Progress Report for January – December 2004

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) 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 have broad expertise in the field of blood and marrow transplantation, including observational research and clinical trials. The IBMTR is a voluntary organization involving more than 400 transplant centers in 47 countries (Appendix 1) that have collaborated to share patient data and conduct scientific studies since 1972. The NMDP was established in 1987 to provide unrelated donors for patients in need of hematopoietic stem cell transplants and also to conduct research to improve the outcome of such transplants. The NMDP Network includes 156 transplant centers, 84 donor centers, 103 collection centers, 84 apheresis centers and 15 cord blood banks (Appendix 2).

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

The IBMTR brings:

- a strong record of clinical research and publications in HCT 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 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 brings:

- 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.

The new 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. IBMTR activities are funded primarily by 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 3) 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 are scheduled for Fall 2005 to select representatives to the Advisory Committee for terms beginning 1/1/06. 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 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

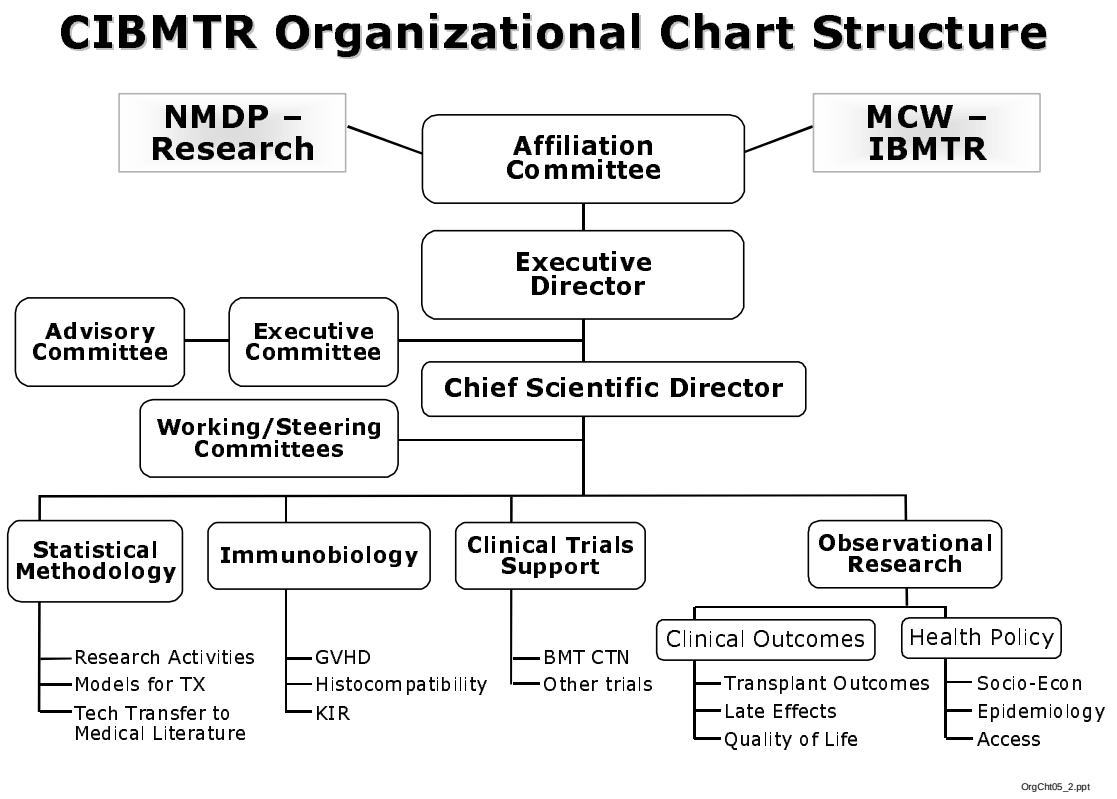
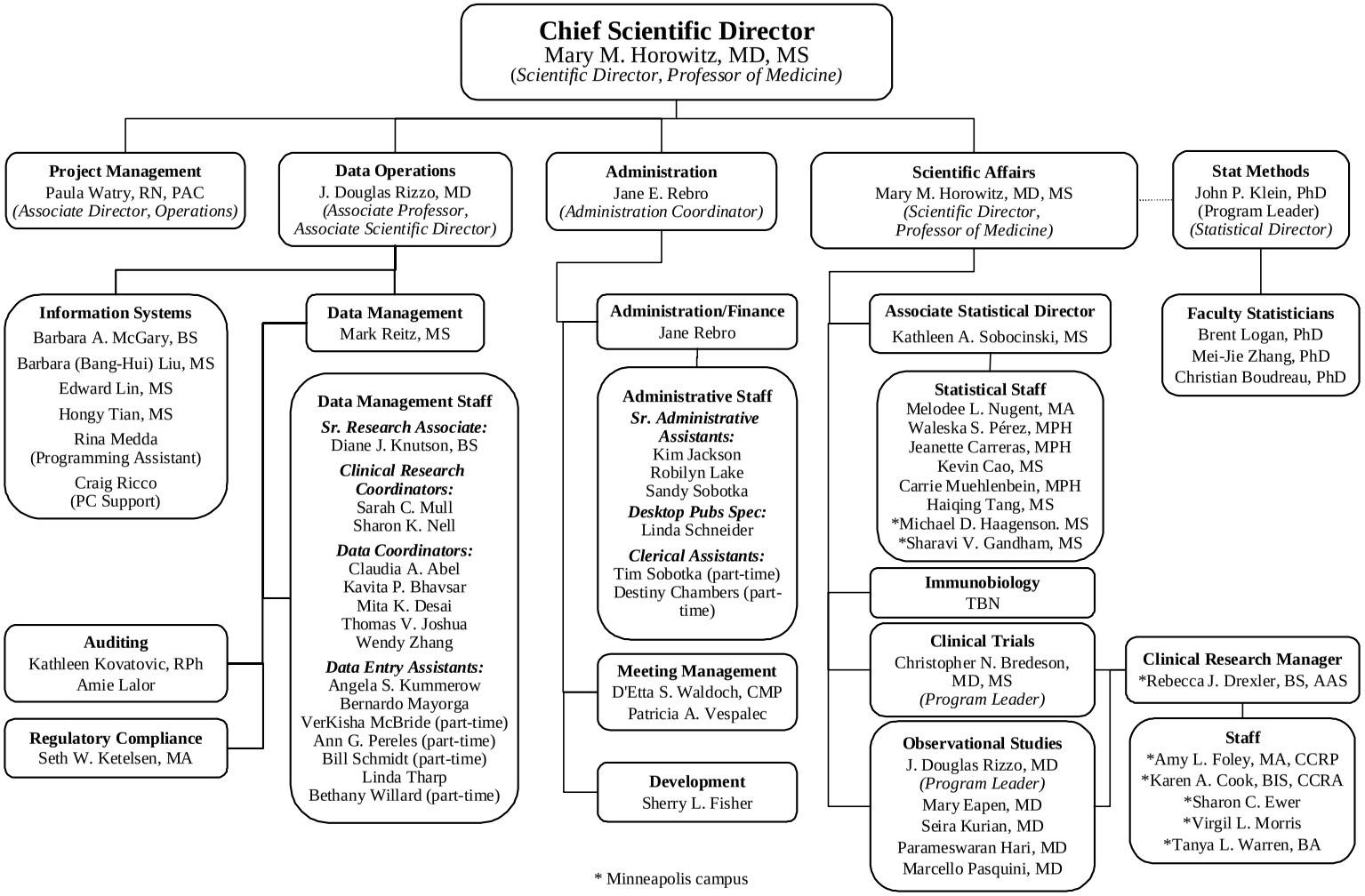


Figure 1.2

CIBMTR Statistical Center Organizational Chart



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 over the coming year can be found in Appendix 4. A summary of the planned 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 (and the use of resources made available through U24-CA76518) 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; and
- 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.

The current Working Committee Structure includes 12 previous IBMTR Working Committees and five new Working Committees with the following indicated areas of responsibility for scientific oversight (Appendix 3):

- Acute Leukemia*: cellular therapy for acute leukemias, preleukemia and myelodysplastic disorders
- Chronic Leukemia*: cellular therapy for chronic leukemias and myeloproliferative disorders
- Lymphoma*: cellular therapy for Hodgkin and non-Hodgkin disease
- Plasma Cell Disorders*: cellular therapy for multiple myeloma and other plasma cell disorders
- Solid Tumors*: cellular therapy for solid tumors
- Pediatric Cancer*: cellular therapy for childhood malignancies and other issues related to use of cellular therapy in children
- Non-Malignant Marrow Disorders*: cellular therapy for aplastic anemia, congenital disorders of hematopoiesis, autoimmune cytopenias and other non-malignant hematopoietic disorders
- Immune Deficiencies/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/Manipulation**: issues related to graft procurement, quality and manipulation
- 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 Services and Psychosocial Issues##: access to cellular therapy including social and economic barriers to care and influence of psychosocial factors on outcome
- Donor Health and Safety##: Donor outcomes

*Existing IBMTR Committee
**Formerly IBMTR Histocompatibility and Graft Sources Committee; histocompatibility issues will now be under purview of Immunobiology Committee
#Formerly under the auspices of the NMDP Histocompatibility Committee
##New Committee

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 Program and the Immunobiology Program. The Steering Committee for the Immunobiology Program is the NMDP Histocompatibility Committee which has the responsibility for reviewing requests for specimens from the NMDP repository. The Committee will include at least one representative from CIBMTR for these deliberations. The Steering Committee for decisions about allocation of resources to conduct clinical trials is not yet appointed; policies and procedures for selecting members are in development. However, no U25-CA76518 funds are used for this purpose.

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. 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, Vice-Chairs, and the three appointed members of the Advisory Committee. Additionally, the CIBMTR Research Advisor, Chief

Scientific Director and Program Leaders serve as Senior ex officio members. 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 will:

- provide direction to the Chief Scientific Director and Statistical Center for scientific activities and policy decisions;
- finalize priorities for scientific studies after obtaining input from the Working Committees;
- review results of audits and recommend measures to correct deficiencies;
- review and assist 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 Committee and Nominating Committee. It will seek input from the CIBMTR Assembly, Advisory Committee and Working Committee chairs in preparing its slate through a mailed request for nominees distributed in March of each year. The slate of candidates will be distributed by e-mailed ballot in September 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 who contribute data and expertise to CIBMTR studies.

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 (Chair, Richard Cooper, M.D.). 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.

Two Associate Directors (Drs. J. Douglas Rizzo and Christopher Bredeson) and two Assistant Scientific Directors (Drs. Mary Eapen and Seira Kurian) also 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. A K23 award funded some of his activities with the CIBMTR until 6/30/04. These 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. He also serves as an attending

physician in MCW's adult HCT unit. Dr. Bredeson is a hematologist and adult HCT transplant physician, formerly of the University of Ottawa, who has an M.S. in Clinical Epidemiology and extensive experience in clinical trials in academic and private settings. He now serves as Clinical Director of the MCW HCT program. He has primary responsibility for developing the Statistical Center's clinical trials support services and also provides medical oversight to the Autoimmune Disease Working Committee.

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. 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 Health Services/Psychosocial Issues Working Committee and the Immune Deficiencies Working Committee.

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. Christian Boudreaux joined the Statistical Center in 2002; his area of expertise is multivariate survival analysis. Other Ph.D. members of the MCW Division of Biostatistics also participate in selected CIBMTR studies. Additionally, there are five Master's prepared 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 Perez, Jeanette Carreras, Haiqing Tang and Catherine Muehlenbein.

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 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 she then did a year as a fellow in Hematopoietic Stem Cell Transplantation and obtained a Masters of Science in Clinical Investigation at Northwestern University in 2004. She serves as Scientific Director of the CIBMTR Infection and Immune Reconstitution Working Committee.

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. 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 has 10 years clinical experience as a Physician's Assistant in the MCW marrow transplant program. See Figures 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 3), 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: IBMTR centers, who must register consecutive transplant recipients, and NMDP centers who must provide outcome data on all transplants facilitated by NMDP.

Table 2.1 shows annual accession of patients from IBMTR 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 IBMTR 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 all patients transplanted in participating centers. Increasing numbers of patients and increasing demands on clinical research associates and data managers in participating centers now make 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 for whom 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 taken over the last few years 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.

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

Table 2.1 Accession of patients (Comprehensive Reports only) into the CIBMTR (IBMTR since 1970, ABMTR since 1991, NMDP since 1987) through June, 2004.

	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			2	2
7/88 - 6/89	1859	9701			74	76
7/89 - 6/90	1936	11637			157	233
7/90 - 6/91	1894	13531			253	486
7/91 - 6/92	2172	15703	9	9	402	888
7/92 - 6/93	2513	18216	874	883	461	1349
7/93 - 6/94	2589	20805	1588	2471	564	1913
7/94 - 6/95	2344	23149	1614	4085	699	2612
7/95 - 6/96	2174	25323	1994	6079	844	3456
7/96 - 6/97	3477	28800	2918	8997	982	4438
7/97 - 6/98	3332	32132	2869	11866	1071	5509
7/98 - 6/99	2723	34855	3540	15406	1130	6639
7/99 – 6/00	2636	37491	2710	18116	1171	7810
7/00-6/01	2602	40093	1756	19872	1266	9076
7/01-6/02	2518	42611	1329	21201	1284	10360
7/02-6/03	2829	45440	1460	22661	1396	11756
7/03-6/04	2519	47959	829	23490	1549	13305

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 Preregistration are found in the Instruction Manual which, along with the required forms, are available on the CIBMTR website (www.cibmtr.org).

Appendix 1 and 2 list institutions currently reporting data to the CIBMTR and the NMDP. We estimate that the CIBMTR collects data on about half of allogeneic HCTs done in North and South America, about 35% of allogeneic transplants done elsewhere and about half of autologous HCTs done in North and South America.

An important early activity of the CIBMTR will be to standardize and coordinate IBMTR and NMDP data collection, analysis and presentation processes. This is a critical goal during the coming grant year; to avoid duplication of effort for reporting cases, ensure that a uniform data is collected for both NMDP and IBMTR cases and that data are easily retrievable in a common format for statistical analysis.

Table 2.2A Distribution of diseases in CIBMTR database (IBMTR since 1970, ABMTR since 1989) through 2004.

	Allogeneic Transplants – IBMTR		Autologous Transplants – ABMTR	
Disease	Registration Data	Comprehensive Data	Registration Data	Comprehensive Data
Acute lymphoblastic leukemia	18572	8997	1332	419
Acute myelogenous leukemia	26801	11895	5792	1750
Chronic myelogenous leukemia	22702	10607	689	270
Chronic lymphocytic leukemia	1436	508	487	109
Hodgkin disease	824	304	10143	1999
Non-Hodgkin lymphoma	6767	2469	25349	5640
Plasma cell disorders	2710	1020	17372	3281
Breast cancer	168	89	22990	7653
Neuroblastoma	161	86	2217	667
Ovarian cancer	18	5	1626	683
Melanoma	43	14	58	2
Lung cancer	9	2	204	124
Sarcoma (soft tissue, bone and other)	32	13	608	201
Ewing sarcoma	50	24	625	214
Wilm tumor	6	2	220	40
Myelodysplastic syndromes	7468	2933	232	69
Other leukemia	1292	562	381	121
Medulloblastoma	4	3	389	92
PNET	1	0	113	33
Germ cell tumor	6	3	418	56
Brain tumors	5	3	929	213
Testicular cancer	7	3	1021	449
Other malignancies[b]	567	210	1244	163
Autoimmune diseases[c]	38	12	267	54
Severe aplastic anemia	7221	4478	-	-
Inherited erythrocyte abnormalities	3906	2581	-	-
SCID and other immunodeficiencies	2709	1224	-	-
Inherited disorders of metabolism	1334	702	-	-
Histiocytic disorders	428	202	-	-
Other non-malignancies	286	46	-	-
TOTAL	105571	48997	94706	24302

[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, 1987-2004 (comprehensive available for all patients).

Disease	Total
Acute myelogenous leukemia	3655
Chronic myelogenous leukemia	3408
Acute lymphoblastic leukemia	2642
Myelodysplastic disorders	1409
Non-Hodgkin lymphoma	981
Severe aplastic anemia	640
Other leukemia	514
Plasma cell disorders	257
Inherited disorders of metabolism	256
SCID and other immunodeficiencies	229
Hodgkin lymphoma	226
Histiocytic disorders	113
Other malignancies	46
Inherited erythrocyte abnormalities	20
Inherited platelet disorders	15
Other	14
TOTAL	14425

3.0 CIBMTR STUDIES

The following section summarizes CIBMTR research activities over the past year and planned for the coming year. Publications include papers published, accepted for publication or submitted for publication, January through December 2004. 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. Because the affiliation between IBMTR and NMDP to establish the CIBMTR only took place in July 2004, only those NMDP studies into which IBMTR personnel had significant input are included in the Publications and Preliminary Results sections.

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: Carrie Muehlenbein, M.S., Mei-Jie Zhang, Ph.D.; Scientific Director: Daniel J. Weisdorf, M.D.

3.1.1 Publications

LK01-01: Cutler CC, Lee SJ, Greenberg P, Deeg HJ, Pérez WS, Anasetti C, Bolwell BJ, Cairo MJ, Gale RP, Klein JP, Lazarus HM, Liesveld JL, McCarthy PL, Milone GA, Rizzo JD, Schultz KR, Trigg ME, Keating A, Weisdorf DJ, Antin JH, Horowitz MM**. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes (MDS): delayed transplantation for low risk myelodysplasia is associated with improved outcome.** *Blood 104:579-585, 2004.* HCT can cure MDS although transplantation carries significant risks of morbidity and mortality. The purpose of this study was to determine the optimal timing of HLA-identical sibling HCT for MDS. A Markov Model was constructed to examine three transplant strategies for newly diagnosed MDS: transplantation at diagnosis, transplantation at leukemic progression and transplantation at an interval from diagnosis but prior to leukemic progression. Analyses using individual patient risk-assessment data from transplant and non-

transplant registries were performed for all four International Prognostic Scoring System (IPSS) risk groups with adjustments for quality of life. For Low and Intermediate-1 IPSS groups, delayed transplantation maximized overall survival. Transplantation prior to leukemic transformation was associated with a greater number of life years than transplantation at the time of leukemic progression. For Intermediate-2 and High IPSS groups, transplantation at diagnosis maximized overall survival. In a cohort of patients under the age of 40, an even more marked survival advantage for delayed transplantation was noted. No changes in the optimal transplantation strategies were noted when quality of life adjustments were incorporated. We concluded that for Low and Intermediate-1 IPSS risk MDS, delayed transplantation from HLA-identical siblings is associated with maximal life-expectancy, while immediate transplantation for patients with Intermediate-2 and High IPSS risk disease is associated with maximal life-expectancy.

LK98-07: 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 MJ, Horowitz MM**. Autotransplantation versus HLA-matched unrelated donor transplantation for acute myeloid leukemia (AML): a retrospective comparison from the National Marrow Donor Program, the International Bone Marrow Transplant Registry and the Autologous Blood and Marrow Transplant Registry.** *Submitted.* About two-thirds of patients with AML do not have HLA-identical sibling donors for HCT. Autotransplants and unrelated donor (URD) transplants often are used in such patients. This study analyzed results of autotransplantation and URD transplantation for AML in first (CR1) or second complete remission (CR2) during 1989 to 1996. Outcomes of 668 autotransplants were compared to outcomes of 476 URD transplants reported to the CIBMTR. Cox proportional hazards regression was used to adjust for differences in prognostic variables. In multivariate analyses, transplant-related mortality was significantly higher and relapse lower with URD transplantation. Adjusted 3-year survival probabilities were 57 (95% confidence interval, 53-61)% with autotransplants and 44 (37-51)% with URD transplants in CR1 (p=0.002); corresponding probabilities in CR2 were 46% (39-53)% and 33 (28-38)% (p=0.006). Adjusted 3-year leukemia-free survival (LFS) probabilities were 53% (48-57)% with autotransplants and 43 (36-50)% with URD transplants in CR1 (p=0.021); corresponding probabilities in CR2 were 39 (32-46)% and 33 (27-38)% (p=0.169). We concluded that while both autologous and URD transplantation produce prolonged LFS in 30-50% of AML patients, high transplant-related mortality substantially offsets the superior anti-leukemia effect of URD transplantation. These data indicate that autotransplantation, in general, offers higher 3-year survival for AML patients in CR1 and CR2. However, cytogenetic data were not available for many of the URD transplant recipients. It is possible that selection bias resulted in generally better risk patients receiving autotransplants and accounted, in part, for the better LFS seen in this group.

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 AML in first remission.** *Submitted.* There is controversy about whether pretransplant consolidation chemotherapy affects outcome of subsequent autotransplantation for AML. We studied the outcomes of 146 patients receiving no consolidation, comparing them to outcomes of 244 patients receiving standard-dose (<1 gm/m^2) and 249 receiving high-dose (1-3 gm/m^2) cytarabine for consolidation prior to autotransplantation, using proportional hazards regression to adjust for differences in prognostic variables. One-year transplant-related mortality was similar among the cohorts. Five-year relapse rates were 49 (39-58)% with no consolidation versus 35 (29-

42)% with standard-dose cytarabine versus 40 (33-48)% with high-dose cytarabine (p=0.07). Five-year 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). 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 first remission should receive consolidation before autotransplantation.

LK00-01 Marks DI, Forman SJ, Blume KG, Pérez WS, Weisdorf DJ, Keating A, Gale RP, Cairo MS, Copelan EA, Horan JT, Lazarus HM, Litzow MR, McCarthy PL, Schultz KR, Smith DD, Trigg ME, Zhang M-J, Horowitz MM. **A comparison of cyclophosphamide and total body irradiation with Etoposide and total body irradiation as conditioning regimens for patients undergoing sibling allografts for acute lymphoblastic leukemia in first or second complete remission.** *Submitted.* We compared the outcome of 298 patients with acute lymphoblastic leukemia (ALL) in CR1 or CR2 who received HLA-identical sibling allografts after cyclophosphamide and total body irradiation (Cy-TBI) conditioning with 204 patients who received etoposide and TBI (Vp16-TBI) conditioning. Initial analyses indicated interactions between Cy, Vp16 and TBI dose. Four groups were compared: Cy-TBI<13 Gy (n=217), Cy-TBI≥13 Gy (n=81),Vp16-TBI<13 Gy (n=53) and Vp16-TBI≥13 Gy TBI (n=151). Among patients receiving ≥13 Gy TBI, transplant-related mortality was lower with Vp16 than with Cy (RR=0.42, p=0.012). Relapse was less likely with TBI doses ≥13 Gy (p=0.01) regardless of whether it was in combination with Vp16 or Cy. Compared to patients receiving Cy-TBI<13 Gy, leukemia-free survival (LFS) was higher among patients receiving Vp16-TBI≥13 Gy (relative risk of treatment failure 0.63, p=0.003). Overall survival was significantly higher in patients who received Cy with ≥13 Gy TBI than with <13 Gy. Causes of death were similar in the four groups with disease recurrence accounting for 47% of deaths. We conclude that among patients results HLA-identical sibling allografts for ALL in CR1 or CR2, there is an advantage to increasing the TBI dose to ≥13 Gy.

3.1.2 Preliminary Results

D0R0-52: Impact of cytogenetics on outcome of HLA-mismatched unrelated donor hematopoietic stem cell transplantation for adults with AML. *Study Chair: M. Tallman, Northwestern University, Chiacago, 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 its efficacy for high-risk cytogenetic subgroups is uncertain. This study analyzed outcomes by cytogenetic risk group in 324 patients in CR1), and 440 in CR2 undergoing NMDP-facilitated unrelated donor HCT from 1988 to 2002. Using the SWOG / ECOG 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 the patients were male and 42% were > 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).

Disease Status	N	Kaplan-Meier Estimate of Survival at 5 years	Kaplan-Meier Estimate of LPS 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 apparent influence on the outcome for patients undergoing URD HCT for AML in CR1. In CR2, results in patients with favorable cytogenetics are somewhat better than 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 for HLA-matched sibling HCT.

3.1.3 Planned Studies

LK01-02: Transplantation versus chemotherapy for relapsed AML. *(Study Chair: M de Lima, MD Anderson Cancer center, Houston, TX, Study Statistician: W. Perez* Data exchange with MD Anderson in progress.

LK02-02: Allogeneic transplants for therapy-related MDS/AML. *(Study Chair: M. Litzow, Mayo Clinic, Rochester, MN , Study Statistician: W. Perez)* Protocol in preparation.

R02-05: Unrelated donor stem cell transplantation in AML and ALL patients who failed an autologous transplant. *(Study Chairs: S. Pavletic, NIH Bethesda, MD, J Foran, University of Alabama, Birmingham, AL; Study Statistician: C. Muehlenbein)*

R02-09: Evaluation of donor leukocyte infusions to treat relapsed hematologic malignancies after related and unrelated donor myeloablative allogeneic hematopoietic stem cell transplantation. *(Study Chair: D. Porter, University of Pennsylvania, Philadelphia, PA; Study Statistician: C. Muehlenbein)*

R02-14: Unrelated donor hematopoietic cell transplantation 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: C. Muehlenbein)*

R03-50: Ph- ALL in adults. *(Study Chair: D. Marks, Bristol Children's Hospital, Bristol, UK; Study Statistician: Sharavi Gandham)* Study file has been prepared; analyses to begin shortly.

LK 03-02: Outcome of Adult Patients aged < 60 years with T(8;21) positive acute myeloid leukemia (AML): Comparison of Cytarabine based chemotherapy with allogeneic stem cell transplantation for consolidation therapy: 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: W. Perez)* Protocol has been developed and data exchange is in progress.

LK03-03: Allogeneic transplants for refractory leukemia. *(Study Chair: M. Duval, Service d'Hemato, Oncologie Hospital Sainte-Justine, Montreal, QC, Canada; Study Statistician: C. Muehlenbein)*

LK04-01: Comparison of autologous hematopoietic stem cell transplantation and allogeneic HCT for patients with acute promyelocytic leukemia (APL) in second complete remission. *(Study Chair: M. Rubinger, Cancercare Manitoba, Winnipeg, Manitoba, Canada, M. Tallman, Northwestern University Chicago, IL; Study Statistician: C. Muehlenbein)*

LK04-02: Transplant outcomes in patients with AML or MDS >55 years of age. (*Study Chair: S. Luger, University of Pennsylvania Philadelphia, PA; Study Statistician: C. Muehlenbein)*

LK04-03: Comparison of autologous blood cell and HLA-identical sibling transplants 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: C. Muehlenbein)*

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., Christian Boudreau, Ph.D.; Scientific Director: Mukta Arora, M.D.

3.2.1 Publications

CK99-01 Passweg JR, Walker I, Sobocinski KA, Klein JP, Horowitz MM, Giralt SA, on behalf of the Chronic Leukemia working committee of the International Bone Marrow Transplant Registry. **Validation and extension of the EBMT risk score for patients with chronic myeloid leukemia (CML) receiving allogeneic haematopoietic stem cell transplants.** *Br J Haematol 125:613-620, 2004.* The recently devised EBMT CML Risk Score used a limited number of variables (donor type, disease stage, recipient age, donor-recipient sex combination, and interval from diagnosis to transplant) to predict survival after HCT for CML. The first objective of this study was to confirm the validity of the EBMT risk score by applying it to an independent population. We studied 3,211 CML patients receiving HCT between 1989 and 1997. 1,737 patients were from centers reporting to both the EBMT and the IBMTR, while 1,474 were from non-EBMT, IBMTR centers. Using Kaplan-Meier curves and Cox regression models, survival probabilities, by EBMT Risk Score, of patients in the EBMT/IBMTR dataset and the independent non-EBMT dataset were almost identical to those in the original EBMT publication. Using the non-EBMT centers as a learning dataset and the EBMT/IBMTR centers as a validation data set, we then 1.) investigated the value of adding other variables to the scoring system; and, 2.) attempted to develop a prognostic score specifically for patients in early first chronic phase of CML. Additional variables considered were CMV antibody status of donor and recipient, Karnofsky performance status, ABO-blood group match and donor

age; only Karnofsky score significantly improved the model in the learning dataset. Cox regression models and measurements of explained variation were used to compare the original EBMT Risk Score with the revised risk score in the validation dataset; the revised score performed only marginally better than the EBMT score. A new risk score for patients in early first chronic phase (CML-CP score) was constructed using the learning dataset and the variables in the EBMT Risk Score, additional variables (as used for the revised score) and the Sokal and Hasford risk scores for newly diagnosed CML. The CML-CP score showed minor improvement over the EBMT risk score in the validation dataset. In conclusion, we validated the prognostic utility of the EBMT risk score for patients receiving allogeneic HCT for CML. Attempts at improving prognostic prediction by adding information from additional variables or designing a risk score specifically for patients in early first chronic phase did not result in improvements of sufficient magnitude to suggest a score revision. The Hasford and Sokal risk scores do not predict survival in recipients of HCT for CML.

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 CML in chronic phase.** *Submitted.* 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.

3.2.1 Preliminary Results

CK98-02: Hematopoietic stem cell transplantation for chronic lymphocytic leukemia (CLL). (*Study Chair: E. Montserrat, Institute of Hematology & Oncology, Barcelona, Spain; Study statistician: K. Sobocinski*) *Manuscript in preparation.* In 1996, we reported on 54 patients receiving allotransplants for CLL in 1984-92. Transplant-related mortality was high but about 40% of patients achieved long-term survival. Since then, numbers of persons receiving allogeneic and autologous transplants for CLL have increased. We studied 242 patients receiving allografts and 83 patients receiving autografts for CLL in 1990-99. Median age was 47 years for allograft recipients and 50 years for autograft

recipients. 211 had received two or more prior treatment regimens; 186 received fludarabine for at least one of these regimens. The median interval between diagnosis and transplantation was 46 months (range, 2-214 months). Allografts tended to be done in patients with more advanced, resistant disease. At time of transplantation, 37% of allograft recipients and 70% of autograft recipients were in clinical CR or had Rai stage 1 disease. 78% of allografts were from HLA-identical siblings, 10% from other relatives and 12% from unrelated donors; 14% were T-cell depleted. Peripheral blood was the graft source for 25% of allografts and 71% of autografts. 72% of autografts were treated to remove CLL cells. The most common conditioning regimens were CyTBI (42%) and CyTBI plus other drug(s) (33%) for allografts and CyTBI (80%) for autografts. 100-day mortality was 18% with HLA-identical sibling transplants, 30% with alternative donor transplants, and 1% with autotransplants. Three-year survival probabilities were 49 (41-57)%, 41 (27-55)%, and 87 (81-96)%, respectively. In preliminary analyses, survival after allografts was better in patients with less advanced disease and good performance status. These data indicate that hematopoietic stem cell transplantation is increasingly used as salvage therapy for CLL with encouraging rates of long-term survival.

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.* We have begun preliminary analyses of 278 transplants for myelofibrosis: 172 from HLA-identical siblings, 33 from other related donors and 73 from unrelated donors. Median age of recipients is 45 years. Outcomes are summarized below. Additional analyses are in progress.

Outcome event	HLA identical sibling donor	Other related Donor	Unrelated donor
Relapse			
@ 1 year	26 (19-33)%	9 (2-21)%	28 (17-39)%
@ 5 years	37 (29-46)%	29 (8-57)%	32 (21-44)%
Transplant-related mortality			
@ 1 year	25 (19-32)%	47 (30-64)%	44 (32-56)%
@ 5 years	32 (25-40)%	55 (37-72)%	48 (36-60)%
100-day mortality	22 (16-28)%	27 (14-43)%	47 (35-58)%
Survival			
@ 1 year	59 (51-66)%	54 (37-71)%	35 (25-47)%
@ 5 years	39 (31-48)%	31 (16-49)%	24 (14-35)%

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 >50x109/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 survival and LFSl were 59 (34-81)% and 43 (20-67)%, respectively. Causes of death included interstitial pneumonitis (N=1) and leukemia (N=8). 5-year cumulative incidence of treatment-related mortality was 5% (0-20%). We used a highly sensitive PCR method to examine post transplant blood (2 patients) or bone marrow (2 patients) samples for the tumor specific IgH gene (CDR)III to assess minimal residual disease (MRD). 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 MRD. No evidence of MRD 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 y follow-up 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 transplant. This study demonstrates that identical twin transplants can be performed in advanced B-CLL with low treatment-related mortality and with a high-rate of durable clinical and molecular remissions. The 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.

CK02-02: Effect of introduction of imatinib on use of HCT for CML. *(Study Chairs: S. Giralt, MD Anderson Cancer Center, Houston, TX; M. Horowitz, IBMTR/ABMTR, Medical College of Wisconsin, Milwaukee, WI; Study statistician: K. Sobocinski) Manuscript in preparation.* The discovery and approval of imatinib drastically changed the therapeutic algorithm for CML. Imatinib is now considered the front-line therapy of choice for patients with CML, including those previously considered candidates for allogeneic HCT. The purpose of this study was to compare numbers of allogeneic HCT performed for CML in North America before and after the introduction of imatinib, as well as before and after publication of, the International Randomized Trial of Interferon and STI571 (IRIS); and, to determine whether the types of patients receiving allogeneic HCT changed after introduction of imatinib and presentation of the IRIS study. We identified the numbers and characteristics of CML transplants performed in North America and reported to the CIBMTR from 1999, when results of the Phase I trial of imatinib were reported, until December 2003, after results of the IRIS study were widely publicized. The number of HCTs for CML reported to the CIBMTR in 1999 was 574; 64% 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. Only 44% were done in first chronic phase and 77% of patients received imatinib prior to transplantation. We concluded that 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 CP1. Most patients now receive a trial of imatinib before proceeding to HCT.

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) Analyses in progress.* 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 busulfan (IV Busulfex, IVBu) 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). All patients received the BuCy2 conditioning regimen. 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 IVBu 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 IVBu patients. No matches could be found for 37 IVBu patients. Of the 101 IVBu 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 IVBu; six (2.9%) oral Bu patients failed to engraft (p=0.19). Overall incidence of HVOD28 was 4.6% (4/83) with IVBu and 20.3% (38/149) with oral Bu (p<0.001). Among autotransplant recipients, 100-day mortality was 0% for those receiving IVBu and 9.3% for those receiving oral Bu (p=0.16). Among allotransplant recipients, 100-day mortality was 8.7% with IVBu 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 IVBu 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 IVBu was superior to oral Bu with regard to the probability of HVOD28 and 100-day mortality. Logistic regression analyses by treatment group indicated that IVBu 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 IVBu compared to oral Bu on the outcome of HCT, with lower early mortality associated with IVBu administration. These findings are consistent with results of other controlled and uncontrolled studies comparing IVBu to oral Bu when either is given as a component of an HCT regimen.

3.2.3 Planned Studies

CK00-03: Effect of TBI on allogeneic HSCT outcome. *(Study Chair: JY Cahn, Hôpital Jean Minjo, Besancon, France; Study statistician: K. Sobocinski)* Protocol complete and data set prepared; analyses to begin shortly.

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

R02-25: Impact of HLA genetic disposition on clinical outcome in unrelated hematopoietic stem cell transplant for chronic myeloid leukemia. *(Study Chair: E. Pettersdorf, Fred Hutchinson Cancer Center, Seattle, Washington; Study Statistician; Mike 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)*

CK03-02: 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)* Data set prepared; preliminary analyses in progress.

CK03-01: Impact of Gleevec on SCT outcome. *(Study Chairs: S. Lee, Dana Farber*

Cancer Institute, Boston, MA; R. Maziarz, Oregon Health Sciences University, Portland, OR; Study statistician: K. Sobocinski). A collaboration with the National Marrow Donor Program. Protocol complete; additional data collection required.

CK 04-01: Comparison of outcome of allogeneic stem cell transplant 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 Lymphoma Working Committee. 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.S.; Scientific Director: Parameswaran Hari, M.D.

3.3.1 Publications

LY98-05: Vose JM, Rizzo JD, Wu JT, Armitage JO, Bashey A, Burns LJ, Christiansen NP, Freytes CO, Gale RP, Gibson J, Giralt S, Herzig RH, LeMaistre CF, McCarthy PL, Nimer SD, Petersen FB, Schenkein DP, Wiernik PH, Wiley JM, Loberiza FR, Lazarus HM, van Besien K, Horowitz MM. **Autologous transplantation for diffuse aggressive non-Hodgkin lymphoma (NHL) in first relapse or second remission.** *Biol Blood Marrow Transplant 10:116-127, 2004.* Data on 429 patients were evaluated to assess outcome of autologous HCT for diffuse aggressive NHL transplanted in first relapse or second complete remission. Transplants were performed between the years of 1989 to 1996 and reported by 93 centers in North and South America. The probability of 3-year survival was 44 (33-55)%; the probability of progression-free survival was 31 (27-36)%). Patients transplanted in second complete remission had a 3-year probability of progression-free survival of 38 (30-46)% compared to 28 (22-33)% for those transplanted not in remission ($p < 0.001$). In multivariate analysis, chemotherapy resistance, increased lactic dehydrogenase (LDH) at diagnosis, short interval from diagnosis to relapse, age $\geq$ 40 years, and use of myeloid growth factors to accelerate post-transplant hematopoietic recovery were adverse predictors of survival. We concluded that high-dose chemotherapy and autologous HCT for patients with diffuse aggressive NHL in first relapse or second remission has better results for patients with chemotherapy sensitive disease, longer relapse free intervals, and younger age (less than 40). Exposure to myeloid growth factors to accelerate recovery after autologous marrow transplantation may increase the risk of progression or death.

LY98-10: Freytes CO, Loberiza FR, Rizzo JD, Bashey A, Cairo MS, Gale RP, Horowitz, MM **Myeloablative allogeneic hematopoietic stem cell transplantation in patients who relapse after autologous stem cell transplantation for lymphoma: a report from IBMTR.** *Blood 104:3797-3803, 2004.* Myeloablative allogeneic HCT (alloHCT) is increasingly used in patients with lymphoma who relapse after autologous HCT (autoHCT), since the allografts are tumor-free and can potentially induce a graft-versus-tumor effect. We analyzed 114 patients treated with this approach from 1990 to 1999, to assess disease progression, progression-free survival (PFS), and overall survival. The cumulative incidence of disease progression at 3 years was 52% while treatment-related mortality was 22%, lower than previously reported. Three-year probabilities of overall survival and PFS were 33% and 25%, respectively, but with more prolonged follow-up nearly all patients progressed and five-year probabilities were 24% and 5%, respectively. Complete remission at time of alloHCT and use of total body irradiation in patients with NHL were associated with lower rates of progression and higher overall survival. In summary, alloHCT is feasible in patients with lymphoma relapsing after autoHCT and can result in prolonged survival for some but is usually not curative. Most likely to benefit are

patients who have an HLA-matched sibling donor, are in remission, and have good performance status.

LY 01-02: Navarro WH, Loberiza, Jr FR, Bajorunaite R, Armitage JO, Ballen K, Bashey A, Bredeson CN, Freytes CO, Gibson J, Hale GA, Horowitz MM, Lazarus HM, LeMaistre CF, Lister J, Marks D, Martino R, Maziarz RT, Pavlovsky S, Schiller G, Schouten HC, Stadtmauer E, van Besien K, Vose JM, Rizzo JD. **Impact of body mass index on mortality of patients with lymphoma undergoing autologous hematopoietic cell transplantation (AutoHCT).** *Submitted.* High-dose therapy with autologous HCT is 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 autoHCT for Hodgkin or non-Hodgkin lymphoma between 1990 and 2000 according to body mass index (BMI). Four groups categorized by BMI were compared using Cox proportional hazards regression to adjust for other prognostic factors. 1,909 patients were categorized as normal weight (BMI=18-25), 121 underweight (BMI<18), 1,725 overweight (BMI>25-30), and 926 obese (BMI>30). Outcomes evaluated include overall survival, relapse, treatment-related mortality, and lymphoma-free survival. Treatment-related mortality was similar among the normal, overweight, or obese groups, although the underweight group had a higher risk of treatment-related mortality (relative risk [RR] 2.46, 95% confidence interval [CI] 1.59-3.82; p<0.0001] compared to the normal BMI group. No differences in relapse were noted among the 4 groups. 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, 95% 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 group. In the light of our inability to find differences in survival between overweight or obese and normal weight patients, we conclude that obesity alone should not be viewed as a contraindication to proceeding with autoHCT for lymphoma when otherwise indicated.

3.3.2 Preliminary Results

LY01-01: Outcome of autologous HSCT for NHL in patients age 60 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 is to compare the clinical outcomes of elderly (age $\geq$ 60 years) NHL patients with younger NHL patients (< 60 years) receiving autologous transplantation while adjusting for patient-, disease-, and treatment-related variables. 535 patients age $\geq$ 60 years receiving an autotransplant for NHL between 1990 through 2000 were reviewed and compared to 2848 patients < 60 years receiving autotransplants for NHL within the same time period. Younger patients were more likely to have follicular lymphoma, 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 transplant was similar in the two groups. Median follow-up was 47 (range 1-136) months. In multivariate analysis, older patients were more likely than younger patients to experience treatment-related mortality, more likely to relapse, more likely to have treatment failure and more likely to die. We conclude that autologous HCT for NHL is feasible in patients $\geq$ 60 years of age but treatment-related toxicity is higher and overall outcome is inferior to younger patients. Further studies addressing supportive care particular to older patients and further work to identify elderly patients most likely to benefit from this approach are recommended.

3.3.3 Planned Studies

D98-10: Unrelated bone marrow transplantation for non-Hodgkin's lymphoma. *(Study Chair: P. Bierman, University of Nebraska Medical Center, Omaha, NE; Study*

Statistician: G. Nelson) Data set has been prepared and analyses are in progress.

LY 02-01: Reduced intensity conditioning in patients with NHL. *(Study Chair: K. van Biesen, University of Chicago, Chicago, IL; Study Statistician: J. Carreras)*

LY03-01: Effects of pre-transplant in-vivo rituximab on the outcomes of autologous hematopoietic stem cell transplantation in patients with Non-Hodgkin lymphoma. (*Study Chair: J Vose, University of Nebraska Medical Center, Omaha, NE; Study Statistician: J. Carreras)*

LY04-01: **Alternative stem cell transplantation for lymphoma.** *(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 CNS involvement. *(Study Chair: R. Maziarz, Oregon Health & Science University, Portland, OR; Study Statistician: J. Carreras)*

3.4 <u>Plasma Cell Disorder Working Committee.</u> Co-Chair: Donna Reece, Princess Margaret Hospital, Toronto, Ontario, Canada; Co-Chair: David H. Vesole, Medical College of Wisconsin, Milwaukee, WI; Co-Chair: Hartmut Goldschmidt, University of Heidelberg, Heidelberg, Germany; Statisticians: Mei-Jie Zhang, PhD, Waleska S. Pérez, M.S.; Scientific Director: Parameswaran Hari, M.D.

3.4.1 Preliminary Results

MM00-01: High dose therapy with autologous HSCT for patients with primary systemic amyloidosis. *(Study Chair: DH Vesole, Medical College of Wisconsin, Milwaukee, WI; Study statistician: W Perez).* Analyses in progress. Primary systemic amyloidosis is a rare plasma cell dyscrasia characterized by progressive systemic amyloid deposition leading to multi-system organ failure and death. The median survival from diagnosis is 18 months. Pilot studies of selected patients treated with high dose therapy with autologous HCT have demonstrated hematologic and organ responses, resulting in improved survival compared to historical controls. We studied outcomes of HCT in 107 patients transplanted between 1995 and 2001 reported by 48 centers. Patient characteristics prior to HCT included: median age 55 (31-71); 3% with cardiac LVEF < 40%, 15% with interventricular septal wall thickness ≥ 15 mm, 45% New York Heart Association ≥ Class II; 70% nephrotic syndrome; 94% with > 200 mg/24 h proteinuria; 41% albumin < 2.5 g/dl; 29% with creatinine > 2 mg/dl; 47% elevated alkaline phosphatase, 26% peripheral neuropathy. At diagnosis, only 20 patients (19%) did not have clinical organ involvement. For patients with organ specific data available, pretransplant organ involvement was as follows: cardiac 22 of 106 (22%), renal 77 of 97 (79%) and hepatic 29 of 104 (28%). Most patients were treated early in their disease course. The numbers of lines of prior therapy were: 0 (35%), 1 (40%), 2 (12%), ≥ 3 (13%). Timing of HCT in the patients' disease courses were: 36% at the 1st treatment, 38% <6 months from 1st treatment, 17% 6-12 months from 1st treatment and 9% >12 months from 1st treatment. Most (81%) patients received high dose melphalan containing regimens. The remaining patients received TBI-based (8%) or other regimens (11%). 7 patients received grafts that had undergone tumor purging. Response to transplant was evaluated at ≤100 days using amyloidosis specific criteria based on involved organs. Responses were seen in at least one organ system (hematologic, renal, hepatic, cardiac)

at one year. Seventeen patients (16%) had a complete remission, 17 (16%) patients had a partial response, 33 (31%) patients had stable disease, 11 (10%) patients had progressive disease and 29 (27%) died of treatment-related mortality. The 100 day mortality was 26 (18-35)%. After a median follow-up of 30 months posttransplant, the overall survival at 1 year and 3 year was 66 (56-75)% and 56 (45-66)%, respectively. One-year survival in patients based on pre-transplant organ involvement (cardiac, renal, hepatic) was: 72 (61-82)% if 0 or 1 organ involved and 54 (38-70)% if ≥ 2 organs were involved. As in previous reports, one-year survival for patients with cardiac involvement was inferior to those without cardiac involvement 56 (37-74)% vs. 69 (58-79)%. This difference was not significant (p=0.25), in part a limitation of the available sample size. These multi-institutional data suggest somewhat higher 100-day mortality and lower rates of hematologic response than reported by single institutions (Gertz et al Am J Med 113, 549, 2002; Sanchorawala et al Bone Marrow Transplant 28:637, 2001), while other organ response rates seem comparable. One and 3 year survival is similar to prior reports as is the poorer results with cardiac or multiple organ involvement. None of the variables tested in the multivariate analysis were significantly associated with survival. HCT appears to improve survival in select patients with amyloidosis. Comprehensive data in a larger patient population are required to determine optimal patient selection and prognostic features for favorable transplant outcomes.

3.4.2 Planned Studies

MM00-02: Outcomes following syngeneic HSCT for multiple myeloma: a matched comparison with autologous and allogeneic HSCT. (*Study Chair: A. Bashey, University of California-San Diego, La Jolla, CA; Study statistician: WS. Pérez*) Preliminary analyses in progress.

D01-117: Comparison of myeloablative vs non-ablative unrelated donor transplant for multiple myeloma. *(Study Chair: D. Vesole, MCW, Milwaukee, WI; Study Statistician: H. Tang)*

MM01-01: High-dose chemotherapy followed by autologous or allogeneic HSCT in patients with Waldenstrom Macroglobulinemia. *(Study Chair: A. Anagnostopoulos, M.D. Anderson Cancer Center, Houston, TX; Study statistician: WS. Pérez)*

MM02-01: Autologous versus allogeneic HSCT for multiple myeloma in patients <45 years of age. *(Study Chair: C. Freytes, University of Texas Health Science Center, San Antonio, TX; Study statistician: WS. Pérez)*

MM02-02: Outcome of HCT for non-secretory multiple myeloma. *(Study Chairs: S. Kumar, Mayo Clinic, Rochester, MN; M. Lacey, Mayo Clinic Rochester, MN; Study statistician: WS. Pérez)*

MM02-03: Comparison of myeloablative vs non-ablative related donor transplants for multiple myeloma. *(Study Chair: O. Ringden, Huddinge University Hospital, Huddinge, Sweden, WI; Study statistician: WS. Pérez*

MM 04-01: DS and ISS as predictors of HCT outcome. *(Study Chair: P. Hari, CIBMTR, Milwaukee, WI; Study Statistician: W. Pérez)*

3.5 <u>Solid Tumors Working Committee.</u> 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 Sobocinski, M.S.; Scientific Director: Mukta Arora, M.D.

3.5.1 Preliminary Results

BC99-01: 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 HSCT between 1992 and 2000. Median age at transplantation was 41 years (range, 25-60 years) and median follow-up for the survivors was 25 months. At time of transplantation, 28 patients (37%) had responsive disease (20 partial responses), 22 (29%) had stable disease, and 18 (24%) had progressive disease. Of the 76 patients, 66 (87%) received stem cells from an HLA-matched sibling and 2 (3%) from an unrelated donor. Sixty-eight patients (90%) received peripheral blood stem cells (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 testes cancer, their value versus a single course of high-dose therapy and HCT is unknown. We performed a retrospective cohort analysis of all cases with detailed research data reported to the ABMTR between 1989-2001. Outcomes were analyzed by the actual number of transplants performed and by "intent to treat" for single versus tandem transplants. To remove waiting time bias for second transplant, calculations were based on patients alive at 4.3 mos, the longest time between 1st and planned 2nd transplant. A total of 303 patients were reported; 259 were analyzed. Their median age was 32; median time from diagnosis to first transplant was 13 months; median follow-up of survivors was 62 months. Of the 259, 165(64%) underwent one planned transplant, 81 (31%) tandem transplants and 13(5%) underwent only one of two planned transplants. Among patients with non-seminoma, 19%, 14% and 33% were in the good, intermediate and poor risk International Prognostic Score groups. First remission transplants were done in 14%; 41%, 20%, and 14% were after 1, 2 or 3 salvage attempts, respectively. Prior to first transplant, 20% had no evidence of disease, 6% were marker positive only, and 74% had measurable disease. Treatment related mortality was 2% at 1 year. PFS was 51% and 39% at 1 and 5 years, respectively. Overall survival was 72% and 34% at 1 and 5 years, respectively. Recurrent cancer was the cause of death in 93%. The groups were balanced for performance status, risk group and seminoma histology. Those receiving one transplant were more likely to be platinum sensitive and to have received more than 2 prior regimens. In univariate analysis, the PFS for patients undergoing one versus both planned transplants was 43% and 34% at 1 and 5 years, respectively; corresponding rates for overall survival were 47% and 35%. For the "intent to treat" analyses, those receiving one planned versus one or both planned tandem transplants, PFS was 43% and 32% at 5 years, respectively. Corresponding overall survival rates were 47% and 33% respectively. The differences were not statistically different. Tandem transplants appear not to offer significant advantages compared to a single transplant.

3.5.2 Planned Studies

ST99-03: Transplants for soft tissue sarcoma. *(Study Chair: K. Antman, Columbia University, New York, NY; Study Statistician: H. Tang)* A data file is in preparation.

ST00-02: Allografts for renal cell cancer. *(Study Chair: A John Barrett, NHLBI/NIH, Bethesda, MD; Study Statistician: K. Sobocinski)* Data collection forms have been revised and accrual of cases is in progress.

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: Carrie Muehlenbein, M.S., Mei-Jie Zhang, Ph.D.; Scientific Director: Mary Eapen, M.D.

3.6.1 Publications

PC 98-03: Warwick A, Zhang M-J, Shuster J, Horowitz, MM, Camitta BM et al**. Chemotherapy versus HLA-identical sibling bone marrow transplantation for higher risk childhood ALL in first remission.** *Submitted.* The use of HC in CR1 for children with higher risk acute ALL is controversial. Results of HLA-identical sibling transplants in 171 children with higher risk ALL in CR1 diagnosed between 1986 and 1994 and reported to the IBMTR were compared with 598 children treated with chemotherapy by the Pediatric Oncology Group. Higher risk T-cell ALL was defined by an initial leukocyte count > 100x10 /L or central nervous system disease. Higher risk B-precursor ALL was defined according to age, gender and initial leukocyte count. Adjusted LFS and overall survival 10 years after CR1 was significantly higher with HCT than with chemotherapy in patients with B-precursor ALL and a gender-matched donor. For all other children, including those with T-cell ALL, 10 year LFS and overall survival were similar with HCT and chemotherapy. Unlike patients with T-cell ALL, a significant proportion of children who relapsed after chemotherapy for B-precursor ALL survived, suggesting successful salvage therapy; few failing HCT for either disease survived. We conclude that, when salvage therapies are considered, most children with higher risk ALL have equivalent long-term survival with either HCT or chemotherapy in CR1.

PC98-05: Godder K, Eapen M, Laver JH, Zhang MJ, Camitta BM, Wayne AS, Gale RP, Doyle JJ, Yu LC, Chen AR, Garvin JH, Sandler ES, Yeager AM, Edwards JR, Horowitz MM. **Autologous hematopoietic stem cell transplantation for children with AML in first or second complete remission — a prognostic factor analysis.** *J Clin Oncol 22:3798-3804, 2004.* The purpose of this study was to determine prognostic factors correlated with outcomes after autologous HCT in children with AML. We studied 219 children who received autologous transplants in first remission and 73 in second remission. Only 29 of the 73 transplanted in second CR, had a first remission duration ≥12 months. The three year cumulative incidences of relapse were 37 (31–44)%, 60 (41–74)%, and 36 (20–53)% for children in first remission, second remission after a short (<12 months) first remission and second remission after a long (≥12 months) first remission, respectively. Corresponding 3-year probabilities of LFS were 54 (47–60)%, 23 (10–39)% and 60 (42–75)%. In multivariate analyses, risks of relapse, mortality and treatment failure (relapse or death, inverse of LFS) were higher for patients in second remission

after a short first remission than for the other two groups. Transplant-related mortality, treatment failure and overall mortality rates were higher in older (>10 years) children. Duration of first CR appears to be the most important determinant of outcome after autotransplants for pediatric AML. Results in children failing conventional chemotherapy support use of autologous HCT as salvage therapy if they achieve a subsequent remission.

PC01-01/HC 01-01: Eapen M, Giralt SA, Horowitz MM, Klein JP, Wagner JE, Zhang MJ, Tallman MS, Marks DI, Camitta BM, Champlin RE, Ringden O, Bredeson CN, Martino R, Gale RP, Cairo MS, Litzow MR, De Lima M. **Second transplantation for acute and chronic leukemia relapsing after first HLA-identical sibling transplantation**. *Bone Marrow Transplant 34:721-727, 2004.* Treatment options for persons with leukemia relapsing after allogeneic transplantation are limited. We analyzed the outcome of 279 patients with acute and chronic leukemia, who relapsed after HLA-identical sibling HCT and received a second allogeneic transplant. The influence of potential risk factors on treatment-related mortality, relapse, treatment failure (relapse or death) and overall survival after the second transplant were assessed using proportional hazards regression. The cumulative incidences of relapse and treatment-related mortality at 5 years were 42 (36-48)% and 30 (24-36)%, respectively. Five year probabilities of both overall and leukemia-free survival were 28 (23-34)%. In multivariate analyses, risks of treatment failure and mortality were lower in younger patients (≤ 20 years), and in those with an interval > 6 months from first transplantation to relapse. Risks of relapse were lower in patients with long intervals from first transplantation to relapse and in complete remission prior to second transplantation but higher with reduced intensity conditioning regimens. The data did not suggest an advantage to using a different HLA-matched related donor for the second transplantation. Though age and disease status influence outcome, duration of remission after first transplantation appears to be the most important determinant of outcome.

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**. *Submitted.* 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 first remission was associated with the lowest disease recurrence, survival and LFS 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 of LFS were 49% and 54% after HLA-matched sibling and unrelated donor transplantation in first remission, 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 first remission using the same eligibility criteria as is currently used for those with HLA-matched sibling donors.

3.6.2 Preliminary results

PC99-02: Auto transplantation for Ewing's sarcoma . *(Study Chair: S. Gardner, The Hassenfeld Children's Center, New York, NY; Study Statistician: J. Carreras)* We have performed preliminary analyses of 136 autologous transplants for Ewing's sarcoma. Median age of recipients is 18 years; 71% are males. 46% of transplants were done as consolidation for disease in complete remission, 43% for disease in partial remission and 11% for stable or progressive sarcoma. Outcomes are summarized below. Additional analyses are in progress.

Outcome event	N Evaluable	Probability (95% CI)[a]
Neutrophils>0.5 x 10^9/L	134	
@ 28 days		97 (80 - 100)
@ 60 days		97 (81 - 100)
Treatment-related mortality	136	
@ 1 year		4 (2 - 8)
@ 3 years		6 (3 - 10)
Relapse/progressive disease	136	
@ 1 year		55 (45 - 64)
@ 3 years		63 (53 - 73)
Disease-free survival	136	
@ 1 year		41 (33 - 50)
@ 3 years		31 (23 - 39)
Overall survival	136	
@ 1 year		62 (53 - 70)
@ 3 years		36 (28 - 45)

[a]Probabilities of neutrophil recovery, treatment-related mortality and relapse were calculated using the cumulative incidence estimate. Disease-free survival and overall survival were calculated using the Kaplan-Meier product limit estimate.

3.6.3 Planned studies

D98-071: Unrelated donor transplantation for myelodysplastic syndrome. *(Study Chair: P. Woodard, St. Jude Children's Research Center, Memphis, TN; Study Statistician: S. Kurian)*

PC99-01: Outcome of HCT for juvenile myelomonocytic leukemia (JMML). (*Study Chair: G. Hale, St. Jude's Children's Research Hospital, Memphis, TN; Study Statistician: C. Muehlenbein*)

D01-59: Unrelated donor transplantation for AML. *(Study Chair: N. Bunin, Children's Hospital of Philadelphia, Philadelphia, PA; Study Statistician: S. Kurian)*

R02-34: Unrelated donor transplantation for Ph+ ALL in children. *(Study Chair: H Frangoul, Vanderbilt University Medical Center, Nashville, TN; Study Statistician: C. Muehlenbein*)

R02-35: Unrelated donor transplantation for Down's/Bloom's syndrome. *(Study Chair: H Frangoul, Vanderbilt University Medical Center, Nashville, TN; Study Statistician: C. Muehlenbein)*

PC03-02: Chemotherapy versus allogeneic transplantation for children with ALL in second remission. *(Study Chair: S. Davies, Children's Hospital, Cincinnati, OH; Study statistician: C. Muehlenbein)*

PC03-05: Chemotherapy vs. allogeneic transplantation for children with isolated central nervous system relapse. *(Study Chair: Mary Eapen, CIBMTR, B.M. Camitta, Children's Hospital of Wisconsin, Milwuakee, WI; Study Statistician: C. Muehlenbein)*

PC04-01: Outcomes after unrelated donor transplantation for Ph+ ALL. *(Study Chair: BM Camitta, Children's Hospital of Wisconsin, Milwaukee, WI, Study Statistician: C. Muehlenbein)*

PC04-02: Outcomes after reduced intensity conditioning regimen for acute leukemia in children. *(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)*

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.S., Christian Boudreau, Ph.D.; Scientific Director: Mary Eapen, M.D.

3.7.1 Publications

AA 00-02: Roy V, Perez WS, Marsh JCW, Pasquini M, Pasquini R, Ball SE, Camitta BM, Eapen M. Gale RP, Gross TG, Hale GA Horan JT, Lipton JM, Mustava MM, Niemeyer CM, Orchard PJ, Bredeson CN. **Bone marrow transplantation for Diamond-Blackfan Anemia.** *Submitted.* Patients with Diamond-Blackfan Anemia (DBA) who are unresponsive or intolerant to corticosteroids, fail other treatments, develop additional cytopenias or clonal disease, or who opt for curative therapy are often treated with allogeneic HCT. We studied transplant outcomes of 61 DBA patients transplanted between 1984 and 2000. Median age (range) was 7 (1-32) years. Among 55 patients with available transfusion information, 35 (64%) had received ≥ 20 units of blood prior transplant. Most patients (67%) received grafts from an HLA-matched related donor. Median time to neutrophil recovery was 17 days (10-119) and platelet recovery was 23 days (9-119). Five patients did not achieve neutrophil engraftment. The 100-day mortality rate was 18 (10-29)%. Grade II-IV acute graft-versus-host disease (GVHD) occurred in 28 (17-39)% and chronic GVHD in 26 (15-39)%. The three-year probability of overall survival was 64 (50-74)%. In univariate analysis, Karnofsky score ≥ 90 and transplantation from an HLA-identical sibling donor were associated with better survival. These data suggest that allogeneic HCT is effective for treatment of DBA. Transplantation prior to deterioration of performance status and from an HLA-identical sibling donor are associated with better outcome.

3.7.2 Preliminary Results

AA 98-02: Bone marrow transplants from mismatched related and unrelated donors for severe aplastic anemia. *(Study Chair: J. Passweg, University of Basel, Basel, Switzerland; Study Statistician: W. Perez) Manuscript in preparation.* Patients with acquired severe aplastic anemia (SAA) without a matched sibling donor and not responding to immunosuppressive treatment, bone marrow transplantation from an alternative donor is often attempted. We examined risks of graft failure, acute and

chronic GVHD and overall survival after alternative donor transplantation between 1988 and 1998 in 318 such recipients. Sixty-six of 318 (21%) received allografts from a one antigen mismatched and 20 of 318 (6%) from >1 antigen mismatched related donor. One hundred and eighty one of 318 (57%) received allografts from matched and 51 of 318 (16%) from a mismatched unrelated donor. Most patients were young, had had multiple red blood cell transfusions and poor performance score at transplantation. After adjusting for other significant covariates, the risks of graft failure and overall mortality did not differ 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 >1 antigen mismatched unrelated donor transplants were 21 (12-32)%, 25 (9-45)%, 15 (10-20)% and 18 (9-29)%, respectively. Corresponding probabilities of overall survival at 5 years were 49 (36-60)%, 30 (12-50)%, 39 (31-46)% and 36 (23-50)%, respectively. Though alternative donor transplantation results in long-term survival in a considerable proportion of patients, risks of mortality after transplantation remain high. Poor performance score and age (>21 years) adversely affect outcomes after transplantation. Therefore, early referral for transplantation should be encouraged for patients with SAA who fail immunosuppressive therapy and have a suitable alternative donor.

AA 98-03: HLA-identical sibling bone marrow transplantation (BMT) for severe aplastic anemia (SAA): Results of a randomized controlled trial. *(Study Chair: R. Champlin, MD Anderson Cancer Center, University of Texas, Houston, TX; Study Statistician: W. Perez) Manuscript in preparation.* Addition of antithymocyte globulin (ATG) to a preparative regimen of high dose cyclophosphamide has been advocated to enhance engraftment after allogeneic BMT for treatment of aplastic anemia. 134 patients with SAA were randomized to receive cyclophosphamide (CY) alone or in combination with ATG as a preparative regimen for allogeneic BMT 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 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	Cy+ATG	P-value
Number of patients	62	72	
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 cyclophosphamide as a preparative regimen for patients with severe aplastic anemia.

AA 00-01: Comparison of allogeneic bone marrow and peripheral blood stem cell transplantation for aplastic anemia: Collaborative study of IBMTR and EBMTR. *(Study Chair: H. Schrezenmeier, University of Berlin, Germany; Study Statistician: Jeanette 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. To date, limited data exist regarding the relative merits of PB versus BM as a graft source in transplantation of non-malignant marrow disorders. We compared results of 151 HLA-identical sibling PBSCTs with results of 722 HLA-identical sibling BMTs 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 posttranplant, and type of GVHD prophylaxis. PBSC recipients were more likely than BM recipients to receive TBI-based conditioning (12% vs 5%) and tended to have a longer interval between diagnosis and transplantation (median 4 vs 2 mos). Recovery of neutrophils and platelets was significantly faster after PBSCT than after BMT (median time to $\geq 0.5 \times 10^9$/L neutrophils 13 versus 19 days, p<0.001; median time to $\geq 20 \times 10^9$/L platelets 25 versus 15 days, p<0.001). The cumulative incidences of acute GVHD at 100 days posttransplant 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 after PBSC and BM transplantation were 67 (58-74)% and 80 (76-82)%, respectively (p < 0.05). In conclusion, other than early hematopoietic recovery, our study suggests no advantage of PBSC over BM for HLA-identical sibling transplantation in acquired aplastic anemia and raises concern about possibly poorer long-term outcomes with this graft source. Further evaluation of PBSC transplantation for AA should be done in the context of controlled clinical trials.

AA 00-03: Comparison of outcome following HLA-Identical sibling bone marrow transplantation for Fanconi Anemia with radiation versus non-radiation conditioning regimes. *(Study Chair: Pasquini R. , Hospital de Clinicas-Federal University , Of Parana-Brazil, Curitiba, Brazil; Study Statistician: J. Carreras) Additional analyses in progress.* We studied 148 patients younger than 21 years receiving their first HLA-identical sibling bone marrow transplant for Fanconi Anemia, between 1991 and 2001. The cases identified came from 35 reporting teams from 16 different countries. 77 received an irradiation-containing conditioning regimen and 71 received a non-irradiation conditioning regimen. The median follow-up of survivors was 96 (9 - 153) months for patients who received an irradiation-containing regimen and 58 (16 - 143) months for those who received a non-irradiation containing regimen. The three-year probability of survival for the entire cohort was 82 (75-87)%. After adjusting for other significant factors, risks of overall mortality were similar after irradiation containing and non- irradiation containing conditioning regimens. Factors associated with higher mortality were older age at transplantation (> 10 years), receiving androgens prior to transplantation and donor and/or recipient positivity for CMV serology.

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). Additional analyses in progress.* While allogeneic transplantation is the only approach that can correct hematological complications of Fanconi anemia, unrelated donor transplantation has

been severely limited by graft rejection and regimen-related toxicity with resultant poor survival. Therefore, we evaluated the impact of potential prognostic factors on hematopoietic recovery, GVHD and overall survival in 98 recipients of unrelated donor transplantation, transplanted in 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 and, 45 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 cyclophosphamide and irradiation and, 46%, a fludarabine-containing preparative regimen (FLU). All patients received bone marrow grafts and 78% were matched at HLA A, B, (low resolution) and DRB1 or mismatched (22%) 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 FLU-containing preparative regimens (median 21 vs. 135 months; FLU 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-FLU containing preparative regimens in patients with DEB mosaicism (cumulative incidence 52%, $p<0.0001$) than without DEB mosaicism (89%); however, neutrophil recovery was not influenced by DEB mosaicism with FLU containing preparatory regimens (94% and 93%). Similarly, platelet recovery (>20,000) was less likely with non-FLU containing preparatory regimens (19% vs. 76%, $p<0.0001$); favorable risk factors were absence of myelodysplasia/leukemia and < 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 recipients of non T cell depleted grafts (62% and 47%, respectively). Mortality was significantly higher with non-FLU containing preparative regimens (RR 3.24, 95% CI 1.86–5.66, $p<0.0001$) than with FLU containing preparative regimens. Corresponding probabilities of overall survival were 17% and 57%, respectively. 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 did not affect mortality. Based on these results significant practice changes should be considered: use of a FLU containing preparative regimen and transplantation prior to > 20 blood product transfusions.

3.7.3 Planned Studies

AA 01-01: Allotransplantation for sickle cell disease. *(Study Chairs: J. Panepinto, Medical College of Wisconsin, Milwaukee, WI, M Walters, Oakland Children's Hospital, CA; N Kamani, Children's National Medical Center, Washington, DC; Study Statistician: J. Carreras)*

AA 02-01/R03-56: Allogeneic HSCT with fluadarabine-based conditioning for severe and very severe aplastic anemia. *(Study Chair: M. Sabloff, Ottawa Hospital, Ottawa, Ontario, Canada, L. Krishnamurti), Children's Hospital of Pittsburgh, Pittsburgh, PA; Study Statistician: J. Carreras)*

AA 02-02: Incidence of post-transplant malignancies among patients receiving HSCT for Fanconi anemia, Schwachmann Diamond, Diamond-Blackfan anemia, congenital neutropenia and dyskeratosis congenita. *Study Chair: J Marsh, St. George's Hospital Medical School, London, UK, R Pasquini, Hospital de Clinicas, Curitiba, Brazil; Study Statistician: J. Carreras)*

AA 02-03: Allogeneic transplants with fludarabine-based conditioning regimens for paroxysmal nocturnal hemoglobinuria. *(Study Chair*: *M. Pasquini, CIBMTR; Study Statistician: J. Carreras)*

AA 03-01: Second transplants for aplastic anemia. *(Study Chair: J. Horan, University of Rochester, Rochester, NY; Study Statistician: J. Carreras)*

AA 03-02: Allogeneic transplants for thalassemia. *(Study Chair: M. Sabloff, Ottawa Hospital, Ottawa, Ontario, Canada; Study Statistician: J. Carreras)*

AA 04-01: Allogeneic HCT for congenital amegakaryocytic thrombocytopenia. *(Study Chair: M. Pasquini, CIBMTR, G. Hale, St. Jude's Children's Research Hospital, Memphis, TN; Study Statistician: J. Carreras)*

3.8 Immune Deficiencies/Inborn Errors Working Committee (previously Immune Deficiency and Metabolic Disorders Working Committee). 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.S., Christian Boudreau, Ph.D.; Scientific Director: Mary Eapen, M.D.

3.8.1 Publications

ID98-03: Hematopoietic stem cell transplantation for Chediak-Higashi syndrome (CHS). *CA DeLaat, M Eapen, MM Horowitz, KS Baker, CN Bredeson, MS Cairo, MJ Cowan, J Kurtzberg, M Matlack, CG Steward, PA Veys and AH Filipovich. Submitted.* We studied 34 children receiving HCT for CHS in 1980–1999. Median age at HCT was 5 (range, 1–19) years. 20 patients reported a history of accelerated phase at some time pretransplant and 9 were in accelerated phase at time of HCT. 13 patients received their allograft from an HLA-identical sibling, 10 from an alternative related donor and 12 from an unrelated donor. 21 patients are alive at last follow-up; 20 are in clinical remission. Although numbers are small, the risk of acute GVHD appears to be higher among recipients of unrelated donor HCT. The risks of treatment failure and mortality were somewhat higher among recipients of alternative related donor HCT. These data suggest that allogeneic HCT may be effective and that unrelated donor HCT may be a suitable alternative in the absence of an HLA-identical sibling donor.

3.8.2 Preliminary Results

ID98-04: HCT for globoid cell leukodystrophy. *(Study chair: C. Peters, Fairview-University of Minnesota Hospitals and Clinics, Mayo, Minneapolis, MN; Study Statistician: M. Eapen). Analyses in progress*. Globoid cell leukodystrophy (GLD) is a rare disorder; there is deficiency of galactocerebrosidase with progressive loss of central and peripheral myelin. HCT has been shown in small studies to be effective in providing the deficient enzyme, thus offering the possibility of cure. We studied 34 children receiving HCT for GLD between 1989-2000. 26 allografts were from unrelated donors, 7 from HLA-identical siblings donors and 1 from an alterative related donor. Twenty-three children received umbilical cord blood HCT, and the remainder, bone marrow. Busulfan/cyclophosphamide was the most frequently used preparative regimen. Post-HCT, 20 children are alive with a median follow-up of 30 (range, 5-115) months. One and 3-year probabilities (95% confidence interval) of overall survival were 67 (48-80)%, and 58 (39-74)% respectively. This analysis represents the largest yet conducted on the outcome of transplantation for GLD and confirms the effectiveness of HCT as therapy for GLD.

ID98-05: Stem cell transplantation for infantile osteopetrosis. *(Study Chair: A. Fasth, Queen Silvia Children's Hospital, Goeteberg, PJ Orchard, University of Minnesota, Minneapolis, MN; Study Statistician: M. Eapen) Manuscript in preparation.* Infantile osteopetrosis is a rare lethal disorder; children are severely affected within months after birth and if left untreated, only about 30% survive to 6 years. HCT has been shown in small studies to be effective in reconstituting osteoclast function thus offering the possibility of cure. We studied 94 children receiving HCT for osteopetrosis between 1978-1999 and reported to the IBMTR and/or NMDP. 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 HCT, one, a peripheral blood HCT and the remainder, bone marrow. Busulfan/cyclophosphamide (77%) was the most frequently used preparative regimen; 18% received total body irradiation. 14% of grafts were T-cell depleted. Post-SCT, 44 children are alive with a median follow-up of 49 (range, 4-266) months. 3-year probabilities (95% confidence interval) 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 represents the largest yet conducted on the outcome of transplantation for osteopetrosis and confirms the effectiveness of HCT as therapy for osteopetrosis.

ID99-02: The role of Hematopoietic Stem Cell Transplantation 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 IBMTR, the European Blood and Marrow Transplantation Registry 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 of the poor prognosis organs (bone marrow, liver or lung) involved. Six patients had stable disease at transplantation and 16, progressive disease. With a median follow up of over 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 include: recurrent/progressive disease (n=2), veno-occlusive disease (n=2), infections (n=7) and diffuse alveolar hemorrhage (n=1). We concluded that while HCT in LCH is feasible for patients who fail conventional therapy, treatment-related mortality is high. It is uncertain whether newer approaches in transplantation such as reduced-intensity conditioning regimens may lower treatment-related mortality.

3.8.3 Planned Studies

ID98-02: HCT for severe combined immuno-deficiency 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 National Medical Center, Washington, DC; Study Statistician: S. Kurian)*

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

ID 02-03: HCT for Hurler syndrome: Comparison of outcomes after HLA-identical sibling and unrelated donor transplants. *(Study Chair: S. Grewal, University of Minnesota, Minneapolis, MN; Study Statistician: 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)*

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, Haiqing Tang, M.S.; Scientific Director: Christopher Bredeson, M.D.

3.9.1 Publications

AI00-04: Snowden JA, Passweg J, Moore JJ, Miliken S, Cannell P, van Laar JM, Verburg R, Szer J, Taylor K, Joske D, Rule S, Bingham S, Emery P, Burt R, Lowenthal RM, Durez P, McKendry R, Pavletic S, Espigado I, Jantunen E, Kashyap A, Rabusin M, Brooks, Bredeson C, Tyndall A. **Autologous HSCT in severe rheumatoid arthritis: a report from the EBMT and ABMTR.** *J Rheumatol, 31:482-488, 2004.* Since 1996, autologous HCT has been used to treat severe rheumatoid arthritis. Published reports describe individual cases or series containing relatively small numbers. This study aimed to combine most of the worldwide experience in one analysis. The Autoimmune Disease databases of the EBMT and the IBMTR were used to identify patients with rheumatoid arthritis treated with autologous HCT. Further information relating to patient and treatment specific parameters was obtained by questionnaire. Seventy-six patients were registered from 15 centers using diverse transplant protocols. Seventy-three patients received autologous HCT and three patients were mobilized but not transplanted; one because of good response and two refused transplant. Transplanted patients (median age 42 years, 74% females, 86% rheumatoid factor positive) had been previously treated with an average of 5 (range 2-9) disease modifying antirheumatic drugs (DMARDs). Significant functional impairment was present with a median health assessment questionnaire (HAQ) score of 1.4 (range 1.1-2.0) and Steinbrocker score mean 2.39 (SD 0.58). The intensive immunosuppressive treatment regimen was Cy alone in most patients, mostly 200 mg/kg (n=62). Seven patients received ATG in addition to Cy, two patients BuCy and one patient CyTBI and ATG. One patient received fludarabine with ATG. Following treatment, one patient received a bone marrow graft; the rest chemotherapy and/or G-CSF mobilized PBSC. The autologous graft was unmanipulated in 28 patients, the rest receiving some form of lymphocyte depletion, mostly through CD34 selection. Median follow-up was 16 months (range, 3-55 months). Responses were measured using the American College of Rheumatology (ACR) criteria. Forty-nine patients (67%) achieved at least ACR 50 at some point following transplant. There was a significant reduction in the level of disability measured by the HAQ ($p \leq 0.005$). Most patients were re-started on DMARDs within six months for persistent or recurrent disease activity, which provided disease control in

approximately half the cases. One patient died 5 months post transplant from infection and an incidental non-small cell lung cancer. Autologous HCT is a relatively safe form of salvage treatment in severe, resistant RA. Further collaborative clinical trials are necessary to develop this approach.

Bredeson CN, Pavletic SZ. **Considerations when designing a clinical trial of hematopoietic stem cell transplantation for autoimmune disease.** *Best Pract Res Clin Haematol 17:327-343, 2004.*

3.9.2 Planned Studies

This committee was recently reorganized and will be meeting in February 2005 to plan a scientific agenda for the coming year.

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; Statisticians: Sharavi Gandham, M.S., John Klein, Ph.D.; Scientific Director: Mary M. Horowitz, M.D.

3.10.1 Publications

GV98-07: Oh H, Loberiza, Jr., FR, Zhang M, Ringdén O, Akiyama H, Asai T, Miyawaki S, Okamoto S, Horowitz MM, Antin J, Bashey A, Bird JM, Carabasi MH, Fay JW, Gale RP, Giller RH, Goldman JM, Hale GA, Harris RE, Henslee-Downey PJ, Kolb HJ, Litzow MR, McCarthy PL, Neudorf SM, Serna DS, Socié G, Tiberghien P, Barrett AJ. **Comparison of graft-vs-host disease and survival after HLA-identical sibling bone marrow transplantation in different ethnic populations.** *Blood, 2005. In press.* 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) transplant-related mortality 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, or 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, but that overall survival after transplantation is similar among ethnic groups.

GV98-09: Cahn J-Y, Klein JP, Lee SJ, Milpied N, Blaise D, Antin JH, Leblond V, Ifrah N, Jouet JP, Loberiza Jr. FR, Ringden O, Barrett AJ, Horowitz MM, Socié G. **Evaluation of two acute graft versus host (GVHD) grading systems: dynamics of onset and predictive factors for survival: A joint Société Francaise de Greffe de Moëlle et Thérapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI) and International Bone Marrow Transplant Registry (IBMTR) prospective study.** *Submitted.* Acute GVHD is a significant cause of morbidity and mortality after allogeneic stem-cell transplantation. The commonly used grading system was introduced thirty years ago by Glucksberg in order to better correlate grading with various outcomes. Rowlings et

al. published a revised grading system, the IBMTR classification, in 1997. To further explore the validity of the two classifications and evaluate dynamic aspects of GVHD for their impact on survival, we conducted a prospective multicenter study of 607 patients scored weekly for GVHD in 18 transplant centers. Median patient age was 36.6 years (range 1-65); patients were treated for leukemia. Sixty-nine percent of donors were HLA-identical siblings and 28%, unrelated donors. All patients received non-T-cell depleted grafts. The conditioning regimen included total body irradiation in 442 (73%) patients. The IBMTR and Glucksberg performed similarly in terms of the percent of variability in survival explained by grade of acute GVHD; the Glucksberg classification was somewhat better at predicting early survival. Comparison of computed versus reported grading showed less physician bias in assigning grades with the IBMTR scoring method. This prospective analysis also allowed us to study the impact of acute GVHD as a dynamic process and its effects on survival over time. We found that with either system, only maximum observed grade had prognostic significance for survival; neither time of onset nor progression after any initially lower grade of acute GVHD was associated with early or late survival. Regardless of the scoring system used, acute GVHD severity explained only a small percentage of observed variability in survival.

GV00-01: Seebach JD, Stussi G, Passweg JR, Loberiza Jr. FR, Gajewski JL, Keating A, Goerner M, Rowlings PA, Tiberghien P, Elfenbein JG, Gale RP, van Rood JJ, Reddy V, Gluckman E, Bolwell BJ, Klumpp TR, Horowitz MM, Ringdén O, Barrett AJ. **ABO blood group barrier in allogeneic bone marrow transplantation revisited** *Submitted.* Some published reports suggest a worse outcome of HCT when donor-recipient pairs are mismatched for ABO-blood groups. These studies, however, included small and heterogenous 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, transplant-related mortality and occurrence of acute and chronic GVHD in a large homogenous group of patients undergoing allogeneic bone marrow transplantation. 3103 patients with early disease stage leukemia, transplanted between 1990 and 1998 with bone marrow from an HLA-identical sibling and reported to the CIBMTR were studied. Median follow-up was 54 months. 2108 (68%) donor-recipient pairs were ABO identical, 451 (14%) 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, transplant-related mortality and grade II-IV acute GVHD, there were no significant differences among the 4 groups. Bidirectional ABO mismatch was associated with a significantly higher risk of grade III-IV acute GVHD (hazards ratio 1.87, 95% CI, 1.19-2.93, p=0.006). Patients with major ABO mismatch received RBC transfusions (p=0.001) for a longer time posttransplant and had a slightly slower neutrophil recovery (p<0.001). We concluded that there is no evidence of a substantial effect of ABO blood group incompatibility on the outcome of conventional BMT among patients with leukemia.

GV02-01: Khoury HJ, Loberiza FR, Jr, Ringdén O, Barrett AJ, Bolwell BJ, Cahn J-Y, Champlin RE, Gale RP, Hale GA, Urbano-Ispizua A, Martino R, McCarthy PL, Tiberghien P, Verdonck LF, Horowitz MM. **Impact of post-transplant G-CSF on outcomes of allogeneic hematopoietic stem cell transplantation.** *Submitted.* Granulocyte-colony-stimulating factor (G-CSF) is often administered after HCT to accelerate neutrophil recovery, but its impact on transplant outcomes is unclean. We analyzed the impact of giving G-CSF within 7 days post-transplant on the outcomes of 2,719 allogeneic transplants for AML (n=1285) and CML (n=1434) performed between 1995 and 2000 using unmanipulated sibling bone marrow (BM, n=1435), peripheral blood stem cell (PBSC) (n=609), or unrelated donor BM (n=675) grafts. Outcomes were compared within each cohort depending on whether or not G-CSF was given. Median follow-up was > 30 months (range, 2-87 months). Probabilities of acute and chronic GVHD, day +30 and

+100 treatment-related mortality, LFS 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 these outcomes. In conclusion, results of this study found no benefit or disadvantage of giving G-CSF posttransplant.

3.10.2 Preliminary Results

GV99-03: Donor leukocyte infusions to treat hematologic malignancy relapse following allogeneic stem cell transplantation in a pediatric population. *(Study Chair: J. Levine, University of Michigan, Ann Arbor, MI; Study Statistician: S. Gandham) Manuscript in preparation.* The effectiveness of donor leukocyte infusions (DLI) in prolonging survival following post-allogeneic stem cell transplantation 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 strategies that employ DLI. 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 posttransplant relapse between July 1991 and December 1999. Forty-seven patients had a 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 months (range, 1–116 months). The median time from relapse to DLI was 45 days (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 MDS/JMML 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.

D96-01: 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). Manuscript in preparation.* Unrelated donor HCT is an effective treatment for malignant and non-malignant diseases of childhood, but significant morbidity and mortality occur as a result of acute GVHD. To determine the incidence and risk factors for acute GVHD in children, we analyzed 2,121 unrelated donor transplants facilitated by the NMDP in which the recipient was <18 years of age, survived at least 21 days, achieved hematopoietic recovery, and had available high resolution HLA DRB1 typing. Risk of acute GVHD was reduced in children younger than 2 years compared with older children, but no significant effect of age was seen in the older patient groups. Independent multivariate models for children with malignant and non-malignant diagnoses showed notable differences by diagnosis. T-cell depletion markedly reduced risk of GVHD in non-malignant diagnoses and, to a lesser degree, in those with malignant diagnoses. The model of non-malignant disease showed no effect of HLA-mismatch on grades III-IV acute GVHD. The model for malignant disease showed significantly increased risk associated with mismatch at HLA DRB1 and HLA B, but borderline significantly increased at HLA A. Acute GVHD was associated with a decreased risk of relapse in children with ALL only (RR 0.41, p=0.0001). Risk of chronic GHVD increased with increasing age and in those receiving T-replete grafts. The data demonstrate that risk factors for acute GVHD in children with malignant disorders are similar to adults and these children can be included in studies testing methods to treat or prevent GVHD in adults. Children with non-malignant diseases have different risk factors and should be considered separately.

3.10.3 Planned Studies

GV00-02: Risk factors for AGVHD. *(Study Chairs: P. McCarthy, Roswell Park Cancer Institute, Buffalo, N.Y., T. Hahn, Roswell Park Cancer Institute, Buffalo, N.Y.; Study Statistician: K. Sobocinski)* A data file has been prepared and preliminary analyses are in progress.

GV01-01: Outcomes of reduced intensity versus conventional conditioning in leukemia. (*Study Chair: O. Ringdén, Huddinge University, Huddinge, Sweden; Study Statistician: C. Bredeson*)

D01-91: Effect of Rituxan 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)*

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

3.11 Graft Sources and Manipulation Working Committee. 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: Haiqing Tang, M.S., Mei-Jie Zhang, PhD; Scientific Director: Mary Eapen, M.D.

3.11.1 Publications

HC 98-02: 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 International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation.** *Submitted.* We previously compared outcomes after allogeneic peripheral blood (PB) and bone marrow (BM) transplantation in 824 patients with leukemia, age ≥ 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 was higher after PB transplants for patients with advanced CML but survival was lower after PB transplants for patients with chronic phase CML (RR 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 transplants in good risk patients as higher risks of chronic GVHD may increase late mortality.

HC 98-05: Rubinstein R, Loberiza FR, Stevens CE, Kurtzberg J, Zhang M-J, Scaradavou A, Champlin RE, Horowitz MM, and Wagner JE. **Unrelated cord blood or bone marrow transplantation in children with hematologic malignancies: A collaborative study from the New York Blood Center and International Bone Marrow Transplant Registry.** *Submitted.* Umbilical cord blood (UCB) is recognized as a source of hematopoietic stem cells for bone marrow (BM) reconstitution. Outcomes of unrelated

CB and BM transplantation performed between 1995 and 1999 in children < 16 years of age with leukemia or myelodysplasia were compared. Patients were recipients of UCB from the National Cord Blood Program of the New York Blood Center (n=331) and BM (n= 274) or UCB recipients from other banks (n=34) reported to the IBMTR. UCB recipients had slower engraftment than did BM recipients, but also had a lower incidence of acute or chronic GVHD. Relapse rates were the same. Transplant-related and overall mortality were higher in UCB recipients than in BM recipients. However, disease-free and overall survival of unrelated UCB transplants was equivalent to or better than that of unrelated BM transplants in children receiving 5/6 or 6/6 HLA matched grafts. Total nucleated cell (TNC) dose affected outcomes in UCB recipients, but not in BM recipients, with higher UCB doses associated with better survival. These data suggest the need for larger UCB inventories to improve patients' chances of finding a suitable match and optimize survival.

HC 02-01: Eapen M, Horowitz MM, Klein JP, Champlin RE, Loberiza FR, Ringden O, and Wagner JE. **Higher mortality after allogeneic peripheral blood transplantation compared with bone marrow in children and adolescents.** *J Clin Oncol 2004; 22: 4872-80.* Peripheral blood stem cells (PBSC) may be used as an alternative to BM for allogeneic transplantation. Despite lack of data on PBSC transplantation in children, there has been a change in clinical practice with increasing numbers of children receiving PBSC allografts. We compared the results of 143 PBSC and 630 BM transplants from HLA-identical sibling donors in children age 8–20 years, with acute leukemia. PBSC transplant recipients were older, more likely to have advanced leukemia, receive growth factors posttransplant and be transplanted more recently. Risks of acute and chronic GVHD, treatment-related mortality, relapse, treatment failure (relapse or death) and overall mortality were compared using Cox proportional-hazards regression to adjust for potentially confounding factors. Hematopoietic recovery was faster after PBSC transplantation. Risks of grades 2-4 acute GVHD were similar, but chronic GVHD were higher after PBSC transplantation (RR 1.85, 95% CI 1.28–2.66, p=0·001). In contrast to reports in adults, treatment-related mortality (RR 1.89, 95% CI 1.28–2.80, p=0.001), treatment failure (RR 1.31, 95% CI 1.03–1.68, p=0·03) and mortality (RR 1·38, 95% CI 1.07–1.79, p=0.01) were higher after PBSC transplantation. Risks of relapse were similar. These data suggest poorer outcomes after PBSC compared to BM transplantation in children after adjusting for relevant risk factors. Given the trend towards increased use of PBSC allografts in children, prospective clinical trials are required to determine their appropriate role in this group of patients.

HC 02-02: Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang M-J, Champlin RE, Stevens C, Barker JN, Gale RP, Lazarus HM, Marks DI, van Rood JJ, Scaradavou A, and Horowitz MM. **Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia.** *N Engl J Med 2004; 351: 2265-75.* Data regarding the outcome of cord blood transplantation in adults are scant, though these grafts are increasingly used in adult transplantation. We compared outcomes of patients, age 16 to 60 years, with leukemia undergoing unrelated donor transplantation using 1 (n=34) or 2 (n=116) HLA-antigen-mismatched cord blood or 1 antigen-mismatched (n=83) or matched (n=367) bone marrow using Cox proportional- hazards models. Cord blood recipients were younger, more likely to have advanced leukemia, and received lower graft cell doses. Hematopoietic recovery was slower with mismatched bone marrow and cord blood transplants. Acute GVHD was more likely after mismatched bone marrow transplantation. Treatment-related mortality, treatment failure and overall mortality were lowest after matched bone marrow transplants. Treatment-related mortality (hazard ratio, 0.99, 95% CI 0.70 to1.40, P=0.96), treatment failure (hazard ratio, 0.94, 95% CI 0.69 to1.28, P=0.69) and overall mortality (hazard ratio, 0.92, 95% CI 0.68 to1.26, P=0.62) were similar after mismatched bone marrow and mismatched cord blood transplantation. There were no differences in leukemia recurrence among the groups. There were no differences in outcome between 1 and 2 antigen-mismatched cord blood transplants. We

conclude that though best results were observed after HLA-matched bone marrow transplants, in a cohort where 77 percent of cord blood transplants were mismatched at 2 HLA loci, outcomes were similar with mismatched bone marrow and cord blood transplants. Therefore, cord blood should be considered an acceptable graft source for adults in the absence of an HLA-matched adult donor.

3.11.2 Preliminary Results

HC 03-01: Prevalence of microbially contaminated hematopoietic stem cell products. *(Study Chair: RE Champlin, MD Anderson Cancer Center, University of Texas, Houston, TX; Study Statistician: 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 posttransplant 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: H. Tang, John Klein).* 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), SAA (3) and other nonmalignant disease (1). Most malignancy patients had advanced disease (60 patients [53%] were beyond CR2 or in relapse). The median prefreeze 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 posttransplant 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, transplant-related mortality 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

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)* A study file is prepared and preliminary analyses are in progress.

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: H. Tang)*

HC04-01: HLA-mismatched related donor transplantation vs. unrelated cord blood transplantation. *(Study Chairs : M. Eapen, J. Wagner, University of Minnesota, Minneapolis, MN, R. Champlin, MD Anderson Cancer Center, University of Texas, Houston, TX; Study Statistician: H. Tang)*

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; Statisticians: Haiqing Tang, MS, John Klein, PhD; Scientific Director: J. Douglas Rizzo, M.D.

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 hematopoietic stem cell transplantation: a multi-center, comparative study.** *J Clin Oncol, 2005. In press.* The purpose of this study was

to examine health-related quality of life (HRQOL) and psychological growth in long-term, adult survivors of hematopoetic stem cell transplantation for a malignant disease. HCT survivors (n=662) were recruited through the IBMTR and were drawn from 40 HCT centers. Survivors completed a telephone interview and a set of questionnaires a mean of 7.0 years post-HCT (range 1.8 – 22.6 years). 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 hematopoietic stem cell transplantation: An international case-control study.** *Blood, 2005. In press.* 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.

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 (FHCRC). We previously reported an increased risk of solid cancers in a large group of patients surviving more than five years after allogeneic bone marrow transplantation. That study had relatively few

patients surviving more than 10 years posttransplant. 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 posttransplant and 2,063 for 10 or more years. Transplantation was done predominantly for leukemia (AML, CML, ALL; 74%), aplastic anemia (10%), lymphoma (5%) and MDS (5%). Average age at transplantation was 27 years (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 hematopoietic stem cell transplant 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 [IND] (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 [DEP] (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 is 50 years (range 22-75 years) and median time since HCT is 7 years (range 2.7-19.5 years). Only 28% of patients practiced all 3 healthy IND 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 DEP 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 $\geq$50 years). In multivariate analysis, IND behaviors were associated with higher education (p=0.001) while greater compliance with DEP 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-SCT 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)

White Paper: Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Blood and Marrow Transplant Group, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow *Transplantation.* *(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.) Manuscript in preparation.* 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, European Group for Blood and Marrow Transplantation (EBMT), and American Society for Bone Marrow Transplantation (ASBMT) 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.

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: H. Tang)*

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: H. Tang)*

LE03-02: Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome after hematopoietic stem cell transplant. *(Study Chair: E. Cohen, Medical College of Wisconsin, Milwaukee, WI; Study statistician: H. Tang)*

3.13 <u>Immunobiology Working Committee.</u> 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., John Klein, Ph.D.; Scientific Director: Mary M Horowitz, M.D.

This is a new Working Committee which will meet in February 2005 to plan its scientific agenda, including setting priorities for the planned studies listed in 3.13.2. Many of these studies will make use of biologic specimens from the NMDP's donor-recipient repository (indicated by an "s" after the study number).

3.13.1 Preliminary Results

SC 02-01: Impact of prior pregnancy on outcomes of allogeneic HCT. *(Study Chair: A Wakoff Loren, University of Pennsylvania Cancer Center, Philadelphia, PA; Study Statistician: M. Haagenson. Manuscript in preparation.* 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. 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 (hazard ratio 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. This multi-center retrospective registry study showed that 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.

R02-07: KIR and transplant outcome. *(Study Chair: S. Farag, The Ohio State University, Columbus, OH; Study Statistician: G. Nelson, Christian Boudreau). Analyses in progress.* KIR ligand incompatibility in the graft-versus-host direction has been associated with a significant reduction in relapse, graft rejection and GVHD in patients with high-risk AML undergoing full haplotype-mismatched, T-cell depleted transplants. The effect in unrelated donor transplantation has been less consistent. This study investigates the effect of KIR ligand mismatching on the outcome of UDT in a large combined data set from the NMDP and the European Group for Blood and Marrow Transplantation, comparing the outcome of 1,816 KIR ligand matched and mismatched transplants for AML (n=501), chronic myelogenous leukemia (n=1024), and myelodysplasia (n=291). All cases had high-resolution HLA typing, and were matched for HLA-A, and -DRB1 alleles. Based on HLA typing for -B and -C alleles, cases were divided into one of 4 groups for comparison of outcome: KIR ligand incompatible in GvH direction (n=156), KIR ligand incompatible in host-versus-graft (HvG) direction (n=185), HLA mismatched for -B and/or -C, KIR ligand compatible (n=301), and fully HLA matched (n=1174). All received myeloablative preparative regimens, and *ex-vivo* T-cell depletion of the graft was performed in 18%, 22%, 16% and 15% of patients in the 4 groups, respectively. Overall, a beneficial effect of KIR ligand incompatibility in the GvH direction could not be demonstrated. KIR ligand incompatibility was associated with increased risk of grade III/IV acute GvHD and worse overall survival (OS). Therefore, full MHC class I matching remains the best option in unrelated donor transplantation.

3.13.2 Planned Studies

D98-125: Cross-reactive groups in HCT. *(Study Chair: J. Wade, University of Toronto, Toronto, ON, Canada; Study Statistician: P. Chitphakdithai). Analyses in progress.*

R01-60: HLA matching based on structure and function. *(Study Chair: L. Baxter-Lowe, UCSF, San Francisco, CA; Study Statistician: M. Haagenson). Analyses in progress.*

R02-10: African-American genotypes. *(Study Chair: P. Fraser, CBR Laboratories, Inc., Boston, MA; Study Statistician: M. Haagenson)*

R02-27: HLA matchmaker analysis of bone marrow transplant outcome. *(Study Chair, R. Duquesnoy, University of Pittsburgh, Pittsburgh, PA; Study Statistician: M. Haagenson). Analyses in progress.*

R02-33s: IL genotype. *(Study Chairs: M. MacMillan, University of Minnesota, Minneapolis, MN, S. Davies, Cincinnati's Children's Hospital Medical Center, Cincinnati, OH; Study Statistician: S. Gandham)*

R02-40s: NK receptor acquisition. *(Study Chair: J. Miller, University of Minnesota, Minneapolis, MN; Study Statistician: M. Haagenson)*

R03-57s: Diversity of immune response genes. *(Study Chair: C. Hurley, Georgetown University Hospital, Boston MA; Study Statistician: M. Haagenson)*

R03-58s: MICA and MICB polymorphisms and gvhd. *(Study Chair: M. Verneris, University of Minnesota Cancer Center, Minneapolis, MN; Study Statistician: M. Haagenson)*

R03-63s: Genetics of KIR genes and haplotypes. *(Study Chair: E. Trachtenberg, Children's Hospital and Research Center, Oakland, CA; Study Statistician: M. Haagenson)*

R03-65s: HY antigens and transplant outcomes. *(Study Chair, D. Miklos, Dana-Farber Cancer Institute, Boston, MA; Study Statistician: S. Gandham)*

R03-70: Chemokine polymorphisms. *(Study Chair: E. Abdi, University of Queensland Toowoomba Hospital, Toowoomba, Queensland, Australia; Study Statistician: S. Gandham)*

R04-74s: KIR functional significance. *(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)*

R04-75s: CGP and post-transplant complication. *(IHWG) (Study Chair: E. Petersdorf, Fred Hutchinson Cancer Research Center, Seattle, WA; Study Statistician: M. Haagenson)*

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

R04-80s: HLA matching in unrelated cord blood transplants. *(Study Chair: S. Rodriguez-Marino, Children's Memorial Hospital, Chicago, IL; Study Statistician: S. Gandham)*

R04-84s: TGF-beta in sclerodermatous chronic GVHD. *(Study Chair: I. Thornley, Dana-Farber Cancer Institute and Children's Hospital, Boston, MA; Study Statistician: M. Haagenson)*

R04-93: Dissimilarity scoring in mismatched stem cell transplant. *(Study Chair: R. Blasczyk, Hannover Medical School, Hannover, Germany; Study Statistician: S. Gandham)*

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

R04-98: Crossmatch testing. *(Study Chair: R. Bray, Emory University, Atlanta, GA; Study Statistician: S. Gandham)*

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

3.14 Regimen-related Toxicity/Supportive Care Working Committee. 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 will be meeting in February 2005 to plan its Scientific Agenda, including setting priorities for the planned studies (reassigned from other Committees) listed below.

3.14.1 Planned Studies

D98-70: Comparative analysis of busulfan and cyclophosphamide versus cyclophosphamide and total body irradiation in unrelated marrow donor transplantation for acute leukemias, CML and myelodysplasia. *(Study Chair: J. Uberti, University of Michigan, Ann Arbor, MI; Study Statistician: M. Haagenson)*

D01-08: Non-ablative or reduced intensity conditioning regimens with volunteer unrelated donor progenitor cell transplantation. *(Study Chair: S. Giralt, MD Anderson Cancer Center, Houston TX; Study Statistician: O. McGaha)*

SC03-01/R02-26: Retrospective study of the impact of obesity on toxicity and outcomes in unrelated donor allogeneic hematopoietic transplants for acute myelogenous leukemia: *(Study Chair: W. Navarro, UCSF, San Francisco, CA, Study Statistician: 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)*

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: Waleska Pérez, M.S., Christian Boudreau, Ph.D.; Scientific Director: Marcie Tomblyn, M.D.

This is a new Working Committee that will be meeting in February 2005 to plan its Scientific Agenda, including setting priorities for the planned studies (reassigned from other Committees) listed below.

3.15.1 Planned Studies

GV02-02: Transplant outcomes from hepatitis B and hepatitis C positive donors. *(Study Chair: K. Ballen, Massachusetts General Hospital, Boston, MA; Study Statistician: W. Pérez)*

LE00-01: Comparison of rates of CMV infection and disease after allogeneic peripheral blood stem cell versus bone marrow transplantation. (*Study Chair: J. Wingard, University of Florida, Gainesville, FL; Study Statistician: H. Tang)*

LE04-02: Bone marrow transplant for malignancies in HIV infected patients. *(Study Chair: V. Gupta, Princess Margaret Hospital, Toronto, Ontario, Canada; Study Statistician: H. Tang)*

R04-90: NK interaction and infection. *(Study Chair, J. van Burik, University of Minnesota, Minneapolis, MN; Study Statistician: M. Haagenson)*

3.16 Donor Health and Safety Working Committee. 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: Michael Haagenson, MS, Brent Logan, PhD; Scientific Director: Dennis Confer, M.D.

This is a new Working Committee that will be meeting in February 2005 to plan its Scientific Agenda.

3.16.1 Planned studies

D01-84: Experience of NMDP peripheral blood stem cell donors. *(Study Chair: D. Confer, NMDP, Minneapolis, MN; Study Statistician: M. Haagenson)*

3.17 Health Services and Psychosocial Issues Working Committee. Co-Chair: Stephanie Lee, Dana Farber Cancer Institute, Boston, MA; Co-Chair: Galen Switzer, University of Pittsburgh Medical Center, Pittsburgh, PA; Statistician: Seira Kurian, MD, MS, MPH, John Klein, PhD; Scientific Director: J. Douglas Rizzo, M.D.

This is a new Working Committee that will be meeting in February 2005 to plan its Scientific Agenda.

3.17.1 Publications

SC00-02: Fausto R. Loberiza, Jr. MD, MS; Mei-Jie Zhang, PhD; Stephanie J. Lee, MD, MPH; John P. Klein, PhD; Charles F. Le Maistre, MD; Derek S. Serna, BS; Mary Eapen, MBBS, MS; Christopher N Bredeson, MD, MS; Mary M. Horowitz, MD, MS; J. Douglas Rizzo, MD **Association of transplant center and physician factors on mortality after hematopoietic stem cell transplantation in the United States.** *Blood, 2005. In press.* Center effects are differences in outcome among treatment centers that cannot be

explained by identifiable differences in patients treated or specific treatments applied and are presumed to result from differences in the ways health care is delivered. This paper summarizes studies of associations between treatment center factors and clinical outcomes in general medicine and surgery and looks more closely at studies addressing this issue in HCT.

Lee SJ, Joffe S, Kim HT, Socie G, Gilman A, Wingard JR, Horowitz MM, Cella D, Syrjala K. **Physicians' attitudes about quality of life issues in hematopoietic stem cell transplantation.** *Blood 104-: 2194-2200, 2004.* Studies investigating quality of life (QOL) after HCT demonstrate the spectrum of QOL outcomes awaiting survivors. Nevertheless, how transplantation physicians interpret and apply QOL information to clinical practice is poorly understood. We conducted a cross-sectional survey of transplantation physicians to address these issues and received 180 (24%) responses from physicians in 29 countries. Seventy-two percent reported that their patients are willing to accept poor QOL for a small chance of cure. Only 28% said that QOL considerations "often or "almost all the time" enter into patients' decisions about transplantation. This contrasted with physicians' reported attention to QOL in their discussions with patients. Although 53% of physicians reported using QOL results to modify practice, 55% would be more likely to use these data if they were more understandable. To ensure generalizability of the results, a validation sample was randomly selected, and these 85 physicians (response rate, 76%) confirmed the findings of the original survey. Given the extensive data regarding posttransplantation QOL, resources should be devoted to exploring how patients and physicians use these data in clinical care and in devising methods to ensure that QOL results are interpretable and relevant to patients and physicians.

3.17.2 Planned Studies

R04-77,79,85,89: Ethnicity and unrelated donor transplant outcomes. *(Study Chairs: 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)*

D00-133: Racial disparities in TNF-alpha. *(Study Chair: S. Davies, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH; Study Statistician: S. Kurian)*

SC01-01: Quality of clinical trials in the HCT literature. *(Study Chair: F. Loberiza, University of Nebraska Medical Center, Omaha, NE; Study Statistician: S. Kurian)*

3.18 Statistical Center Methodologic Studies

3.18.1 Multistate Models

Several papers have been written on multistate models for HCT data: Tshu, 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.

3.18.2 Competing Risks

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

Bajorunaite, R and Klein, JP. **Two Sample Test of the Equality of Two Cumulative Incidence Functions,** *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 and Bajorunaite, R. Chapter 16 **Inference for Competing Risks**. *Handbook Of Statistics. Vol 25, Advances in Survival Analysis.* Elsevier Science, 291-312, 2004. In this paper, we survey methods for comparing cumulative incidence functions.

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.
Klein, JP and Andersen, PKA **Regression Modeling of Competing Risks Data Based on Pseudo-Values of the Cumulative Incidence Function**. *Biometrics* 2005. *In Press.* 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.** *Biometrika (Submitted, Revision).* 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, Sun, JG and Zhang MJ. **Modeling the Subdistribution of a Competing Risk.** *Statistica Sinica (Submitted, Revision).* In the paper, we model the subdistribution hazard through a general model. Robust variance estimates were presented. The model-fitting problem was investigated.

3.18.3 Regression Models for Censored Data

Andersen, PKA, Hansen, MA and Klein, JP. **Regression Analysis of Restricted Mean Survival Time Based on Pseudo-Observations.** *Life Time Data Analysis (In Press).* A novel regression technique for censored lifetime data based on pseudo-values was applied to estimate a mean survival time in a regression analysis setting.

Bhattacharyya, M. and Klein, JP. **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, PKA, Ekstrom, C. Klein, JP**,** Shu, Y. and Zhang, M-J. **Simulation Based Goodness of Fit Tests for a Copula Based on Bivariate Right-Censored Data** *(Submitted).* 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,** *Canadian Journal of Statistics* (*Submitted).* In this paper we propose methods 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 and Wu, JT. Chapter 2. **Discretizing a Continuous Covariate In Survival Studies.** *Handbook Of Statistics. Vol 25, Advances in Survival Analysis*. *Elsevier Science, 27-44, 2004.* In this paper, we extend this approach to the accelerated failure time model and to the multivariate case.

Klein, JP. **Multivariate Weibull Distributions.** In *The Weibull Distribution: Theory, Methods and Applications* (Balakrishnan and Basu, Eds.), Gordon and Breach Publishers, Amsterdam, 2005. *In Press.* We survey the properties of Multivariate Weibull Distributions and its applications in biomedical researches.

Klein, JP. **The Weibull Distribution in Biometry.** In *The Weibull Distribution: Theory, Methods and Applications (*Balakrishnan and Basu, Eds.), Gordon and Breach Publishers, Amsterdam, 2005. In Press. We survey the properties of the Weibull Distributions and its applications in biomedical researches.

Klein, JP, Logan, B, Harhoff, M and Andersen, PK **Analyzing Survival Curves at a Fixed Point in Time.** *Statistics in Medicine (Submitted).* In this paper, we focused on testing for the equality of survival curves at a fixed point in time.

Logan, B.R., Wang, H., and Zhang, M.-J. **Pairwise Multiple Comparison Adjustment in Survival Analysis.** *Statistics in Medicine, 2005. In Press.* In this paper, we investigated 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, 2005. In Press*. In this paper, we proposed designs 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.

- *Data collection instruments*: CIBMTR data collection forms are the basis for data collection forms for several clinical trials including the NHLBI-sponsored cord blood 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 two or so years. The forms have deliberately never been copyrighted and 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

Dr. J.P. Klein serves as Statistical Director of the CIBMTR and 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 have collaborated often on professional writings. They, along with Brent Logan, PhD and Christian Boudreau, PhD participate in ongoing CIBMTR research studies contributing to statistical integrity, and influencing 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. Dr. Klein contributed a chapter, Statistical Analysis in Hematopoietic Stem Cell Transplantation, for a volume of *Clinical Bone Marrow and Blood Stem Cell Transplantation* now in its third edition in 2004. Also in 2004, Dr. Klein participated in writing a chapter, Inference for Competing Risks, in *Handbook of Statistics. Vol 25, Advances in Survival Analysis.*

All CIBMTR PhD statisticians are members of The Division of Biostatistics (Health Policy/MCW) and function as consultants for CIBMTR staff and all have teaching responsibilities as well. Both Drs. Klein and Zhang made presentations at our 2004 Tandem meeting.

4.0 OTHER ACTIVITIES

4.1 Presentations

In 2004, there were 171 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 2004, the CIBMTR, through its Information Resource Program, provided information in response to more than 1200 requests for information. Table 4.2.1 summarizes these requests. The most frequent users of the CIBMTR Information Resource Program are physicians or patients seeking information regarding outcome of transplants in specific situations for assistance in clinical decision-making. The CIBMTR is generally able to provide such information, not readily available from the medical literature, within 24-48 hours. Individuals and organizations also increasingly use registry data in planning and interpreting results of clinical trials. Additionally, the Statistical Center provides educational materials (slides, graphics) for many presentations and distributes a set of slides summarizing current use and outcome of blood and marrow transplants to all participating teams. It also maintains a website (www.cibmtr.org) where answers to the most frequently asked questions can be found. During 2004, there were more than 15,000 visits to this Website 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, 2004.

TYPE OF ORGANIZATION	**TOTAL**
Physician	761
Medical Society	22
Patient or Relative	81
Federal Government Agency	23
State Government	3
Insurance Company	46
Pharmaceutical Company	189
Consulting Firm	9
Market Research Firm	26
Law Firm	11
Donor Registry/Blood Bank	20
Student	14
News media	15
TOTAL	**1220**

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 ~1600 participants attending the Tandem Meetings in 2004. 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. In 2004, Pharmacists, BMT nurses and BMT Center Administrators were included in the participant profile. Continuing education (CME) and continuing education (CE) credits are issued for attending the 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 are held during the Tandem BMT Meetings, as well as by telephone or in conjunction with meetings of national hematology (ASH) and oncology (ASCO) societies.

The first CIBMTR Transitional Advisory Committee meeting was held in October 2004 during the annual NMDP Council Meetings in Minneapolis. (The NMDP Council meetings are attended by representatives of donor, collection, apheresis and cord blood storage centers as well as NMDP officers and staff.) The next meeting will be at the Tandem BMT meetings in Keystone, Colorado in February 2005. The Executive Committee of the CIBMTR will meet monthly by conference call. 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 will be published in January 2005. Numerous announcements were made to CIBMTR participants as well as to the general public at the time of the affiliation in July 2004.

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 early focus of the CIBMTR*

is to simplify and unify reporting data to the IBMTR and the NMDP; CIBMTR staff are meeting regularly to agree on a common data set and case report form. We hope to complete work on this project during 2005. 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 3to 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.

- 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.*

- The CIBMTR 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 CIBMTR 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.*

- CIBMTR 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 centers do not fall under the purview of NMDP-Research and do not involve CIBMTR personnel.

5.1 Data collection

IBMTR data collection forms are continually reviewed to assess needs for revision and are updated accordingly. Three additional inserts were developed in 2004 for collecting disease specific information for the following diseases: X-linked Lymphoproliferative Syndrome (XLP), Paroxysmal Nocturnal Hemoglobinuria (PNH) and Renal Cell Carcinoma. Form revisions and additions are done in collaboration with the NMDP in order to achieve uniformity in content and format. *TED on the Web* was also released earlier this year 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.

Harmonization of NMDP and IBMTR forms is in progress, under the auspices of a combined NMDP/CIBMTR Forms Committee that has the goal of completing this task in the next year. As noted above, the CIBMTR recently received 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.

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 2004, in conjunction with the Annual Meeting in Orlando, Florida. 182 data managers attended. Participants indicated a high level of satisfaction with topics covered and training provided. Another three day training session was also conducted by CIBMTR personnel in September 2004 in Milwaukee. 130 data managers attended. Discussions are in progress to combine future fall sessions with the NMDP Council Meetings, allowing 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 Audit Committee.

Thirty allogeneic and twenty-one autologous HCT programs were audited in 2004; an additional eight programs will be audited by February 28th, the end of the current U24 funding period. To date, overall accuracy is 98.3% with < 1% major errors (improved since last year). There is no evidence of biased or selective reporting. This year's audit volume was somewhat less than 2003 because there were a number of teams audited ahead of schedule last year due to planned closure of the data file for our "Quality of Life" study (LE99-01). All audit reports are reviewed by the CIBMTR Executive Committee.

5.4 Computer Capabilities

Computer resources for the CIBMTR Statistical Center are shared with the Department of Biostatistics of MCW and consists of a network of 2 SUN Ultra-4 UNIX servers, Sun-Fire V 250 Server, 23 SUN/Unix workstations, a Dell NT network server and Dell Pentium workstations for each staff member. The network resides on the MCW network infrastructure. 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 NT passwords as needed for confidentiality.

We continue to refine our comprehensive data system based on ORACLE RDBMS to warehouse and process data collected over the 30-year history of the CIBMTR. The system provides a data repository and the applications programs necessary for collection, tracking, validation, reimbursement and provides access for statistical analysis The resulting client/server database system combines the security and power of a dedicated UNIX database server with the ease-of-use of access to the data from a PC desktop interface built using Microsoft Visual Basic.

The CIBMTR Statistical Center continued the 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 designing a database system 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. During 2004, we contracted for one FTE systems analyst from the BRC. The contract with the BRC also increased programmer resources needed to continue to revise and enhance the components of the data system.

Specific changes in 2004 include the following.

- *TED on the Web* is available on two external servers for secure, uninterrupted access to entry of TED, MTED, PREREG and TED-FU forms.

- A data retrieval and exchange process was implemented to extract Report Form data for patients on BMT CTN trials and upload this data via an encrypted site to the EMMES Corporation (contracted to manage the CTN trials) to merge with enrollment and other data collected directly by EMMES.

- A tracking system was developed for preliminary identification of patients eligible for CTN protocols and reporting of compliance of enrolling patients at CTN teams.

- Forms revisions were done in 2004, to the CORE, COREFU, Allo PB, Allo BM, DCI (Donor Cell Infusion) inserts as well as DCI graft inserts. In 2004 StemSoft Software Inc released v 3.1 and v 3.2 to support these revisions as well as support for all DCI forms including DCI Report Forms, DCI disease and supplement inserts. Programming efforts were completed to adjust the database structure for these changes and upgrade our internal applications and retrievals for these revisions. Programming support was also developed to support export files for all the new inserts produced by StemSoft BMTbase Reports.

- A new V250 Sun Workstation was purchased in September of this year to replace the previous database server. This new platform gives us disk capacity increased by 10 fold, retrieval performances increase from 5 fold to 20 fold. Newly designed

disk layout and mirroring give us improved data integrity and insurance from disaster loss. Also, in September we migrated all of our patient data and supporting applications from Oracle 8.0.5 to Oracle 9.2 which incorporates Oracle 9i Enterprise. This was a significant effort, testing all components before and after the migration. This was accomplished within only 2 days when the system was not available to our administrative staff and with no interruption to the cycle of SAS data sets available to the statisticians for analysis.

- A new method of logging in Research Report Forms has been implemented. This new program checks more of the Report Form's required fields for consistency with information received in the TED registration process and makes it possible to report these problems before the Report Forms are fully entered by our keying staff. This will allow us to resolve issues closer to the time that the Report Forms are received.

- 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. The data sets exchanged include approximately 100 fields identified by the statistical staff as the essential elements for accrual and preliminary analysis. The data sets exchanged are in identical format for all allogeneic and autologous transplants reported to the IBMTR and all unrelated transplants reported to the NMDP.

6.0 HUMAN SUBJECTS/HIPAA COMPLIANCE

All work funded by U25-CA76518 uses existing data derived from records of patients treated in participating CIBMTR institutions. In no instance does the CIBMTR direct or suggest how patients in participating institutions are treated. Studies performed using this database have been continuously reviewed by the Institutional Review Committee 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.

IBMTR 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 are trained in ethical conduct of clinical research. Additionally, <u>all</u> personnel, including administrative and data entry staff, have completed the NIH tutorial on clinical research ethics available on the web

(http://ohsr.od.nih.gov); certificates of completion are on file. Many others on staff, including all Scientific Directors, have more extensive training and experience in the ethical conduct of research and have been required to take the Collaborative IRB Training Initiative Program (CITI) course in 2004. Those certificates are on file in the Department of Medicine, Division of Neoplastic and Related Diseases office.

6.1 Health Insurance Portability and Accountability Act (HIPAA)

The NMDP (including NMDP-Research, the Minneapolis campus of the CIBMTR) is exempt from 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 IBMTR 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 posttransplant 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 89% of our participating centers in the United States. Data use agreements have been executed with 76% 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 recent affiliation with NMDP to form the CIBMTR will increase 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 pretransplant 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 posttransplant 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.

Appendix 1

CIBMTR™
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Institutions participating in the CIBMTR—Milwaukee

Alexander Fleming Institute	Buenos Aires	Argentina	Registration
British Hospital of Buenos Aires	Buenos Aires	Argentina	Registration
Clinica-Angelica Ocampo	Buenos Aires	Argentina	Research
Fund Dr Mainetti	Buenos Aires	Argentina	Registration
Fundaleu-Angelica Ocampo	Buenos Aires	Argentina	Research
Hospital de Pediatria S.A.M.I.C.	Buenos Aires	Argentina	Registration
Hospital Privado de Oncologia	Buenos Aires	Argentina	Registration
Institutos Medicos Antartida	Buenos Aires	Argentina	Research
Navy Hospital Pedro Mallo	Buenos Aires	Argentina	Research
Unidad de Investigaciones Oncohematologicas	Buenos Aires	Argentina	Research
Hospital Privado de Cordoba	Cordoba	Argentina	Research
Sanatorio Allende	Cordoba	Argentina	Research
Hospital de Ninos La Plata	La Plata	Argentina	Research
Centramor	Santa Fe	Argentina	Registration
Hanson Center for Cancer Research	Adelaide	Australia	Research
Royal Children's Hospital	Brisbane	Australia	Registration
Royal Brisbane Hospital	Brisbane	Australia	Research
Royal Prince Alfred Hospital	Camperdown	Australia	Research
St Vincent's Hospital	Darlinghurst	Australia	Registration
Alfred Hospital	Melbourne	Australia	Research
Royal Children's Hospital	Parkville	Australia	Research
Royal Melbourne Hospital	Parkville	Australia	Research
Princess Margaret Hospital for Children	Perth	Australia	Research
Royal Perth Hospital	Perth	Australia	Research
Prince Wales Sydney Children's Hospital	Randwick	Australia	Research
Royal North Shore Hospital	St Leonards	Australia	Research
Prince of Wales Hospital	Sydney	Australia	Research
Newcastle Mater Hospital	Waratah, Newcastle	Australia	Research
Ludwig Blotzmann Institute (LBI)	Vienna	Austria	Registration
Children's Hospital at Westmead	Westmead	Australia	Research
Westmead Hospital	Westmead	Australia	Research
Univ. of Graz	Graz	Austria	Research
Univ. Klink fur Innere Nedizin I	Vienna	Austria	Registration
St. Anna's Children's Hospital	Vienna	Austria	Registration
AZ Sint-Jan	Brugge	Belgium	Registration
Children's Univ. Hospital	Brussels	Belgium	Registration
Cliniques Univ. Saint-Luc	Bruxelles	Belgium	Research
Univ. Hospital Antwerp	Edegem	Belgium	Research

Appendix 1

Institutions participating in the CIBMTR

Univ. Ziekenhuis Gasthuisberg	Leuven	Belgium	Research
Univ. De Liege	Liege	Belgium	Registration
Centro de Oncologia Campinas	Campinas, Sp	Brazil	Registration
Hemocentro UNICAMP	Campinas	Brazil	Research
Univ. Estadual de Campinas	Campinas	Brazil	Research
Hospital de Clinicas	Curitiba	Brazil	Research
Fed. U. of Minas Gerais, Clinicas Hospital	Minas Gerais	Brazil	Registration
Hospital de Clinicas de Porto Alegre	Porto Alegre	Brazil	Research
Hospital de Porto Alegre	Porto Alegre	Brazil	Registration
Real Institute de Medulla Ossea	Recifo	Brazil	Research
Univ. de Sao Paulo	Ribeirao Preto	Brazil	Registration
Institute Nacional de Cancer	Rio de Janeiro	Brazil	Research
Univ. Federal Rio de Janeiro	Rio de Janeiro	Brazil	Research
Central de Transplante	Salvador, Bahia	Brazil	Research
De Sao Jose De Compos	Sao Paulo	Brazil	Registration
Hospital A C Camargo	Sao Paulo	Brazil	Research
Hospital Amaral Carvalho	Sao Paulo	Brazil	Registration
Hospital de Base	Sao Paulo	Brazil	Research
Santa Casa Medical School	Sao Paulo	Brazil	Research
Univ. Federal de Sao Pualo-EPM	Sao Paulo	Brazil	Registration
Univ. Sao Paulo- INCOR	Sao Paulo	Brazil	Research
Instituto de Oncologia Pediatrica	Sao Paulo	Brazil	Registration
Alberta Children's Hospital	Calgary-Alberta	Canada	Research
Tom Baker Cancer Center	Calgary-Alberta	Canada	Research
QE II Health Sciences Center	Halifax	Canada	Research
Victoria General Hospital/Dalhousie	Halifax	Canada	Research
Chedoke-McMaster Hospitals	Hamilton-Ontari	Canada	Research
London Health Sciences Center-Ontario	London-Ontario	Canada	Research
Hopital Saint-Justine	Montreal	Canada	Research
Montreal Children's Hospital	Montreal-Quebec	Canada	Registration
Royal Victoria Hospital	Montreal-Quebec	Canada	Registration
Hotel Dieu de Quebec Hospital	Quebec City	Canada	Registration
Hopital du Saint-Sacrement	Quebec City	Canada	Registration
Saskatoon Cancer Clinic- Stem Cell	Saskatoon	Canada	Registration
Northeastern Ontario Center	Ontario	Canada	Research
Ottawa General Hospital	Ottawa	Canada	Research
St John's Health Sciences Center	St Johns	Canada	Research
Toronto General Hospital	Toronto	Canada	Research
Princess Margaret Hospital	Toronto Ontario	Canada	Research
Hospital for Sick Children	Toronto-Ontario	Canada	Research
British Columbia's Children's Hospital	Vancouver-BC	Canada	Research
Vancouver's Hospital & Health Science Center	Vancouver-BC	Canada	Research
Cancer Care Manitoba	Winnipeg-Manito	Canada	Research

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Institutions participating in the CIBMTR

Universidad Catolica de Chile	Santiago	Chile	Research
Bei Tai Ping Lu Hospital	Beijing	China	Research
Beijing Medical Univ.	Beijing	China	Research
Inst. de Trans. de Medula Osea de la Costa Caribe	Barranquilla	Colombia	Registration
Fundacion Clinica Valle del Lili	Cali-Valle	Colombia	Research
Hospital Mexico	San Jose	Costa Rica	Research
Institute de Hematologia y Immunologia	Havana	Cuba	Registration
Univ. Hospital	Bratislava	Czech Republic	Registration
Charles Univ. Hospital	Pilsen	Czech Republic	Research
Institute Hem-Blood Transf	Prague	Czech Republic	Registration
Univ. Hospital Motol	Prague	Czech Republic	Registration
Rigshospitalet	Copenhagen	Denmark	Research
NCI Cairo Univ.	Cairo	Egypt	Registration
Cairo University	Giza	Egypt	Research
Mansoura Univ. Hospital	Mansoura	Egypt	Registration
Birmingham Heartlands Hospital	Birmingham	England	Registration
Birmingham Children's Hospital	Birmingham	England	Research
Queen Elizabeth Medical Center	Birmingham	England	Research
Bristol Royal Hospital for Sick Children	Bristol	England	Registration
Addenbrook's Hospital	Cambridge	England	Research
St James Univ. Hospital	Leeds	England	Research
Great Ormond St Hospital for Children	London	England	Research
Imperial College School of Medicine	London	England	Research
London Clinic	London	England	Registration
Royal Free Hospital	London	England	Research
Royal London Hospital, Whitechapel	London	England	Research
St George's Hospital Medical School	London	England	Research
Royal Victoria Infirmary	Newcastle	England	Research
Royal Marsden Hospital	Sutton	England	Research
Helsinki Univ. Central Hospital	Helsinki	Finland	Registration
Turku University Central Hospital	Turku	Finland	Research
Universitaire D'Angers	Angers	France	Registration
Hospital Jean Minjoz	Besancon	France	Research
Hospital A. Michallon	Grenoble	France	Registration
Centre Hospitalier Regional de Lille	Lille	France	Registration
Hopital Debrousse-Peds	Lyon	France	Research
Hopital Edouard Herriot	Lyon	France	Registration
Institute J. Paoli I Calmettes	Marseille	France	Research
Hopital des Enfants Malades	Paris	France	Registration
Hopital Robert-Debre	Paris	France	Registration
Hopital Saint Louis	Paris	France	Research
Hotel Dieu de Paris	Paris	France	Registration

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Institutions participating in the CIBMTR

Hospital Jean Bernard	Poitiers	France	Research
Univ. Hospital Charite	Berlin	Germany	Registration
Heinrich-Heine Univ./Children's Hospital	Dusseldorf	Germany	Registration
Albert-Ludwig Univ.	Freiburg	Germany	Research
Martin-Luther Univ. Halle-Witt	Halle	Germany	Registration
Univ. of Hamburg	Hamburg	Germany	Research
Medical School of Hannover	Hannover	Germany	Registration
Ruprecht-Karls-Univ.	Heidelberg	Germany	Research
Christian-Albrechts Univ.	Kiel	Germany	Research
Univ. Munchen/Klinikum Grosshadern	Munich	Germany	Research
Univ. Munchen-Kinderklink	Munich	Germany	Research
Klinikum der Univ. Regensburg	Regensburg	Germany	Registration
Children's Hospital	Tubingen	Germany	Registration
Medizinische Universitatsklinik	Tubingen	Germany	Registration
Universitat Ulm	Ulm-Donau	Germany	Registration
Deutsche Klinik fur Diagnostik	Wiesbaden	Germany	Research
Evangelismos Hospital	Athens	Greece	Registration
Queen Mary Hospital	Hong Kong	Hong Kong	Registration
Chinese Univ. Hong Kong	Shatin	Hong Kong	Research
National Institute of Haematology	Budapest	Hungary	Registration
Tata Memorial Hospital	Bombay	India	Research
Institute Rotary Cancer Hospital	New Delhi	India	Research
Irch Aiims	New Delhi	India	Research
Christian Medical College Hospital	Tamil Nadu	India	Research
Medical Science Univ. of Tehran	Tehran	Iran	Research
Al Mansur Children's Hospital	Baghdad	Iraq	Registration
St. James Hospital	Dublin	Ireland	Research
Hadassah Univ. Hospital	Jerusalem	Israel	Research
The Chaim Sheba Medical Center	Tel-Hashomer	Israel	Research
Chaim Sheba Medical Center	Tel-Hashomer	Israel	Registration
S Orsola University Hospital	Bologna	Italy	Registration
Univ. di Bologna-Ped	Bologna	Italy	Registration
Spedali Civili-Brescia	Brescia	Italy	Registration
Universita'degli Studi di Brescia-Peds	Brescia	Italy	Research
Ospedale Ferrarotto	Catania	Italy	Registration
Univ. di Firenze BMT Unit	Firenze	Italy	Research
Ospedale San Martino	Genoa	Italy	Registration
Ospedale di Civile-Pesaro	Pesaro	Italy	Research
Hospital Of Pescara	Pescara	Italy	Research
Univ. Cattolica Sacro Cuore	Roma	Italy	Registration
University Tor Vergata St. Eugenio Hospital	Roma	Italy	Research
Osped S Camillo	Roma	Italy	Research

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Institutions participating in the CIBMTR

St Eugenio Hospital	Roma	Italy	Research
Univ. La Sapienza	Roma	Italy	Registration
De Midollo Osseo Ospedale Molinette	Torino	Italy	Registration
Univ. of Torino	Torino	Italy	Registration
Udine Univ. Hospital	Udine	Italy	Research
Chiba Univ. School of Medicine	Chiba	Japan	Registration
Imamura-Bun-im Hospital	Kagoshima	Japan	Registration
Tokai University School of Medicine	Kanagawa	Japan	Research
Niigata Univ. Medical Hospital	Niigata	Japan	Registration
Osaka University Medical School	Osaka	Japan	Research
Jichi Medical School	Tochigi-Ken	Japan	Registration
National Cancer Center Hospital	Tokyo	Japan	Research
Kanagawa Cancer Center	Yokohama	Japan	Research
BMT Center Chonnam National Univ.	Kwangju	Korea	Registration
Asan Medical Center	Seoul	Korea	Research
Samsung Medical Center	Seoul	Korea	Research
St Mary's-Seoul	Seoul	Korea	Research
Fauclty of Medical, Kuwait Univ.	Safat	Kuwait	Research
Univ. of Malaya	Kuala Lumpur	Malaysia	Registration
Hospital Angeles de las Lomas	Mexico City	Mexico	Registration
Hospital Especialidades Centro Medico	Mexico D.F.	Mexico	Research
Centro Medical National Del Norte	Monterrey	Mexico	Research
Hospital San Jose-Tec de Monte	Monterrey	Mexico	Research
Hospital Santa Engracia	Monterrey	Mexico	Research
University Hospital J.E. Gonzales	Monterrey	Mexico	Registration
Centro de Hem. y Medical Intna	Puebla	Mexico	Registration
Academic Hospital Maastricht	Maastricht	Netherlands	Registration
Univ. of Nijmegen	Nijmegen	Netherlands	Registration
Auckland Hospital	Auckland	New Zealand	Research
Starship Children’s Hospital	Auckland	New Zealand	Research
Christchurch Hospital	Christchurch	New Zealand	Research
Wellington School of Medical	Wellington	New Zealand	Research
Bismillah Taqer Blood & Disease Center	Karachi	Pakistan	Research
Bone Marrow Transplant Center	Rawai Pindi	Pakistan	Registration
Instituto Oncologico Nacional	Panama	Panama	Research
Hospital Rebag Liati	Lima	Peru	Research
Medical Univ. of Gdansk	Gdansk	Poland	Research
Silesian Medical Academy	Katowice	Poland	Research
Institute Internal Medical	Poznan	Poland	Registration
K Marcinkowski Univ.	Poznan	Poland	Research
K. Dluski Hospital	Wroclaw	Poland	Research
Institute Portugues de Oncologia	Lisbon	Portugal	Research

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Institutions participating in the CIBMTR

Institute Port-Oncolog	Porto	Portugal	Research
Institute Portugues de Oncologia Centro de Porto	Porto	Portugal	Research
Clinical Hospital Number 6	Moscow	Russia	Registration
Morozoff Children's Hospital	Moscow	Russia	Registration
National Research Center for Hematology	Moscow	Russia	Registration
Research Institute of Pediatric Hematology	Moscow	Russia	Registration
Petrov Research Institute of Oncology	St Petersburg	Russia	Research
Russian Institute of Hematology	St Petersburg	Russia	Research
Armed Forces Hospital	Riyadh	Saudi Arabia	Registration
King Faisal Specialist Hospital	Riyadh	Saudi Arabia	Research
King Faisal Hospital-Peds	Riyadh	Saudi Arabia	Research
Royal Infirmary of Edinburgh	Edinburgh	Scotland	Registration
Glasgow Royal Infirmary	Glasgow	Scotland	Research
Royal Hospital for Sick Children	Glasgow	Scotland	Research
Children's Medical Institute	Singapore	Singapore	Research
Singapore General Hospital	Singapore	Singapore	Research
Univ. of Cape Town Medical School	Cape Town	South Africa	Research
Constantiaberg Medi-Clinic	Cape Town	South Africa	Research
Medical Oncology Center of Rosebank	Johannesburg	South Africa	Registration
University of Witwardersrand	Johannesburg	South Africa	Research
Mary Potter Oncology Center	Pretoria	South Africa	Research
Hospital de la Santa Creui Sant Pau	Barcelona	Spain	Registration
Hospital Infantil Vall d'Hebron	Barcelona	Spain	Research
Institute Catala d'oncologia	Barcelona	Spain	Research
Univ. of Barcelona	Barcelona	Spain	Registration
Hospital G U Gregorio Maranon	Madrid	Spain	Research
Hospital Infantil La Paz	Madrid	Spain	Registration
Hospital Puerta de Hierro	Madrid	Spain	Research
Hospital Nino Jesus	Madrid	Spain	Research
Hospital Regional Carlos Haya	Malaga	Spain	Research
Son Dureta Hospital	Palma de Mallor	Spain	Research
Clinica Univ. de Navarra	Pamplona	Spain	Registration
Hospital Marques de Valdecilla	Santander	Spain	Registration
Hospital La Fe	Valencia	Spain	Research
Univ. of Goteborg	Goteborg	Sweden	Research
Huddinge Hospital	Huddinge	Sweden	Research
Univ. of Lund	Lund	Sweden	Registration
Basel Kantonsspital	Basel	Switzerland	Research
Univ. Hospital Bern	Bern 3010	Switzerland	Registration
Klinik Im Park	Zurich	Switzerland	Research
Univ. Hospital-Zurich	Zurich	Switzerland	Registration
Sun Yat Sen Cancer Center	Taipei	Taiwan	Registration

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Institutions participating in the CIBMTR

National Taiwan Univ. Hospital-Peds	Taipei	Taiwan	Research
Tri Service General Hospital	Taipei	Taiwan	Research
Vet General Hospital	Taipei	Taiwan	Research
Ankara University Medical School	Ankara	Turkey	Registration
Gulhane Military Medical Academy	Ankara	Turkey	Research
Institute Of Oncology/Hacettepe Univ.	Ankara	Turkey	Registration
St. George's Hospital Medical School	London	UK	Research
Asociacion Espanola 1 de Socorros	Montevideo	Uruguay	Research
British Hospital & Faculty of Medicine	Montevideo	Uruguay	Research
Center de Transplante de Medula Osea	Montevideo	Uruguay	Research
Hospital Maciel	Montevideo	Uruguay	Research
Children's Hospital Medical Ctr.	Akron	US	Research
New York Oncology Hematology PC	Albany	US	Registration
Phoebe Cancer Ctr.	Albany	US	Research
Harrington Cancer Center	Amarillo	US	Research
Univ. of Michigan	Ann Arbor	US	Registration
Univ. of Michigan-Ped	Ann Arbor	US	Registration
Arlington Cancer Center	Arlington	US	Registration
Blood & Marrow Group of GA	Atlanta	US	Research
Emory University	Atlanta	US	Research
Greater Baltimore Medical Center	Baltimore	US	Registration
Sinai Hospital of Baltimore	Baltimore	US	Research
Johns Hopkins Oncology Center	Baltimore	US	Research
Univ. of Maryland Cancer Center	Baltimore	US	Registration
Our Lady of The Lake Reg. Center	Baton Rouge	US	Research
Alta Bates Medical Center	Berkeley	US	Research
National H L B Institute	Bethesda	US	Registration
National Institute of Health	Bethesda	US	Registration
NIH-NCI	Bethesda	US	Research
Univ. of Alabama-Birmingham	Birmingham	US	Research
St. Luke's Research Medical Center	Boise	US	Research
Beth Israel Deaconess Medical Center	Boston	US	Registration
Dana Farber Cancer Institute	Boston	US	Registration
Massachusetts General Hospital	Boston	US	Registration
BMT Stem Cell Transplant Institute at Bethesda	Boynton Beach	US	Research
Montefiore Medical Center	Bronx	US	Registration
Our Lady of Mercy Medical Center	Bronx	US	Research
Roswell Park Cancer Institute	Buffalo	US	Research
Lahey Hitchcock Clinic	Burlington	US	Registration
Univ. of North Carolina at Chapel Hill	Chapel Hill	US	Research
Medical Univ. of South Carolina	Charleston	US	Registration
Roper Hospital	Charleston	US	Research

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Institutions participating in the CIBMTR

Carolinas Medical Center	Charlotte	US	Research
Univ. of Virginia	Charlottesville	US	Registration
Children's Memorial Hospital	Chicago	US	Research
Northwestern Memorial Hospital	Chicago	US	Research
Michael Reese Hospital/N.W. Univ.	Chicago	US	Research
Univ. of Chicago Children's Hospital	Chicago	US	Registration
Univ. of Chicago Medical Center	Chicago	US	Research
Univ. of Illinois at Chicago	Chicago	US	Research
Children's Hospital Medical Center	Cincinnati	US	Research
Jewish Hospital Cincinnati	Cincinnati	US	Registration
Case Western Reserve University Hospital	Cleveland	US	Research
Cleveland Clinic	Cleveland	US	Research
Univ. Hospital of Cleveland	Cleveland	US	Research
Rainbow Babies & Children's Univ. Hospital	Cleveland	US	Research
Rocky Mountain Cancer Center	Colorado Spring	US	Research
Children's Hospital	Columbus	US	Registration
Ohio State Univ. Medical Center	Columbus	US	Research
Spohn Hospital	Corpus Christi	US	Research
Baylor Univ. Medical Center	Dallas	US	Research
Children's Medical Center of Dallas	Dallas	US	Research
Medical City Dallas Hospital	Dallas	US	Research
Univ. of Texas Southwestern Medical Center	Dallas	US	Research
Penn State Geisinger Medical Center	Danville	US	Research
Miami Valley Hospital	Dayton	US	Research
Halifax Medical Center	Daytona Beach	US	Research
Oakwood Hospital & Medical Center	Dearborn	US	Research
Dekalb Medical Center-Transplant Unit	Decatur	US	Research
Rocky Mountain BMT Program	Denver	US	Registration
Univ. of Colorado Health Sciences Center	Denver	US	Registration
Henry Ford Hospital	Detroit	US	Research
Wayne State University	Detroit	US	Research
City of Hope National Medical Center	Duarte	US	Registration
Duke Univ. Medical Center	Durham	US	Research
El Paso Cancer Treatment Center	El Paso	US	Research
Fairfax Stem Cell Transplant Program	Falls Church	US	Registration
Cook Children's Medical Center-Peds	Fort Worth	US	Research
Univ. of Florida Shands Hospital	Gainesville	US	Research
Cancer & Hematology Centers of W MI	Grand Rapids	US	Research
DeVos Children's Hospital	Grand Rapids	US	Research
Cancer Center of Carolinas	Greenville	US	Research
Pitt County Memorial Hospital	Greenville	US	Research
Hackensack Medical Center	Hackensack	US	Research

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Institutions participating in the CIBMTR

Hershey Medical Center	Hershey	US	Research
Penn State Geisinger Health System	Hershey	US	Research
Queens Medical Center	Honolulu	US	Registration
St Francis Medical Center Honolulu	Honolulu	US	Registration
Center For Cell & Gene Therapy	Houston	US	Research
M.D. Anderson Cancer Center	Houston	US	Research
Texas Children's Hospital	Houston	US	Research
Comprehensive Cancer Institute	Huntsville	US	Research
Methodist Hospital of Indiana Cancer Center	Indianapolis	US	Research
Oncology Hematology Associates	Indianapolis	US	Research
Riley Hospital For Children	Indianapolis	US	Registration
St. Vincent Hospital & Health Care Center	Indianapolis	US	Research
Univ. Iowa Hospitals & Clinics	Iowa City	US	Research
Univ. of Iowa Department of Pediatrics	Iowa City	US	Research
Univ. of Mississippi Medical Center	Jackson	US	Registration
Mayo Clinic Jacksonville	Jacksonville	US	Research
Nemours Children’s Clinic	Jacksonville	US	Registration
Children’s Mercy Hospital	Kansas City	US	Research
St Luke’s Hospital of Kansas City	Kansas City	US	Research
Univ. of Kansas Medical Center	Kansas City	US	Research
Thompson Cancer Survival Center/UT	Knoxville	US	Registration
Univ. of California-San Diego	La Jolla	US	Research
SCRIPPS Clinic Research Foundation	La Jolla	US	Research
Wilford Hall USAF Medical Center	Lackland	US	Research
Arkansas Cancer Research Center	Little Rock	US	Registration
Southwest Cancer Clinic	Las Vegas	US	Research
Dartmouth-Hitchcock Medical Center	Lebanon	US	Research
Loma Linda University Medical Center	Loma Linda	US	Research
Ceders-Sinai Medical Center	Los Angeles	US	Research
Children’s Hospital of LA	Los Angeles	US	Research
UCLA-Center for Health Sciences	Los Angeles	US	Research
UCLA-Center for Health Sciences –Peds	Los Angeles	US	Research
USC/Norris Cancer Hospital	Los Angeles	US	Research
Univ. Louisville-James Brown Cancer Center	Louisville	US	Research
Texas Tech. Univ. Health Science Center	Lubbock	US	Research
Univ. of Wisconsin Hospital & Clinics	Madison	US	Research
North Shore Univ. Hospital	Manhasset	US	Registration
Marshfield Clinic	Marshfield	US	Research
Loyola Univ. Medical Center	Maywood	US	Research
Baptist Cancer Institute	Memphis	US	Registration
Methodist Hospital Central	Memphis	US	Registration
St. Jude Children’s Research Hospital	Memphis	US	Registration

Appendix 1

Institutions participating in the CIBMTR

Miami Children's Hospital	Miami	US	Registration
Univ. of Miami School of Medicine	Miami	US	Registration
Froedtert Memorial Lutheran Hospital	Milwaukee	US	Registration
Medical College of Wisconsin-Milwaukee	Milwaukee	US	Research
St. Luke's Medical Center	Milwaukee	US	Research
Abbott Northwestern Hospital	Minneapolis	US	Research
Children's Hospital & Clinics	Minneapolis	US	Research
Univ. of Minnesota	Minneapolis	US	Research
Missoula Oncology and Infectious Disease	Missoula	US	Registration
West Virginia Univ. Hospitals	Morgantown	US	Research
Hanhe Health System	Morristown	US	Research
Vanderbilt Univ.	Nashville	US	Research
Cancer Institute of New Jersey	New Brunswick	US	Research
Yale Cancer Center	New Haven	US	Research
Schneider Children's Hospital of North Shore	New Hyde Park	US	Research
Children's Hospital LSU	New Orleans	US	Research
Memorial Medical Center	New Orleans	US	Research
Tulane Univ. Medical Center	New Orleans	US	Research
Univ. Hospital Louisiana State Medical Center	New Orleans	US	Research
Columbia Presbyterian Hospital	New York	US	Research
Hassenfield Children's Center	New York	US	Research
Memorial Sloan-Kettering Cancer Center	New York	US	Research
Mount Sinai Medical Center	New York	US	Research
New York Hospital Cornell Medical Center	New York	US	Research
New York Presbyterian Hospital/Cornell Medical	New York	US	Research
St. Vincent Hospital Manhattan	New York	US	Registration
Hoag Cancer Center	Newport Beach	US	Registration
Virginia Oncology Associates	Norfolk	US	Registration
Children's Hospital of Oakland	Oakland	US	Research
Cancer Care Assoc. of Oklahoma City	Oklahoma City	US	Research
Univ. of Oklahoma Health Science Center	Oklahoma City	US	Research
Immanuel Cancer Center	Omaha	US	Registration
Univ. of Nebraska Medical Center	Omaha	US	Research
St Joseph Hospital/Regional Cancer Center	Orange	US	Research
UCI Medical Center	Orange	US	Registration
Children's Hospital of Orange County	Orange Co	US	Research
Walt Disney Memorial Cancer Institute	Orlando	US	Research
Lutheran General Hospital	Parkridge	US	Registration
St Joseph's Hospital & Medical Center	Paterson	US	Research
Methodist Medical Center	Peoria	US	Research
Hahnemann Univ./Institute for Cancer	Philadelphia	US	Research
Children's Hospital of Philadelphia	Philadelphia	US	Registration

Appendix 1

Institutions participating in the CIBMTR

Temple Univ. Comprehensive Cancer Center	Philadelphia	US	Registration
Thomas Jefferson Univ. Hospital	Philadelphia	US	Research
University of Pennsylvania Hospital	Philadelphia	US	Research
Children's Hospital of Pittsburgh	Pittsburgh	US	Research
Hillman Cancer Center	Pittsburgh	US	Research
West Pennsylvania Cancer Institute	Pittsburgh	US	Research
Legacy Good Samaritan Hospital	Portland	US	Research
Oregon Health Sciences University-Ped	Portland	US	Research
Oregon Health Sciences University –Adult	Portland	US	Research
Providence Portland Medical Center	Portland	US	Research
Roger Williams Medical Center	Providence	US	Research
Raleigh	Raleigh	US	Registration
Cancer & Blood Institute of the Desert	Rancho Mirage	US	Registration
Medical College of Virginia	Richmond	US	Research
Mayo Clinic Rochester	Rochester	US	Research
Strong Memorial Hospital	Rochester	US	Research
Sutter Memorial Hospital	Sacramento	US	Registration
Univ. of California-Davis Cancer Center	Sacramento	US	Registration
LDS Hospital/Intermountain Health	Salt Lake City	US	Research
Univ. of Utah Medical Center	Salt Lake City	US	Research
Santa Rosa Children’s Hospital	San Antonio	US	Registration
South Texas Cancer Institute	San Antonio	US	Research
Texas Transplant Institute	San Antonio	US	Research
Univ. of Texas-Health Science Center	San Antonio	US	Research
Children’s Hospital San Diego	San Diego	US	Registration
Univ. California/Moffitt Hospital	San Francisco	US	Research
Univ. of CA-San Francisco Medical Center	San Francisco	US	Research
Univ. of CA-San Francisco Pediatrics	San Francisco	US	Research
Univ. of Puerto Rico	San Juan	US	Research
Guthrie Clinic, Ltd	Sayre	US	Research
Mayo Clinic	Scottsdale	US	Research
Fred Hutchinson Cancer Research Center	Seattle	US	Registration
LSU Medical Center	Shreveport	US	Research
Avera Cancer Institute	Sioux Falls	US	Research
Spartanburg Regional Medical Center	Spartanburg	US	Registration
Cardinal Glennon Children’s Hospital	St Louis	US	Research
St Louis U H S Center	St Louis	US	Research
St. Louis Children’s Hospital	St Louis	US	Research
St. Louis Univ. Medical Center	St Louis	US	Research
Washington Univ. School of Medicine	St Louis	US	Research
All Children's Hospital	St Petersburg	US	Registration
Minn. Oncology Hematology-St. Paul	St Paul	US	Registration

Appendix 1

Institutions participating in the CIBMTR

Bennett Cancer Center	Stamford	US	Research
Stanford Univ. Medical Center	Stanford	US	Research
SUNY at Stony Brook	Stony Brook	US	Research
Suny Upstate Medical Univ.	Syracuse	US	Research
H. Lee Moffitt Cancer Center	Tampa	US	Research
St. Vincent Mercy Medical Center	Toledo	US	Research
Arizona Oncology Associates	Tucson	US	Research
Univ. of Arizona Cancer Center	Tucson	US	Registration
St. Francis Hospital	Tulsa	US	Registration
Cancer Care Assoc.	Tulsa	US	Research
New York Medical College	Valhalla	US	Research
John Muir Medical Center	Wallnut Creek	US	Research
Children's National Medical Center	Washington	US	Registration
George Washington Univ. Medical Center	Washington	US	Registration
Georgetown Univ. Medical Center	Washington	US	Research
Waukesha Memorial Hospital	Waukesha	US	Research
Good Samaritan Medical Center	West Palm Beach	US	Registration
Via Christi/St. Francis	Wichita	US	Research
Alfred I. DuPont Hospital for Children	Wilmington	US	Research
Medical Center of DE	Wilmington	US	Registration
Bowman Gray/Wake-Forest Univ.	Winston-Salem	US	Research
Piedmont Hem/Onc Associates PC	Winston-Salem	US	Registration
Univ. of Massachusetts Medical Center	Worcester	US	Research
Cancer Treatment Center of America	Zion	US	Research
Hospital de Clinicas Caracas	Caracas	Venezuela	Research
Hospital de Central de Valencia	Valencia	Venezuela	Research

Appendix 2

CIBMTR™
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

NMDP Transplant Centers

Alexander Fleming Institute	Argentina
Universidade Federal Do Parana	Brazil
Peking University People's Hospital	China
The First Affil Hosp/Med College of Zhejiang Univ	China
University Hospital	Denmark
Helsinki University Central Hospital	Finland
Clinic of Bone Marrow Transpl. & Hem./Onc.	Germany
University of Munich	Germany
Universitaetsklinikum Hamburg-Eppendorf	Germany
DKD - Wiesbaden	Germany
Universitatsklinik Dresden	Germany
Leipzig University BMT Center	Germany
Charite - Campus Virchow Klinikum (Adults)	Germany
University Hospital-Mainz	Germany
University Hospital Charite-Virchow	Germany
Universitat Heidelberg	Germany
University of Tuebingen	Germany
University Hospital of Essen	Germany
Freiburg University Medical Center	Germany
Universitatsklinik Ulm	Germany
University Medical Center Dusseldorf	Germany
Univ. of Hong Kong & Queen Mary Hospital	Hong Kong
Chaim Sheba Medical Center (Pediatric)	Israel
Chaim Sheba Medical Center (adult)	Israel
Schneider Children's Med Ctr. of Israel	Israel
Rambam Medical Center	Israel
Hadassah Medical Organization	Israel
Rikshospitalet - The National Hospital	Norway
Silesian Medical Academy	Poland
Lower Silesian Center for Cellular Transplant	Poland
King Faisal Specialist Hosp & Res. Ctr.	Saudi Arabia
Constantiaberg Medi-Clinic	South Africa
Sahlgrenska University Hospital	Sweden
University Hospital - Uppsala	Sweden
Lund University Hospital	Sweden

Appendix 2

NMDP Transplant Centers

Karolinska University Hospital		Sweden
Leiden University Medical Centre		The Netherlands
Dr. Daniel Den Hoed Cancer Center		The Netherlands
University Medical Center Nijmegen		The Netherlands
University of Alabama at Birmingham	AL	USA
University of Arkansas for Medical Sciences	AR	USA
City of Hope Samaritan	AZ	USA
University Medical Center	AZ	USA
Children's Hospital and Health Center	CA	USA
UCSD Medical Center	CA	USA
University of California-Davis	CA	USA
Cedars-Sinai Medical Center	CA	USA
Children's Hospital & Research Center Oakland	CA	USA
Scripps Green Hospital	CA	USA
University of California (UCLA)	CA	USA
Children's Hospital of Los Angeles	CA	USA
UCSF Medical Center	CA	USA
City of Hope National Medical Center	CA	USA
Stanford Hospital and Clinics	CA	USA
Children's Hospital of Orange County (CHOC)	CA	USA
University of Colorado - Children's Hospital	CO	USA
Presbyterian/St. Lukes Medical Center	CO	USA
Yale University/Yale New Haven Hospital	CT	USA
Georgetown University Hospital	DC	USA
Children's National Medical Center	DC	USA
Christiana Care Health Services	DE	USA
Alfred I. duPont Hospital for Children	DE	USA
Miami Children's Hospital	FL	USA
University of Miami	FL	USA
Shands Hospital - University of Florida	FL	USA
All Children's Hospital	FL	USA
H. Lee Moffitt Cancer Center & Research Inst.	FL	USA
Children's Healthcare of Atlanta at Egleston	GA	USA
Northside Hospital	GA	USA
Emory University Hospital	GA	USA
Hawaii Bone Marrow Transplant Program	HI	USA
University of Iowa Hospitals and Clinics	IA	USA
The Children's Memorial Medical Center	IL	USA

Appendix 2

NMDP Transplant Centers

Loyola University Medical Center	IL	USA
Univ. of Illinois at Chicago (UIC) Med. Ctr.	IL	USA
Northwestern Memorial Hospital	IL	USA
Univ of Chicago Stem Cell Transplant Program	IL	USA
Rush-Presbyterian-St. Luke's Medical Center	IL	USA
St. Francis Hospital and Health Centers	IN	USA
Indiana U. Bone Marrow/Stem Cell Transpl Prog.	IN	USA
University of Kansas Medical Center	KS	USA
University of Kentucky Medical Center	KY	USA
Univ Medical Center, Inc., Univ. of Louisville Hosp.	KY	USA
Memorial Medical Center	LA	USA
Children's Hospital/LSUHSC	LA	USA
Tulane University Hospital and Clinic	LA	USA
UMASS Memorial Health Care	MA	USA
Beth Israel Deaconess Medical Center	MA	USA
Dana Farber/Partners Cancer Care	MA	USA
Tufts-New England Medical Center	MA	USA
Greenbaum Cancer Center; U. of Maryland	MD	USA
Johns Hopkins University	MD	USA
Henry Ford Health System	MI	USA
DeVos Children's Hosp/Spectrum Health	MI	USA
Oakwood Hospital and Medical Center	MI	USA
Karmanos Can Inst/Wayne St Univ & Harper Hos	MI	USA
University of Michigan Medical Center	MI	USA
Univ. of MN BMT Program/Fairview UMC	MN	USA
Mayo Clinic Rochester	MN	USA
Cardinal Glennon Children's Hospital	MO	USA
Kansas City Blood/Marrow Transpl. Program	MO	USA
Barnes-Jewish Hosp/Washington U Sch of Med	MO	USA
St. Louis University Medical Center	MO	USA
University of Mississippi Medical Center	MS	USA
UNC Hospitals	NC	USA
Duke University Medical Center	NC	USA
Wake Forest University Baptist Medical Center	NC	USA
The Nebraska Medical Center	NE	USA
Hackensack University Medical Center	NJ	USA
St. Joseph's Regional Medical Center	NJ	USA
New York Presbyterian Hospital at Cornell	NY	USA

Appendix 2

NMDP Transplant Centers

The Children's Hospital of New York	NY	USA
Schneider Children's Hospital	NY	USA
Memorial Sloan-Kettering Cancer Center	NY	USA
Strong Memorial Hospital	NY	USA
Roswell Park Cancer Institute	NY	USA
North Shore University Hospital	NY	USA
Mount Sinai Hospital	NY	USA
Zalmen A. Arlin Cancer Institute	NY	USA
The Jewish Hospital	OH	USA
Cleveland Clinic Foundation	OH	USA
Arthur G James Canc H/Richard J Solove Res Ins	OH	USA
Cincinnati Children's Hospital Medical Center	OH	USA
University Hospitals of Cleveland	OH	USA
HCA Health Services of Oklahoma, Inc.	OK	USA
Oregon Health & Science University	OR	USA
Temple University	PA	USA
Thomas Jefferson University Hospital, Inc.	PA	USA
University of Pennsylvania Medical Center	PA	USA
Penn State Milton S. Hershey Medical Center	PA	USA
Hahnemann University Hospitals	PA	USA
University of Pittsburgh Cancer Center	PA	USA
Children's Hospital of Philadelphia	PA	USA
W. Pennsylvnia Cancer Inst; The W. PN Hosp.	PA	USA
Roper Hospital	SC	USA
Medical University of South Carolina	SC	USA
Vanderbilt University Medical Center	TN	USA
St. Jude Children's Research Hospital	TN	USA
Texas Transplant Institute	TX	USA
Children's Medical Center of Dallas	TX	USA
Medical City Dallas Hospital	TX	USA
Texas Children's Hospital	TX	USA
The Univ of Texas SW Medical Center at Dallas	TX	USA
Texas Tech University Health Sciences Center	TX	USA
M.D. Anderson Cancer Center	TX	USA
Baylor University Medical Center	TX	USA
Cook Children's Medical Center	TX	USA
University of Utah	UT	USA
INOVA Fairfax Hospital	VA	USA

Appendix 2

NMDP Transplant Centers

Medical College of Virginia	VA	USA
Seattle Cancer Care Alliance	WA	USA
VA Puget Sound Health Care System	WA	USA
University of Wisconsin Hospital and Clinics	WI	USA
Froedtert Memorial Lutheran Hosp. Can. Ctr.	WI	USA
Childrens Hosp of WI/Midwest Childrens Canc Ctr	WI	USA
West Virginia University Hospitals, Inc.	WV	USA

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CIBMTR TRANSITIONAL ADVISORY COMMITTEE

IBMTR Executive	**ABMTR Executive**	**NMDP RAP**	**NMDP Histo**
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 *(ex officio-ASHI)*
J Apperley	ED Ball	A Feldmar	C Hurley *(ex officio-Navy)*
JR Passweg	D Vesole	N Collins	R Hartzman *(ex officio-Navy)*
J Szer	BJ Bolwell	K Ballen	R Baitty *(ex officio-HRSA)*
R Pasquini	DE Reece	S Giralt	R Ashton *(ex officio-HRSA)*
MM Horowitz *(ex officio)*	MM Horowitz *(ex officio)*	R Hartzman *(ex officio-Navy)*	D Confer *(ex officio)*
JP Klein *(ex officio)*	JP Klein *(ex officio)*	R Baitty *(ex officio-HRSA)*	M Setterholm *(ex officio)*
		R Ashton *(ex officio-HRSA)*	P Coppo *(ex officio)*
		D Confer *(ex officio)*	
		D Weisdorf *(ex officio)*	

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CIBMTR Working Committees

Acute Leukemia Working Committee
Chairs: Armand Keating, MD, Princess Margaret Hospital, Toronto, Ontario, Canada
Jorge Sierra, MD, Hospital Sant Pau Creu I Sant Pau, Barcelona, Spain
Martin Tallman, MD, Northwestern Memorial Hospital, Chicago, IL
Scientific Director: Daniel Weisdorf, MD
Statisticians: Catherine Muehlenbein, 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
Christian Boudreau, PhD

Lymphoma Working Committee
Chairs: Julie Vose, MD, University of Nebraska Medical Center, Omaha, NE
Hillard Lazarus, MD, University Hospitals of Cleveland, 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, Medical College of Wisconsin, Milwaukee, WI
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

Pediatric Cancer Working Committee
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Stephan Grupp, MD, Children's Hospital of Philadelphia, Philadelphia, PA
Stella Davies, MD, Children's Hospital Medical Center, Cincinnati, OH
Scientific Director: Mary Eapen, MD, MS
Statisticians: Catherine Muehlenbein, MPH
Mei-Jie Zhang, PhD

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

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Scientific Director: Mary Eapen, MD, MS
Statisticians: Seira Kurian, MD, MS, MPH
Christian Boudreau, PhD

Autoimmune Diseases Working Committee
Chairs: Richard Nash, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
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Scientific Director: Christopher Bredeson, MD, MSc
Statisticians: Haiqing Tang, MS
Brent Logan, PhD

Immunogenetics Working Committee
Chairs: Effie Petersdorf, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Carolyn Hurley, PhD, Georgetown University School of Medicine, Washington, DC
Machteld Oudshoorn, PhD, Leiden University Medical Center, Leiden, The Netherlands
Scientific Director: Mary Horowitz, MD, MS
Statisticians: Michael Haagenson, MS
John Klein, 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
Statisticians: Haiqing Tang, MS
Mei-Jie Zhang, PhD

Regimen-Related Toxicity/Supportive Care Working Committee
Chairs: Karen Ballen, MD, Massachusetts General Hospital, Boston, MA
Andrea Bacigalupo, MD, San Martino Hospital, Genova, Italy
Scientific Director: Doug Rizzo, MD
Statisticians: Sharavi Gandham, MS
Brent Logan, PhD

Infection and Immune Reconstitution Working Committee
Chairs: Jan Storek, MD, PhD, University of Calgary, Calgary, Alberta, Canada
Jo-Anne van Burik, MD, University of Minnesota, Minneapolis, MN
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Scientific Director: Marcie Tomblyn, MD, MS
Statisticians: Waleska S. Perez, MPH
Christian Boudreau, 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: Mary Horowitz, MD, MS
Statisticians: Sharavi Gandham, MS
John Klein, 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: Doug Rizzo, MD
Statisticians: Haiqing Tang, 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: Michael Haagenson, MS
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: Doug Rizzo, MD
Statisticians: Siera Kurian, MD, MS, MPH
John Klein, PhD

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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 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:** Christopher Bredeson, MD, MSc, Medical College of Wisconsin, Milwaukee, WI
CIBMTR Program Leader/Observational Studies:** Douglas Rizzo, MD, Medical College of Wisconsin, Milwaukee, WI
Three appointed members of the Advisory Committee: Arthur Flatau, PhD and 2-TBN

* **terms expire 12/05.** Assembly elections are scheduled for Fall 2005 for terms starting January 1, 2006.

** ***ex officio***

CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH

Committee Structure

1.0 INTRODUCTION

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research program formed in July 2004 through an affiliation between the International Bone Marrow Transplant Registry (IBMTR) and Autologous Blood and Marrow Transplant Registry (ABMTR) of the Medical College of Wisconsin and National Marrow Donor Program (NMDP) – Research, a subsidiary of the NMDP. The IBMTR/ABMTR is a voluntary organization involving more than 400 transplant centers in 47 countries that have collaborated to share patient data and conduct scientific studies since 1972. The NMDP was established in 1987 to provide unrelated donors for patients in need of hematopoietic stem cell transplants and to conduct research to improve the outcome of such transplants. The NMDP Network includes more than 150 transplant centers and 90 donor centers. The CIBMTR brings together the research efforts of both organizations to create a unique resource of data and statistical expertise for studying hematopoietic stem cell transplantation.

2.0 OVERALL STRUCTURE OF THE CIBMTR

The organizational structure of the CIBMTR is shown in Figure 1. The Chief Scientific Director has primary responsibility for administrative and scientific operations. The Center will have four major areas or programs of research activity: Observational Research, Clinical Trials, Immunobiology and Statistical Methodology. Each of these areas will be directed by a Program Leader who is an M.D. or Ph.D. The CIBMTR Statistical Director has responsibility for the statistical quality of all CIBMTR studies.

2.1 Observational Studies

Observational research using the large clinical databases of the IBMTR/ABMTR and NMDP to address important issues in blood and marrow transplantation will be a core activity of the CIBMTR. The affiliation plans to develop new areas of observational research to include more in depth evaluation of health policy issues and access to care.

2.2 Clinical Trials Support

The purpose of this program is to facilitate clinical trials focusing on issues in hematopoietic stem cell transplantation (HSCT). Coordinating activities for the U.S. Blood and Marrow Transplant Clinical Trials Network (BMT CTN) will fall under this program but other trials will be conducted as well. Additionally, support may be provided through this office to assist individuals or groups planning trials that will not use CIBMTR or BMT CTN resources to conduct the trials (e.g. statistical consulting, assessment of feasibility using the IBMTR/NMDP databases). Proposals for non-CTN trials will be reviewed and overseen by a Clinical Trials Steering Committee (to be formed). Working Committees wishing to develop a non-CTN clinical trial in their topic area must have their proposal approved by the Clinical Trials Steering Committee before resources are committed. Proposals for CTN trials will follow standard CTN procedures.

2.3 Immunobiology

The purpose of this program will be to facilitate high quality studies using the NMDP unrelated donor/recipient specimen repository. Additionally, this office will be charged with development and management of a related donor/recipient repository. Proposals for repository specimens will be reviewed and overseen by a Repository Steering Committee (to be formed). Working Committees wishing to conduct a study that incorporates analysis of repository specimens must have their proposal approved by the Repository Steering Committee before resources are committed.

2.4 Statistical Methodology

The purpose of this program will be to facilitate development of new statistical approaches, to prepare educational review articles on analysis of HSCT data and to provide input to other scientific projects. The Statistical Director will serve as head of this program.

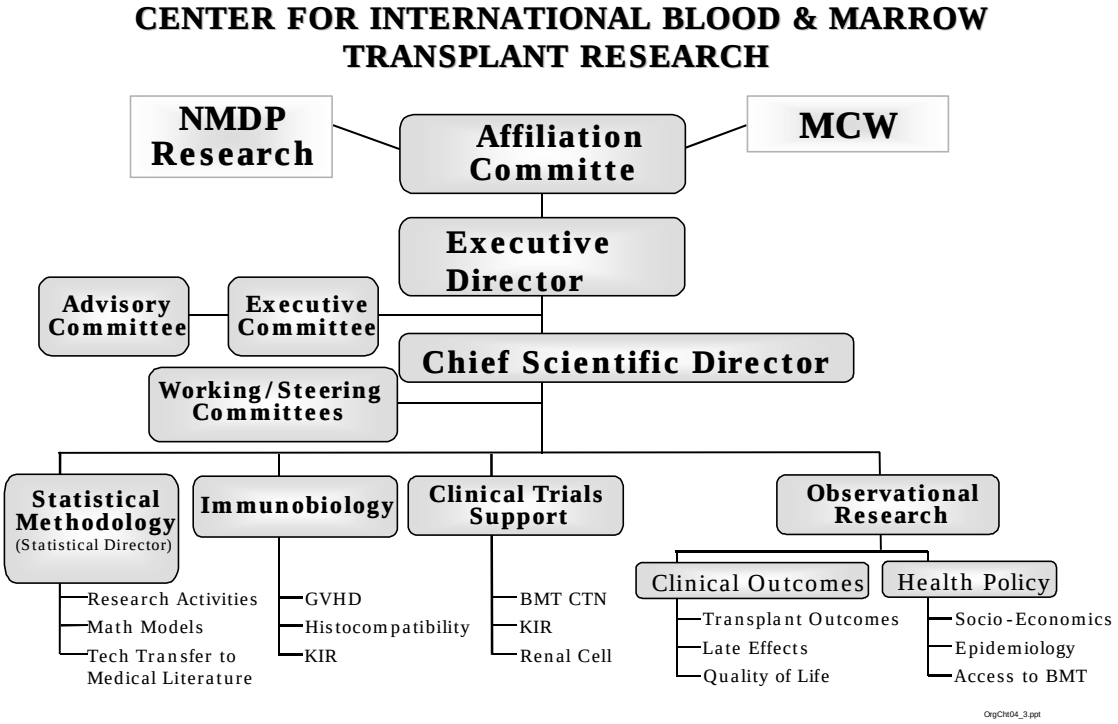

Figure 1. Organizational structure of CIBMTR

2.5 Proposal submission and evaluation

Anyone may propose a study using CIBMTR data or resources. The Statistical Center and relevant Working or Steering Committee Chair reviews the proposal. Statistical Center staff are available to assist in preparing the proposal for review. Studies deemed feasible and consistent with the CIBMTR's scientific goals are forwarded to the appropriate Working or Steering Committee for further input and assignment of priority. Studies are initiated at the discretion of the Working or Steering Committee Chair, Scientific Director and the Executive Committee Chair based on priority scores, competing projects and available resources. Additional guidelines for operation of the Clinical Trials and Repository Steering Committees in evaluating proposals will be developed as noted above.

3 CIBMTR COMMITTEES

CIBMTR Committees are composed of experts in various disciplines related to HSCT and the diseases for which transplantation is done. The 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.

3.1 CIBMTR Assembly

CIBMTR transplant centers will include all current IBMTR/ABMTR transplant centers and NMDP transplant centers. Centers will be designated as Registration Centers (provide only Transplant Essential Data) or Research Centers (submit comprehensive Report Forms for a subset of their patients; *Note: This includes all NMDP transplant centers*). Each CIBMTR

Research Center may designate one representative to participate in the CIBMTR Assembly. Assembly members will receive periodic summaries of CIBMTR activities and will elect the members of the CIBMTR Advisory Committee and Nominating Committee (see below). The Assembly will meet once a year at the Annual Tandem BMT Meetings.

3.2 Advisory Committee

The Advisory Committee (Figure 2) will be composed of elected and appointed representatives using selection designed to ensure adequate a.) expertise in adult and pediatric autologous, related donor and unrelated donor transplantation; b.) expertise in donor selection and graft collection and manipulation; c.) representation of U.S. and non-U.S. transplant centers; d.) inclusion of patient, family and donor representatives; e.) familiarity with both IBMTR/ABMTR and NMDP operations. The Committee will have 32 members, including the following:

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: 1; 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 Research Advisor (appointed by NMDP)
- CIBMTR Chief Scientific Director
- CIBMTR Statistical Director
- CIBMTR Program Leaders (4)

The CIBMTR Assembly will hold its first elections in Fall 2005 for terms to begin in January 2006.

The CIBMTR Advisory Committee will review, at least annually, scientific and other activities of the CIBMTR. A meeting of the Advisory will be conducted annually at the Tandem BMT Meetings. At least one additional meeting by conference call will be held annually.

3.3 Executive Committee

The 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, Vice-Chairs, and the three appointed members of the Advisory Committee. Additionally, the CIBMTR Research Advisor, Chief Scientific Director and Program Leaders serve as *ex officio* members. The Executive Committee is responsible for ensuring that the organization carries out its mission and fulfills the requirements of CIBMTR policies and procedures. The committee will meet at least annually at the Tandem BMT Meetings and by conference call at least quarterly.

3.4 Nominating Committee

The Assembly will elect five members to a Nominating Committee, each serving staggered two-year terms. The Nominating Committee is responsible for preparing a slate of candidates for the Advisory Committee and Nominating Committee. The Nominating Committee will seek input from the CIBMTR Assembly, Advisory Committee and Working Committee chairs in preparing its slate through a mailed request for nominees distributed in March of each year. The slate of candidates will be distributed for mailed ballot in September of each year.

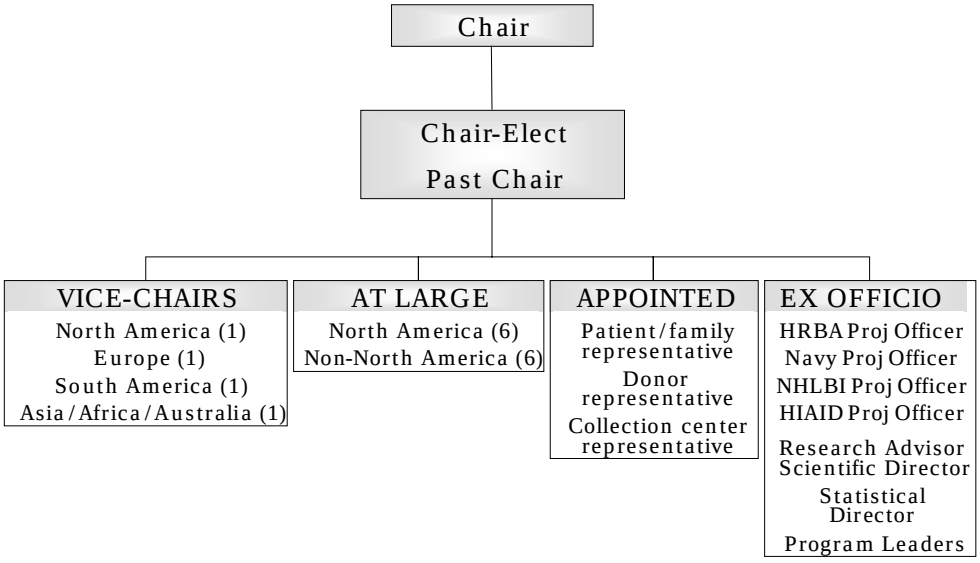

Figure 2. CBIMTR Advisory Committee

3.5 Transition to New Advisory/Executive/Nominating Committee Structure

Initially, a Transitional Advisory Committee will be formed by the current IBMTR and ABMTR Executive Committees and the NMDP RAP and Histocompatibility Committees. This includes the following the individuals listed in Table 3.5. Additionally, the IBMTR NCI, NHLBI and NIAID Project Officers and the CIBMTR Senior Advisor and Program Leaders will be invited as *ex officio* members. The plan is to move to the new Advisory/Executive Committee structure of 32 members (18 elected, 3 appointed, 11 *ex officio)* by January of 2006. A meeting of the Transitional Advisory Committee will be held in Fall 2004, at which time the Committee members will elect an interim Chair, 4 Vice-chairs and a Donor Center representative to be chosen from the Transitional Advisory Committee membership. These individuals plus the current chairs of the IBMTR and ABMTR Executive Committees and the NMDP RAP and Histocompatibility Committees will serve on the Interim Executive Committee through 2005. An Interim Nominating Committee, including the current chairs of the IBMTR and ABMTR Nominating Committees and the NMDP RAP and Histocompatibility Committees and the CIBMTR Research Advisor, will prepare a slate of candidates for the Assembly to elect

an Advisory Committee at the end of 2005 to begin terms in January 2006. Terms for these positions will have staggered expiration dates as outlined below:

Chair – 2006-2007
Vice-Chair North America – 2006-2007
Vice-Chair Europe – 2006-2008
Vice-Chair South America – 2006-2007
Vice-Chair Asia/Africa/Australia – 2006-2008
At large North America:
3 positions – 2006-2007
3 positions – 2006-2008
At large non-North America:
3 positions – 2006-2007
3 positions – 2006-2008
Nominating Committee:
3 positions – 2006-2007
2 positions – 2006-2008

Table 3.5. Members of the Transitional Advisory Committee

IBMTR Executive	ABMTR Executive	NMDP RAP	NMDP Histocompatibility
Name *(IBMTR title)*	Name *(ABMTR title)*	Name *(RAP title)*	Name *(Histo title)*
O. Ringden *(Chair)*	RE Champlin *(Chair)*	NR Kamani *(Chair)*	C Anasetti *(Chair)*
S. Giralt *(Chair-elect)*	MR Litzow *(Chair-elect)*	A Flatau*(Pt/Fam/Don)*	RA Bray *(Vice-chair)*
A. Filipovich *(Past Chair)*	JM Vose *(Past Chair)*	S. Bearman*(TC/CC Rep)*	M Oudshoorn *(Histo exp)*
M. Bishop *(Secy/Treas)*	PJ Stiff *(Secy/Treas)*	J. Casper *(TC/CC Rep)*	FO Smith *(Histo exp)*
H. Lazarus *(Nominating Comm Chair)*	E Stadtmauer *(Nominating Comm chair)*	J. Gajewski*(TC/CC Rep)*	SY Yang *(Histo exp)*
M. Litzow *(At large-No America)*	E. Copelan *(At large)*	Nademanee *(DC Rep)*	SJ Mack *(Gene exp)*
AJ Barrett *(At large–No America)*	JF DiPersio *(At large)*	R. Strauss *(DC Rep)*	S Rosen-Bronson *(ex offi ASHI)*
J. Apperley *(At large-Europe)*	ED Ball *(At large)*	N. Collins *(Expertise)*	C. Hurley *(ex officio Navy)*
JR Passweg *(At large-Europe)*	D. Vesole *(At large)*	K. Ballen *(Expertise)*	R. Hartzman *(ex officio Na*
J. Szer *(At large-Other)*	BJ Bolwell *(At large)*	S. Giralt *(Expertise)*	R. Baitty *(ex officio HRSA*
R. Pasquini *(At large-Other)*	DE Reece *(At large)*	R. Hartzman *(ex officio Navy)*	R. Ashton *(ex officio HRS*
MM Horowitz *(ex officio)*	MM Horowitz *(ex officio)*	R. Baitty *(ex officio HRSA)*	D. Confer *(ex officio)*
JP Klein *(ex officio)*	JP Klein *(ex officio)*	R. Ashton*(ex officio HRSA)*	M. Setterholm *(ex officio)*
		D. Confer *(ex officio)*	P. Coppo *(ex officio)*
		D. Weisdorf *(ex officio)*	

TC=Transplant Center; DC=Donor Center; CC=Collection Center

For the year 2006, there will be 4 Past Chairs (the current Chairs of the IBMTR and ABMTR Executive Committees and the NMDP RAP and Histocompatibility Committees). Thereafter, there will a single Chair-elect OR Past-Chair. The individual elected to Chair for 2006-2007 will select the three appointed members of the Committee, as outlined above. In January 2006, *ex officio* members will be limited to those listed in Section IVb above. Although some three year terms are required during this initial period to achieve staggered terms, all subsequent terms will be two years as described above.

3.6 Working Committees

Observational research using the large clinical databases of the IBMTR/ABMTR and NMDP will continue to be a core activity of the CIBMTR. Development and prioritization of studies

will be done using a Working Committee structure modeled on the one currently used by the IBMTR/ABMTR. All existing IBMTR/ABMTR and NMDP scientific Committees will be moved into the new structure. These include:

- IBMTR/ABMTR: Acute Leukemia; Chronic Leukemia; Lymphoma; Plasma Cell Disorders; Solid Tumors; Pediatric Cancer; Non-malignant Marrow Disorders; Immune Deficiencies/Inborn Errors of Metabolism (IOEM); Autoimmune Disease; Histocompatibility/Graft Sources; Graft vs Host Disease (GVHD)/Immune Reconstitution; Late Effects

- NMDP: RAP; Histocompatibility

The CIBMTR will have the following Working Committees with indicated areas of responsibility for scientific oversight:

- Acute Leukemia*: cellular therapy for acute leukemias, preleukemia and myelodysplastic disorders
- Chronic Leukemia*: cellular therapy for chronic leukemias and myeloproliferative disorders
- Lymphoma*: cellular therapy for Hodgkin and non-Hodgkin disease
- Plasma Cell Disorders*: cellular therapy for multiple myeloma and other plasma cell disorders
- Solid Tumors*: cellular therapy for solid tumors
- Pediatric Cancer*: cellular therapy for childhood malignancies and other issues related to use of cellular therapy in children
- Non-Malignant Marrow Disorders*: cellular therapy for aplastic anemia, congenital disorders of hematopoiesis, autoimmune cytopenias and other non-malignant hematopoietic disorders
- Immune Deficiencies/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/Manipulation**: issues related to graft procurement, quality and manipulation
- 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
- Immunogenetics#: histocompatibility and other genetic and immunologic issues related to cellular therapy
- Infection/Immune Reconstitution##: prevention and treatment of posttransplant infections and issues related to recovery of immune function
- Regimen-Related Toxicity and Supportive Care##: preparative regimens, prevention and treatment of early non-GVHD toxicities and supportive care in the early posttransplant period
- Health Services and Psychosocial Issues##: access to cellular therapy including social and economic barriers to care and influence of psychosocial factors on outcome
- Donor Health and Safety##: Donor outcomes

*Existing IBMTR/ABMTR Committee
**Formerly IBMTR/ABMTR Histocompatibility and Graft Sources Committee; histocompatibility issues will now be under purview of Immunogenetics Committee
#Formerly NMDP Histocompatibility Committee
##New Committee

Working Committees have responsibility for setting priorities for CIBMTR observational studies. Membership is open to any individual willing to take an active role in development of studies using CIBMTR data and/or resources. Chairs must generally be members of CIBMTR Research Teams, unless an exception is granted by the Executive Committee. 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. Working Committees are headed by 2-4 chairs who are appointed by the Executive Committee to a single five-year term. Individuals may serve more than once but not consecutive terms. 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/ABMTR and NMDP activities. Each Working Committee will be allocated a specific amount of CIBMTR resources, including statistician time, to be determined by the Chief Scientific Director in consultation with the Statistical Director and Program Leader.

3.7 Steering Committees

Use of CIBMTR resources for the conduct of clinical trials through the Clinical Trials Support Program and for studies using the NMDP Repository through the Immunobiology Program require careful, fair and expert oversight since the resources for these types of studies may be extensive and, in the case of specimens, irreplaceable. Each of these programs will have a Steering Committee appointed by the CIBMTR Executive Committee to review proposals. The policies and procedures for selecting Steering Committee members and for reviewing and approving studies will be developed in the first year of the CIBMTR.

3.8 External Review Committee

At least every three years, the Affiliation Board will convene a panel to review the scientific accomplishments of the CIBMTR and make recommendations to the Affiliation Board. The Committee will consist of experts in the field of blood and marrow transplantation, statistics, clinical research, cancer and other fields pertinent to the goals and activities of the CIBMTR.