: Armand Keating, MD, Princess Margaret Hospital, Toronto, Ontario, Canada
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: Kathleen A. Sobocinski, MS; 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
Hartmut Goldschmidt, MD, University of Heidelberg, Heidelberg, Germany
Scientific Director: Parameswaran Hari, MD
Statisticians: Waleska S. Perez, 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; Brent Logan, PhD

Appendix 2

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
Statistician: Mei-Jie Zhang, PhD

Non-Malignant Marrow Disorders Working Committee
Chairs: Ricardo Pasquini, MD, Hospital de Clinicas, Federal Univ. 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
Chairs: Alexandra Filipovich, MD, Children's Hospital Medical Center, Cincinnati, OH
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: Seira Kurian, MD, MS, 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: Marcello Pasquini, MD
Statisticians: Manisha Kukreja, MBBS, MPH; Brent Logan, PhD

Immunobiology Working Committee
Chairs: Effie Petersdorf, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
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Machteld Oudshoorn, PhD, Leiden University Medical Center, Leiden, The Netherlands
Scientific Director: Mary Horowitz, MD, MS
Assistant Scientific Director: Stephen Spellman, MS
Statisticians: Michael Haagenson, MS; Tao Wang, PhD

Graft Sources and Manipulation Working Committee
Chairs: John Wagner, MD, University of Minnesota, Minneapolis, MN
Hans Johnsen, MD, Herlev Hospital, Herlev, Denmark
Adrian Gee, PhD, Baylor College of Medicine, Houston, TX
Scientific Director: Mary Eapen, MD, MS
Statistician: Mei-Jie Zhang, PhD

Appendix 2

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: Sharavi Gandham, MS; 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

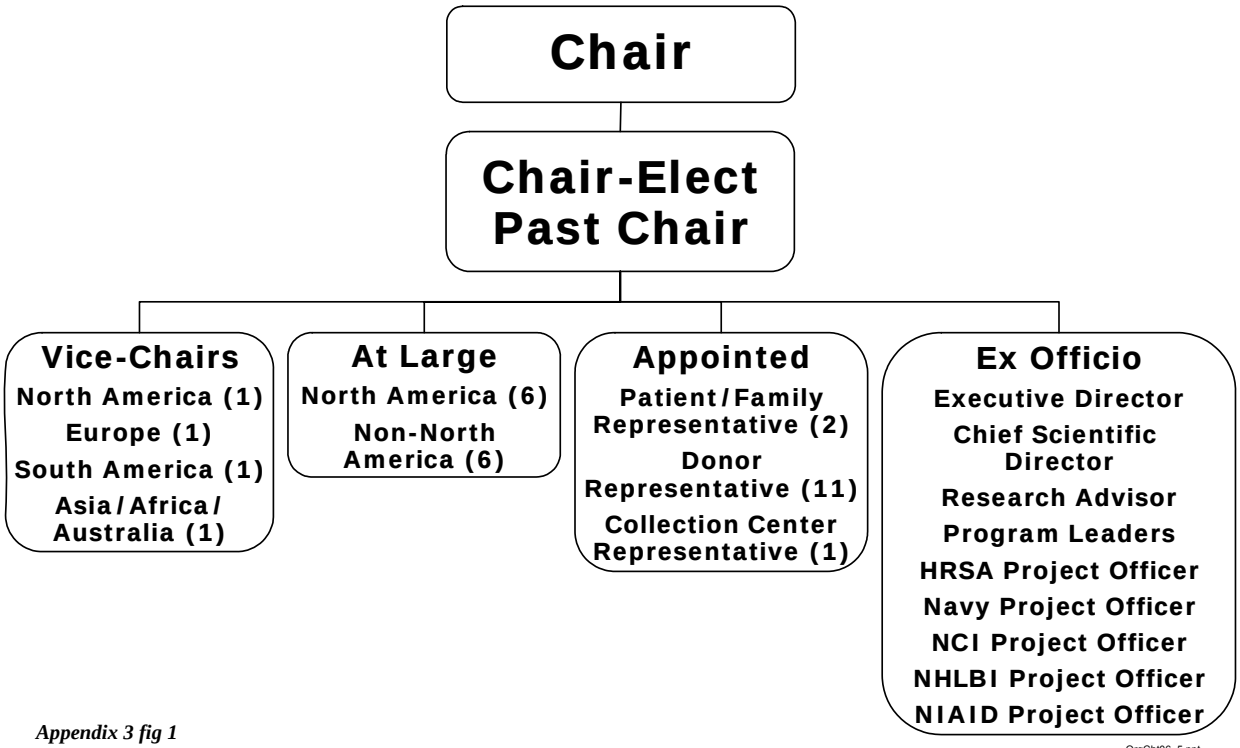
Graft-vs-Host Disease Working Committee
Chairs: A. John Barrett, MD, National Institutes of Health, Bethesda, MD
Olle Ringden, MD, PhD, Huddinge University Hospital, Huddinge, Sweden
Claudio Anasetti, MD, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL
Steven Pavletic, MD, National Cancer Institute, Bethesda, MD
Scientific Director: Mukta Arora MD, MS
Statisticians: Sharavi Gandham, 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
Statistician: Kathy Sobocinski, MS; John 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: Seira Kurian, MD, MS, MPH; Brent Logan, PhD

Health Policy Working Committee
Chairs: Stephanie Lee, MD, Dana-Farber Cancer Institute, Boston, MA
Galen Switzer, PhD, University of Pittsburgh Medical Center, Pittsburgh, PA
Scientific Director: J. Douglas Rizzo, MD
Statisticians: Seira Kurian, MD, MS, MPH; John Klein, PhD

CIBMTR Advisory Committee Structure
Terms Effective March 1, 2006



Appendix 3 fig 1

CIBMTR Advisory Committee

Terms for these positions will have staggered expiration dates (always following the BMT Tandem meetings) as outlined below:

Chair – March 2006-February 2008
Vice-Chair North America – March 2006- February 2007
Vice-Chair Europe – March 2006- February 2008
Vice-Chair South America – March 2006- February 2007
Vice-Chair Asia/Africa/Australia – March 2006- February 2008
At large North America:
- 3 positions – March 2006- February 2007
- 3 positions – March 2006- February 2008

At large non-North America:
- 3 positions – March 2006- February 2007
- 3 positions – March 2006- February 2008

Nominating Committee:
- 3 positions – March 2006- February 2007
- 2 positions – March 2006- February 2008

The CIBMTR Assembly held its first elections in November 2005 for terms to begin on March 1, 2006, following the 2006 BMT Tandem meetings. Subsequent officer term changes will occur following each annual meeting.

Elected members:

- Chair: two year position; the position will alternate between individuals with primarily allogeneic versus autologous transplant expertise
- Chair-elect: one year position prior to serving as chair
- Immediate Past Chair: one year position after serving as chair
- Vice chairs by region: North America (1); South America (1); Europe (1); Asia/Pacific/Africa (1); two year positions, may serve two consecutive terms
- At large members: 12; 6 from North America and 6 from elsewhere; two year positions, may serve two consecutive terms

Appointed members:

- Patient/family representative: 2 appointed by the Chair with input from the Nominating Committee; two year position, may serve two consecutive terms
- Donor representative: 1; appointed by the chair with input from the Nominating Committee; two year position, may serve two consecutive terms
- Collection Center representative: 1; NMDP Council designee; two year position, may serve two consecutive terms

Ex officio members:

- HRSA NMDP Project Officer or representative
- U.S. Navy NMDP Project Officer or representative
- IBMTR National Cancer Institute Project Officer
- IBMTR National Heart Lung and Blood Institute Project Officer
- IBMTR National Institute Allergy and Infectious Disease Project Officer
- CIBMTR Executive Director
- CIBMTR Research Advisor (appointed by NMDP)
- CIBMTR Chief Scientific Director
- CIBMTR Statistical Director
- CIBMTR Program Leaders (4)

For the first year only, there will be four Past-Chairs (the previous Chairs of the IBMTR and ABMTR Executive Committees and the NMDP RAP and Histocompatibility Committees). These terms will expire on February 28, 2007. Thereafter, there will be a single Chair-elect OR Past Chair

The individual elected to Chair for 2006-2008 will select the four appointed members of the Committee. Although some three year terms are required during this initial period to achieve staggered terms, all subsequent terms will be two years.

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