CIBMTR Working Committees in the Spotlight

We continue our series focusing on the work of the Working Committees of the CIBMTR. The Working Committees provide scientific oversight for the use of CIBMTR data and statistical resources.

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

Working Committees have responsibility for setting priorities for observational studies using CIBMTR’s large clinical databases. These observational studies are a core activity of the CIBMTR. For a full listing of the 19 Working Committees and their leadership, point your browser to http://www.cibmtr.org/COMMITTEES/Working_Committees/index.html.

In this issue, we highlight the work of the Late Effects and Graft Sources and Manipulation Working Committees.

The Late Effects Working Committee

The Late Effects Working Committee (LEWC) conducts clinical research on late effects following hematopoietic stem cell transplantation. We take advantage of the large clinical database of the CIBMTR to study long-term effects of transplant, ranging from second-malignancies to quality-of-life studies. With the increasing number of transplants being performed and better supportive care, there are more and more long-term survivors and our mission is to understand their late effects.

The LEWC is headed by 3 co-chairs: Brian Bolwell, MD (Cleveland Clinic Foundation), John Wingard, MD (University of Florida) and David Jacobsohn, MD (Children’s Memorial Hospital). The chairs are assisted by the Scientific Directors J. Douglas Rizzo, MD, MS and Navneet S. Majhail, MD, MS and statisticians Kathleen Sobocinski, MS and Jerry (Zhiwei) Wang, MS, Ruta Bajorunaite, PhD and John P. Klein, PhD.

The LEWC promotes and develops the scientific agenda, establishes priorities, and ensures the progress of the research studies and publications. The committee meets yearly at the BMT Tandem Meetings and the co-chairs meet monthly by teleconference with the CIBMTR staff.

This year, our committee has identified 3 target areas of post-transplant late-effects that deserve specific attention: fertility, liver toxicity, and quality-of-life after transplant. Subcommittees have been formed and are meeting by conference calls. The goals are to conduct studies on late effects that will lead to more and more long-term survivors and our mission is to understand their late effects.

CIBMTR Graft Sources and Manipulation Working Committee

The Graft Sources and Manipulation Working Committee (GSMWC) addresses scientific questions related to graft procurement, quality, and manipulation and is one of the most active and prolific committee’s of the CIBMTR. This committee has collaborated with other registries, national and international, and the resulting publications have led to practice changes with respect to graft choices when considering HLA-matched sibling and unrelated donor transplantations for leukemia.

The Statistical Center and the committee would like to acknowledge the leadership and scientific contributions of Dr. John Wagner who served as committee co-chair for over a decade. The committee is now chaired by Adrian Gee, PhD (Baylor College of Medicine), Richard E. Champlin, MD (M.D. Anderson Cancer Research Center), and Mary J. Laughlin, MD (Case Western Reserve University). The chairs are assisted by the Scientific Director, Mary Eapen, MD, MS and statisticians Fangyu Kan, MS, MA and Mei-Jie Zhang, PhD.

Our committee membership is comprised of investigators of diverse backgrounds and experience in clinical transplantation and cell processing and manipulation, providing the opportunity for synergy in scientific interactions, stem cell technology development, and new ideas. Our committee is a lively and interactive group that

CIBMTR Newsletter Survey

Please take a few minutes to participate in our brief survey about the CIBMTR Newsletter. Thank you!

Find it online at:
http://www.surveymonkey.com/s.aspx?sm=YbVOIMVbHcmNYmTqlGtv_2bw_3d_3d
Update on the Stem Cell Therapeutics Outcomes Database (SCTOD)

by J. Douglas Rizzo, MD, MS

Two years have passed since the CIBMTR received the contract to collect data for all allogeneic hematopoietic cell transplants (HCT) in the United States (US) as part of the C.W. Bill Young Cell Transplantation Program. Although much work remains, considerable progress has been made in bringing this program to fruition.

Data Collection

Virtually all transplant centers in the US, and a large majority of those who collaborate with the CIBMTR internationally are now aware of the changes brought by the SCTOD. US and international centers continue to complete and submit new (or updated) Data Transmission Agreements (DTA) that provide for the exchange of data (and payment for data) between centers and the CIBMTR. Centers with outstanding DTAs are encouraged to complete these documents. Reimbursement for Report Forms submitted to CIBMTR is conditional upon receipt of a completed DTA. Similarly, the new observational database research protocol and consent documents covering submission of data to the CIBMTR are in their second year, and a majority of US centers have completed the necessary steps to gain approval of these important documents from local IRBs. Consent for use of data for research should be sought from every patient for whom data will be sent to the CIBMTR, regardless of whether the data is submitted on a TED level or comprehensive Report Form level.

New TED level and comprehensive Report Forms released in December of 2007 are generally working well for data collection. Questions regarding these forms suggest thoughtful consideration by data professionals at the centers, and several of these questions will lead to changes in the forms with the next iteration. CIBMTR does not intend to make large-scale changes to any of the data collection forms over the course of the next year, to allow sufficient time for electronic and other systems to reach stability. Small changes that affect form completion logic will happen intermittently.

FormsNet™

Along with the release of new data collection instruments, CIBMTR has also launched the FormsNet™ application to capture data electronically. As of this writing, all US HCT centers have the ability to access FormsNet™ along with the majority of international centers. Almost 200 centers are using FormsNet™ to enter at least some of their data, and more than 60,000 individual forms have been processed by FormsNet™ since inception. This represents a considerable shift in data submission for most HCT centers, a trend which we anticipate will continue over the next few years with increasing adoption of electronic data submission. CIBMTR staff also use this application for data entry, and provide important feedback about the application.

As with the launch of any major software application, there has been considerable turbulence in the first 9 months of the FormsNet™ life cycle. Information services staff on both the Milwaukee and Minneapolis campus have been devoted to resolving issues with the application. Issues addressed include improvements in the error message and error correction screens, enhanced search features in the centers’ forms due screen, improvements in system stability, and various bug fixes. Perhaps the largest system repair currently in process involves the forms due listing. The complexities of bringing together two separate databases and data systems into a consolidated work list involving more than 260,000 patient records led to several problems with creation of forms due lists for each transplant center. CIBMTR has been in the process of implementing the repairs, with progressive improvement visible to FormsNet™ users since July 2008. To accommodate the needs of centers to have an accurate Forms Due listing, the Continuous Process Improvement (CPI) program has been placed on hold until the forms due reports can be issued. Teams are still expected to complete the appropriate forms for related and unrelated HCT recipients, but formal CPI reports are suspended. Once the forms due repairs are complete, CPI expectations will be resumed. Information about the FormsNet™ application is regularly communicated with users via email, as well as a Google User “Tip of the Week” and Google User Group. These communication tools augment the direct communication with CIBMTR staff dedicated to each center, as well as postings of frequently asked questions on the CIBMTR website.

Several enhancements to FormsNet™ are planned over the coming months, some in response to user requests. These will include features to improve the work processes of data personnel such as: improved patient and center forms due screens which can be sorted, filtered and exported to Excel; tools for team liaisons that will allow them to assist centers with forms and data corrections; and general enhancements to improve stability and add functionality. Additionally, for HCT programs outside the US who wish to provide comprehensive data to the CIBMTR, functionality to accept pre-TED data from the EBMT via a dataset provided from ProMiSe and generate a request for comprehensive Report Forms is in process. Likewise, centers who wish to provide data to CIBMTR for all patients at their center to establish a complete dataset, regardless of provision of consent for research, will be able to accomplish this in the coming months. An agreement will be needed between the interested centers and CIBMTR before this can be put into effect.

AGNIS - Messaging System

Work continues on the AGNIS system to better facilitate electronic data exchange between centers and the CIBMTR. Data elements are being “curated” with the NCI’s cancer data standards repository (caDSR) such that all data exchanged will comply with a national data standard. CIBMTR staff actively collaborate with staff from the NCI team to increase the efficiency of the process. Curation occurs on a form by form basis, and as of the time of this writing, the 2400, 2450, 2004, 2005 forms are fully defined, with several of the Report Forms in process. Data has been exchanged for some of these forms using the AGNIS messaging system in collaboration with the AGNIS user group. Parties interested in learning more about AGNIS, or joining the AGNIS user group are encouraged to visit www.agnis.net. In addition to StemSoft, several other software development companies have expressed interest in learning more about AGNIS, and may begin to develop applications for the HCT environment. Potential users making queries of software vendors are encouraged to learn more about the vendor’s intentions to use AGNIS in their product. As AGNIS becomes more robust, CIBMTR will be creating a web-based seminar series to provide further specific information to potential transplant and IT users, as well as considering subsequent in-person meetings in a format similar to the IT Summit held in Minneapolis in January 2008.

Systems used to collect data on behalf of the HRSA are required to pass a rigorous security audit conducted by the HRSA Office of Information Technology. After a year of preparation, CIBMTR completed an extensive System Test and Evaluation in June of 2008, and anticipates full certification and authorization before the end of 2008. Similar status is already held by NMDP, and should bolster confidence that protected health information submitted to CIBMTR systems is indeed held under secure conditions.

Center Specific Outcomes

The new Program requires that CIBMTR conduct analyses of HCT outcomes on a center by center basis and make such reports available to the public. CIBMTR is committed to conducting an equitable center-specific
analysis report with scientific rigor to fulfill these requirements for allogeneic HCT recipients in the United States. To achieve this, we have been working with the ASBMT Quality Outcomes committee to be certain current data collection instruments collect data relevant to this task. Recently, a forum was held in Milwaukee in September to discuss and develop a plan to conduct these analyses. A group of nearly 50 people representing the HCT community, solid organ transplant experts (who conduct similar analyses annually), experts from other medical communities conducting and reporting hospital outcomes, payors, government agencies, and patients attended the 2 day meeting. A report will be generated and circulated to Transplant Center directors before the 2009 BMT Tandem Meetings, and the plan will be presented at the Medical Directors conference during the 2009 BMT Tandem Meetings.

CIBMTR anticipates that 2009 will be a year of ongoing improvement in the functionality of the systems supporting the SCTOD. We appreciate the patience of HCT centers, banks, and other entities interacting with the CIBMTR as the complex program is being implemented.

Perspectives

by Stella M. Davies, MBBS, PhD, MRCP
Chair, CIBMTR Advisory Committee,
Professor of Pediatrics, Cincinnati Children’s Hospital Medical Center

Funding the CIBMTR

The large CIBMTR database and the outstanding and unique research that comes from it is an expensive proposition. Funding the registry is like painting a bridge; as soon as you are done for one year it is time to start again for the next year. Over the years, funding has come from a U24 grant from the US government, competitive grant applications from a range of agencies and foundations, and from fundraising efforts, bringing in donations from family foundations, industry partners and individuals. Recently the NIH announced that funding would be cut across the board and individuals. Recently the NIH announced that funding would be cut across the board and individuals. Recently the NIH announced that funding would be cut across the board and individuals. Recently the NIH announced that funding would be cut across the board and individuals. Recently the NIH announced that funding would be cut across the board and individuals. Recently the NIH announced that funding would be cut across the board and individuals. Recently the NIH announced that funding would be cut across the board and individuals. Recently the NIH announced that funding would be cut across the board and individuals. Recently the NIH announced that funding would be cut across the board and individuals.

The recruitment and HLA-typing of such a large group of individuals has lead to enormous improvements in HLA-typing techniques with molecular methods of typing now in general use, offering greatly improved allele discrimination compared with older serological techniques. The high volume of typing required by NMDP has pushed laboratories to make typing assays more rapid and less costly, and in the near future it is hoped that the majority of new donors recruited to the registry will have molecular typing at HLA-A,B,C and DRB1. The NMDP’s achievements of the first 20 years are detailed in a very encouraging analysis report with scientific rigor to fulfill these requirements for allogeneic HCT recipients in the United States. To achieve this, we have been working with the ASBMT Quality Outcomes committee to be certain current data collection instruments collect data relevant to this task. Recently, a forum was held in Milwaukee in September to discuss and develop a plan to conduct these analyses. A group of nearly 50 people representing the HCT community, solid organ transplant experts (who conduct similar analyses annually), experts from other medical communities conducting and reporting hospital outcomes, payors, government agencies, and patients attended the 2 day meeting. A report will be generated and circulated to Transplant Center directors before the 2009 BMT Tandem Meetings, and the plan will be presented at the Medical Directors conference during the 2009 BMT Tandem Meetings.

CIBMTR anticipates that 2009 will be a year of ongoing improvement in the functionality of the systems supporting the SCTOD. We appreciate the patience of HCT centers, banks, and other entities interacting with the CIBMTR as the complex program is being implemented.

2009 BMT Tandem Meetings

The combined annual meetings of the Center for Blood and Marrow Transplant Research (CIBMTR) and the American Society for Blood and Marrow Transplantation (ASBMT) are North America’s largest international gathering of blood and marrow transplant clinicians and investigators, laboratory technicians, transplant nurses, pharmacists and clinical research associates, since 1995.

REGISTER TODAY! for the 2009 BMT Tandem Meetings which will be held February 11-15 at the Tampa Convention Center in Tampa, Florida. Scientific Program Chairs for 2009 are Drs. Mark Litzow representing CIBMTR and James Ferrara for ASBMT.

Detailed information about the 2009 BMT Tandem Meetings will be continuously updated on the CIBMTR (www.cibmtr.org) or ASBMT (www.asbmt.org) web sites, including online conference registration and hotel reservations. Check back periodically for updates to the provisional agenda.

In addition to five days of scientific and clinical meetings, related peripheral meetings will include: BMT CTN Steering Committee, BMT CTN Coordinator and Investigator Sessions, FACT Training Workshops, Clinical Research Professionals’ Data Management Conference, BMT Center Administrators’ Conference, BMT Pharmacists’ Conference, Transplant Nurses Conference and BMT Center Medical Directors’ Conference. Watch the web sites for updates regarding dates and times for peripheral conferences. Sessions targeted primarily to pediatric cancer will be held on Thursday, February 12.

Vol. 14 No. 2 December 2008
The Blood and Marrow Transplant Clinical Trials Network

History

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN), established in October 2001 as a National Institutes of Health (NIH)-funded initiative to conduct large, multi-institutional clinical trials addressing important questions in hematopoietic stem cell transplantation (HCT), was first described in the CIBMTR Newsletter in January 2003. Since then, the fundamental infrastructure had been set in place and the first 2 protocols were under development. Since 2003, the Network has evolved into a dynamic and successful enterprise focused on improving survival for patients undergoing HCT. Over 2400 patients have been enrolled on 15 protocols during the past 5 years.

The primary goal of the BMT CTN is to provide answers to critical questions in current HCT medical practice that can change practice and improve patient outcomes. To achieve this goal, the Network emphasizes trials that require resources beyond the capability of any single institution. The large databases and statistical capabilities of the CIBMTR greatly enhance the Network's ability to design and plan trials and are an invaluable asset for the activities of the BMT CTN.

Organizational Structure

The BMT CTN is a multifaceted organization (see Figure 1) that is comprised of several interactive components including:

- The original 16 Core Clinical Centers (some of which are consortia of two or more centers) each with a cooperative agreement from NHLBI and NCI to participate in the Network
- 80 Affiliate (previously known as non-Core) Centers contributing ~25% of the total number of patients accrued to Network trials
- A Steering Committee which is responsible for the selection, design, execution and analysis of all Network studies
- Administrative and Technical Committees which are responsible for addressing specific areas of Network activity
- Study-specific protocol teams which develop, implement and monitor BMT CTN trials and participate in data review
- Ad-hoc committees which address specific issues such as the development of protocol concepts in particular subject areas
- The Data and Coordinating Center (DCC) which is a consortium of 3 organizations and the base unit supporting all Network activities. The Center for International Blood and Marrow Transplant Research (CIBMTR), National Marrow Donor Program (NMDP) and the EMMES Corporation (see Figure 2). The DCC is responsible for maintaining the continuity of operations and effective communication, data management and statistical support activities.

Each organization and committee brings both shared and unique skills that are vital to the overall success of the Network.

Protocol Activity

Since activation of the first trial in late 2003, three protocols have completed planned accrual. Currently there are 12 open protocols actively accruing patients. Two more protocols will open soon and 3 new protocol concepts were presented to the BMT CTN Steering Committee in July 2008 and approved for further development. For more information on the completed and ongoing protocols, visit the BMT CTN public website at www.bmtctn.net.

Not only is it important to prioritize, select, design and implement protocols wisely, but timely enrollment of patients to open protocols is critical. Research answers are needed while the question is still relevant. Since initiation of the Network, attention has been focused on establishing good working relationships with Affiliate Centers and with the NCI-funded Cooperative Groups that perform clinical trials for diseases for which HCT may be a treatment consideration. In recent years, collaboration with these groups has resulted in enhanced accrual both to BMT CTN-led trials and to several trials led by the Cooperative Groups. Representatives from the Southwest Oncology Group (SWOG), Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG) and Children’s Oncology Group (COG) have all collaborated with the BMT CTN in disease-specific protocol development as well as in the approval of NIH guidelines addressing logistical issues of working together. All agree that there is benefit to working together early in protocol development to avoid duplication of scientific research efforts. In the process:

- The enrollment of the NCI credit system has been preserved
- A collaborative per-patient payment system has been established
- Network trials have been opened through the NCI Clinical Trials Support Unit (CTSU)
- A mechanism has been established for an expedited review by a single scientific review committee, either the NHLBI-appointed Protocol Review Committee (PRC) or Clinical Trials Evaluation Program (CTEP).

Through its early experiences, the BMT CTN has learned much about the potential barriers to accrual to BMT Trials and now considers these in the very earliest concept discussions. A full-time Accrual Specialist focuses on developing protocol-specific plans to proactively address accrual for each trial from design through completion.

Research Agenda

Prior to the initiation of the Network, a State of the Science Symposium was convened in collaboration with the American Society for Blood and Marrow Transplantation (ASBMT) and the NIH. Six key areas were identified as high need for clinical investigations and became the blueprint for trial prioritization. These are:

- Expanding and evaluating alternative donor and graft sources;
- Reducing regimen related toxicity;
- Improving graft versus host disease (GVHD) prevention and therapy;
- Decreasing risks of recurrent malignancy post transplant;
- Decreasing post transplant infections and enhancing immune recovery;
- Prevention and treatment of late effects and improving quality of life after HCT

The BMT CTN Steering Committee added a seventh focus area; evaluating and improving the outcome of HCT for rare diseases. All of the noted areas have been addressed as the primary or secondary specific aims of one or more trials.

In June 2007, a second BMT State of the Science Symposium was held to determine the future research agenda of the Network. Advance work prior to this Symposium resulted in the development of 12 Working Committees which brought together scientific leaders, domestic and international, from the fields of HCT, oncology, hematology, immunology and biostatistics to determine the most critical issues in HCT still requiring investigation. This forum generated eleven protocols rated by the BMT CTN Steering Committee as high priority (6 of which were rated as “very high priority”). A summary of
these proceedings was published and can be found at: Biol Blood Marrow Transplant. 2007 Nov;13(11):1268-85.

Future Activity
Several of the trials already completed or close to completion have set the stage for follow-up studies requiring resources beyond the next several years. As it looks to the future, and building on past accomplishments, the BMT CTN, now in its 8th year, is actively involved in the process of securing approval from the Institutes for renewal in 2011. The Network continues to look forward to successful completion of clinical trials, activating new studies in preparation for follow-up studies requiring resources for follow-up studies.

Recent Activity
Several of the trials already completed or close to completion have set the stage for follow-up studies requiring resources beyond the next several years. As it looks to the future, and building on past accomplishments, the BMT CTN, now in its 8th year, is actively involved in the process of securing approval from the Institutes for renewal in 2011. The Network continues to look forward to successful completion of clinical trials, activating new studies in preparation for follow-up studies requiring resources for follow-up studies.

Recent publications:


**Studies in progress:**

**HC03-01** Prevalence of microbially contaminated hematopoietic stem cell products and its impact on hematopoietic recovery and early survival. (PI Dr. Champlin)

**R02-42** Quantization of the cellular composition of bone marrow and peripheral blood progenitor cells and its effect on outcomes after unrelated donor transplantation. (PI Drs. Collins and Wiesdorf)

**GS05-01** Outcomes after cord blood transplants: examining processing methods. (PI Dr. Chow)

**GS05-02** Comparison of outcomes after transplantation of G-CSF mobilized bone marrow versus non-mobilized bone marrow grafts or peripheral blood grafts from HLA-matched sibling donors for patients with severe aplastic anemia. (PI Dr. Chu)

**GS06-01A** Donor characteristics as risk factors in recipients after transplantation of bone marrow or peripheral blood from HLA-identical donors. (PI Dr. Passweg)

**GS06-01B** Donor characteristics as risk factors in recipients after transplantation of bone marrow or peripheral blood from unrelated donors. (PI Dr. Passweg)

**GS06-02** The role of HLA-C matching on hematopoietic recovery and survival after umbilical cord blood transplantation. (PI Drs. Eapen and Rocha)

**GS07-01** Reduced intensity transplant conditioning regimen: relative efficacy of peripheral blood progenitor cells and bone marrow. (PI Dr. Champlin)

**GS07-03** Unrelated donor transplantation for pediatric acute leukemia: relative efficacy of peripheral blood progenitor cells and bone marrow. (PI Dr. Ringdén)

**GS08-01** Impact donor age on outcomes after unrelated donor bone marrow or peripheral blood progenitor cells. (PI Dr. Kollman)

**GS08-02** Are transplant-outcomes inferior (or superior) if an elderly matched sibling is the donor of choice compared to a matched adult unrelated donor for older patients with hematological malignancies? (PI Drs. Alousi and Champlin)

**GS08-03** To determine the clinical benefit, if any, of in-vivo T-cell depletion of grafts from adult unrelated donors with reduced intensity transplant conditioning regimens. (PI Drs. Ho and Soffier)

**GS08-04** Are two-year leukemia-free survival rates comparable after unrelated donor (bone marrow or peripheral blood progenitor cells) and mismatched cord blood (single unit) transplants in adults with acute leukemia? (PI Dr. Wagner)

**GS08-05** Higher total nucleated cell dose and CD34+ content improves hematopoietic recovery and survival after unrelated donor cord blood: examine the role of single versus double umbilical cord blood transplantations. (PI Dr. Sphal)

The Late Effects Working Committee

Continued from Page 1

to determine whether the current database adequately meets our needs to collect information that address these issues. If not, the subcommittees will recommend specific questionnaires to be incorporated into the CIBMTR forms. Furthermore, the subcommittees may plan publications based on what is learned regarding these late effects with the current database.

Recent publications:


Studies in progress:


**LE99-01** Quality of Life and Relationships after Blood and Marrow Transplantation (Study Chairs: Michelle Bishop, John Wingard)

**LE00-02** Late effects of auto-transplants for Leukemia/Lymphoma. (PI Chairs: J. Douglas Rizzo, Hillard Lazarus, and Navneet Majhail)

**LE06-01** Single nucleotide polymorphism analysis in patients who developed AML or MDS after auto SCT for Lymphoma (Study Chair: Timothy Fenske).

**LE07-01** Second malignancies and late effects in patients treated with hematopoietic cell transplantation using reduced intensity conditioning regimens (Study Chairs: Olle Ringdén, Navneet Majhail, Jonas Mattsson).

**LE07-02** Duration CgVHD and late effects in HCT survivors (Study Chair: Navneet Majhail).

**LE07-03** Long-term survival and late deaths after allogeneic hematopoietic cell transplantation (Study Chairs: John Wingard, Gerard Socie, Brian Bolwell).

**LE08-01** Risk of 2nd solid cancers in BuCy hematopoietic cell transplantation (Study Chairs: Navneet Majhail, Ronald Soboecks, John Wingard, Brian Bolwell, Gerard Socie).

We invite all members of CIBMTR to participate in our committee and provide new proposals or get involved by providing input in design and conduct of ongoing studies. Proposals may be submitted throughout the year and are reviewed during our monthly conference calls and at our annual committee meeting during the BMT Tandem Meetings.
CLINT Review
by Jane Apperley and Fiona McDonald on behalf of the CLINT Project Steering Committee

The CLINT project is aimed at supporting the European Group for Blood and Marrow Transplantation (EBMT) in developing the infrastructure to conduct trans-European clinical trials and facilitate international prospective clinical trials in HCT.

Together with the EBMT, Imperial College London, the Centre for Professional Ethics at the University of Central Lancashire in the UK and the CIBMTR as an Associated Partner, this two year project is funded by the European Union from April 2007 – March 2009.

The key goals of the CLINT project are to:

- Establish the methodology to support prospective clinical trials in Europe,
- Standardize essential data collection and develop a clinical trials database to enable data sharing for meta-analysis with other national and international transplant organizations,
- Overcome ethical and legal challenges for trans-national HCT research,
- Develop a portal for information exchange on clinical trials in HCT and to link to external databases and systems, including AGNIS,
- Improve bio-statistical methodology for the analysis of HCT data.

CIBMTR plays an important role in the CLINT project through sharing the experience of building a clinical trials infrastructure through BMT CTN and by collaborating in the harmonization of data collection forms, database linking, development of bio-statistical methodology and information sharing; all of which will facilitate international prospective clinical trials in HCT in the future.

Background and overview of obstacles to academic led clinical trials in Europe:

There is a good history of prospective clinical trials in Europe run through individual transplant centres, national study groups and the EBMT. But in recent years it has become increasingly difficult to run such studies in the academic setting due to the introduction of new legislative, administrative and ethical requirements to satisfy the European Union Directives on Clinical Trials. National differences in the implementation of the Directives have also added to the complexity and cost of running trans-national prospective clinical trials, making the task of ‘Sponsor’ a particularly onerous one.

Recognized obstacles in trans-national collaboration in HCT

- Difficulties in implementing the EU Clinical Trials Directive for both academic & multinational studies
- Differences in national resources available for the infrastructure for HCT and clinical trial participation
- Difficulties in exchange of patient derived information and material across national boundaries
- National differences in approaches to the ethics of clinical trial participation and of collection and use of tissue for research
- National differences in establishing informed consent
- Lack of systems to exchange information
- Fragmentation of databases and the information stored therein
- Lack of consensus on statistical methodologies across Europe
- Lack of dissemination of information to all interested parties

The CLINT project sets out to develop the EBMT’s clinical trials infrastructure to meet the demands of sponsorship under the EU directive and to overcome other obstacles to pan European studies. It will work toward facilitating international prospective clinical trials in HCT through the development of common data sets, linking of databases, building international consensus on bio-statistical methodology and better information sharing on clinical trials.

Project overview:

Establishing the methodology to support prospective clinical trials

The focus over the last 18 months has been on the development and implementation of an internal review process for EBMT sponsored trials. An overview of the process is included on the Clinical Trials section of the CLINT webportal (www.clint.ebmt.org).

A core set of Standard Operating Procedures (SOPs) has also been produced and these are currently being expanded and updated to ensure that the EBMT is able to meet standards required for Registration-level clinical trials’ management.

Over the course of the project CIBMTR and EBMT have shared knowledge and experience on methodology for the approval and conduct of prospective clinical trials, including documentation and processes. The input of CIBMTR through their association with the BMT CTN has proved to be very beneficial in this regard.

Ten prospective clinical trials are currently being run under the EBMT umbrella. An overview of all major prospective clinical trials in HCT at the national and international level is to be made available on the CLINT webportal in order to improve information sharing amongst investigators and to inform the public on clinical trials activity in the field.

Standardizing essential data collection and development of a clinical trials database

Standardization of data collection is an ongoing and long-term project of the EBMT and CIBMTR and this area of the project is being jointly chaired by Mary Horowitz, CIBMTR Chief Scientific Director and Carmen Ruiz, Head of the EBMT Registry.

Standardization is essential for reducing the data reporting budget and labor burden placed on transplant centres and this is a key objective of both organizations. The initial focus of this work was on reviewing the Minimum Essential Data (MEDA/TED) and reaching agreement on a core data set.

This was accomplished by June 2007 and the new MED A form was implemented in the EBMT database in January 2008. A number of additional items required by CIBMTR have been included in an appendix to the MED A in order to facilitate reporting by centres who wish to submit data to both EBMT and CIBMTR. The appendix has been implemented in the EBMT database to facilitate the transfer of this data to CIBMTR.

Given the successful progress in this area of the project, it was decided to extend the project deliverables to include comparison and agreement of a core data set for cord blood transplantation. At the end of 2007 Vanderson Rocha went to the CIBMTR for 10 months to harmonize the reporting elements and data flow and the goal is to finalise the data set and produce a common cord blood form. It is also expected to improve data sharing at a broader level by providing a link from AGNIS to the EBMT database and CLINT portal.

In March 2007 the EBMT, in collaboration with the CIBMTR, the Asia Pacific Blood and Marrow Transplant Registry (APBMT) and the World Marrow Donor Association (WMDA), convened a meeting in Lyon to discuss the establishment of a global network of outcome registries called the Worldwide Network for Blood and Marrow Transplantation (WBMT). The WBMT will seek to maintain consensus on a common data set for donors and recipients at a global level. At the 3rd WBMT meeting, held in Florence on 2 April 2008, CIBMTR gave an update on the development of AGNIS and plans for implementing a data pipeline for the sharing of cord blood data between EBMT, CIBMTR and Eurocord. Work is currently ongoing to curate the cord blood and fundamental transplant data elements to enable the linking of systems as soon as this is technically feasible. In the future this will facilitate the sharing of clinical trials data for meta analysis between different trials groups.

Overcoming ethical and legal challenges for trans-national HCT research

The Centre for Professional Ethics at the University of Central Lancashire in the UK has been working closely with the EBMT to evaluate how to overcome ethical and legal challenges for trans-national HCT research. This includes a series of questionnaires and workshops organized at EBMT annual meetings to evaluate:
RCI BMT—Another Addition to the Alphabet Soup for Clinical Trials in Transplantation!

Marcie Tomblyn, MD, MS and Rebecca Dreixel

Clinical trials remain the cornerstone for advancing medical care. The spectrum of clinical trials requires the innovation of investigator initiated, single center pilot trials followed by smaller phase II trials before conducting the larger phase II and pivotal phase III clinical trials. In the field of blood and marrow transplantation, many centers perform too few transplants in a single disease to answer even preliminary clinical questions in a timely manner. This leads to delay in conducting the necessary larger trials that move the field forward. Recognizing this, in 2005 the CIBMTR formed the Resource for Clinical Investigation in Blood and Marrow Transplantation (RCI BMT) to provide statistical expertise and data management services for smaller multi-center phase I/II trials.

The goal of the RCI BMT is to bridge the gap between these single-center pilot studies and the larger phase II and phase III studies conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), also coordinated by the CIBMTR in collaboration with the National Marrow Donor Program and the EMMES Corporation. Led by Myriam Labopin and Aurelien Latouche at the EBMT Data & Study Office in Paris, a review of existing bio-statistical literature has been completed and a manuscript on end point definitions has been prepared and is being externally reviewed by John Klein, PhD of the Medical College of Wisconsin. There are plans for further methodological papers aimed at providing information and guidance for clinicians. Publications aimed at bio-statisticians are also envisaged under the project and will be made available on the Statistics section of the CLINT portal.

The importance of building relationships between statisticians in Europe and the US in order to reach international consensus is recognized and collaborative work between Myriam Labopin (EBMT), Aurelien Latouche (EBMT), Jason Fine (North Carolina), Jan Beyersmann (Freiburg) and Ruta Bajorunaite (CIBMTR) has already begun. As part of this process, Drs Fine and Beyersmann were invited to participate in a round table discussion at the EBMT 2008 meeting to consider methodological issues relevant to HCT. Regular meetings and collaboration between statisticians will be fostered over the course of the project and a second roundtable discussion is planned at the EBMT 2009 meeting with the participation of Mei-Jie Zhang, PhD from CIBMTR.

Work is underway to create the Information Technology (IT) structure on the CLINT portal for exchange of data and analyses and to incorporate the software. Aurelien Latouche will work with the statistical department at the University of Freiburg on this aspect of the project. Software has also been developed at the University of Leiden to enable interactive visualization of statistical analyses underlying publications. This enables interaction between statisticians and offers a valuable educational tool. This tool will be made available via the CLINT portal and authors will be encouraged to make their statistical analyses widely available in this way.

The future

The CLINT project lays the foundation for future international collaboration in the field of HCT and will strengthen the potential for essential academic-led clinical trials requiring a trans-national or international focus. This will hasten the evaluation of new treatment strategies and improve the outcome for patients worldwide. For further information on the CLINT project visit: http://portal.ebmt.org/CLINT/Pages/CLINT.aspx or contact: clint@ebmt.org.
Our Supporters

Thanks to the many contributors who have joined our international collaboration for research in blood and marrow transplantation. We gratefully acknowledge the support of the Medical College of Wisconsin; the National Marrow Donor Program; the National Cancer Institute; the National Heart, Lung and Blood Institute; the National Institute of Allergy and Infectious Disease; Office of Naval Research; Health Resources and Services Administration (DHHS) and the generosity of the supporters listed below.

The views expressed in this newsletter do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, or any other agency of the U.S. Government.

AABB
* Aetna
* American Society for Blood and Marrow Transplantation
* Amgen, Inc.
* Anonymous donation to the Medical College of Wisconsin
* Association of Medical Microbiology and Infectious Disease Canada

CIBMTR Advisory Committee Members

Jane Apperley, MD, Imperial College London, London, England
Robert Baity, MPP, HRSA
Nancy Burin, MD, Children’s Hospital of Philadelphia, Philadelphia, PA
†Jeffrey Chell, MD, MMTP, Minneapolis, MN
†Dennis Confer, MD, CIBMTR, MMTP, Minneapolis, MN
Corey Cutler, MD, MPH, Dana Farber Cancer Institute, Boston, MA
†Stella Davies, MD, Cincinnati Children’s Hospital, Cincinnati, OH (Chair)
Nancy Diffonzo, PhD, NHLBI
†Andrea Feldmar, Consumer Advocacy Committee
Randall Gale, MPH, HRSA
†Sergio Giralt, MD, MD Anderson Cancer Center, Houston, TX
tElaine Gluckman, MD, Hôpital St. Louis, Paris, France
Linda Griffith, MD, PhD, NIHAD
Robert Hartzman, MD, Capt. MC, NIAID
†Mary M. Horowitz, MD, MS, CIBMTR, Milwaukee, WI
†John P. Klein, PhD, Medical College of Wisconsin, Milwaukee, WI
Alan Leaigh, Executive-Administration, Inc., Chicago, IL
Katarina LeBlanc, MD, Huddinge University Hospital, Stockholm, Sweden
Jane Liesveld, MD, University of Rochester Medical Center, Rochester, NY
Jeff Lipton, MD, Princess Margaret Hospital, Toronto, Ontario, Canada
†Mark Litowitz, MD, Mayo Clinic, Rochester, MN
Alison Loren, MD, Hospital of the University of Pennsylvania, Philadelphia, PA
Stephen Mackinnon, MD, Royal Free Hospital, London, England
James Nelson, United Health Group, Minnetonka, MN
Ricardo Pasquini, MD, Hospital Nossa Senhora das Graças, Brazil
David Porter, MD, University of Pennsylvania Hospital, Philadelphia, PA
†Thomas H. Price, MD, Medical Director, Puget Sound Blood Center
†J. Douglas Rizzo, MD, MS, CIBMTR, Milwaukee, WI
†Carme Maria Sales-Bonfim, MD, Hospital de Clinicas, Curitiba, Brazil
Raqgel Schears, MD, MPH, Mayo Clinic, Rochester, MN
Peter Shaw, MD, The Children’s Hospital at Westmead, Westmead, Australia
†CIBMTR Executive Committee members

Please address correspondence to:
CIBMTR™ Milwaukee Campus
Medical College of Wisconsin
9200 W. Wisconsin Ave., Ste. C550
Milwaukee, WI 53226 USA
Telephone: (414) 805-0700
Fax: (414) 805-0714
Website: www.cibmtr.org
Email: cibmtr@mcw.edu

Please contact the CIBMTR Statistical Center with address updates or to add a colleague to the CIBMTR Newsletter mailing list. We welcome your suggestions and comments.

This newsletter has been published for and on behalf of the CIBMTR by:

W222 N6251 Sherman Drive
Waukesha, WI 53186
(262) 521-1365
www.cibmtr.org

CIBMTR™ Minneapolis Campus
National Marrow Donor Program
3001 Broadway Street N.E. Ste. 110
Minneapolis, MN 55413-1753 USA
Telephone: (612) 884-8600
Fax: (612) 884-8661
Website: www.cibmtr.org
E-mail: cibmtr-contact@nmdp.org

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

AABB
* Bayer HealthCare Pharmaceuticals.
* BloodCenter of Wisconsin
* Blue Cross and Blue Shield Association
* Bone Marrow Foundation
* Canadian Blood and Marrow Transplant Group
* Celgene Corporation
* CellGenix, GmbH
* Centers for Disease Control and Prevention
* Cellular Immune Labs
* CTR Clinical Trial and Consulting Services
* Cubist Pharmaceuticals
* Cyteogen
* DOR BioPharma, Inc.
* Dynal Biotech, an Invitrogen Company
* Enzon Pharmaceuticals, Inc.
* European Group for Blood and Marrow Transplantation
* Gambro BCT, Inc.
* Gamida Cell, Ltd.
* Genzyme Corporation
* Histogenetics, Inc.
* HKS Medical Information Systems
* Hospira, Inc.
* Infectious Diseases Society of America
* Kiadis Pharma
* Kirin Brewery Co., Ltd.
* Merck & Company
* The Medical College of Wisconsin

Astellas Pharma US, Inc.
Baxter International, Inc.
† Bayer Healthcare Pharmaceuticals.
† BloodCenter of Wisconsin
† Blue Cross and Blue Shield Association
† Bone Marrow Foundation
† Canadian Blood and Marrow Transplant Group
† Celgene Corporation
† CellGenix, GmbH
† Centers for Disease Control and Prevention
† Cellular Immune Labs
† CTR Clinical Trial and Consulting Services
† Cubist Pharmaceuticals
† Cyteogen
† DOR BioPharma, Inc.
† Dynal Biotech, an Invitrogen Company
† Enzon Pharmaceuticals, Inc.
† European Group for Blood and Marrow Transplantation
† Gambro BCT, Inc.
† Gamida Cell, Ltd.
† Genzyme Corporation
† Histogenetics, Inc.
† HKS Medical Information Systems
† Hospira, Inc.
† Infectious Diseases Society of America
† Kiadis Pharma
† Kirin Brewery Co., Ltd.
† Merck & Company
† The Medical College of Wisconsin

MGI Pharma, Inc.
Michigan Community Blood Centers
* Millennium Pharmaceuticals.
Miller Pharmacal Group
† Milliman USA, Inc.
† Miltenyi Biotec, Inc.
National Marrow Donor Program
Nature Publishing Group
New York Blood Center
Novartis Oncology
Oncology Nursing Society
† Osiris Therapeutics, Inc.
† Otsuka Pharmaceutical Development & Commercialization, Inc.
Pal Life Sciences
Pfizer Inc.
Saladax Biomedical, Inc.
† Schering Plough Corporation
Society for Healthcare Epidemiology of America
* StemCyte, Inc.
* StemSoft Software, Inc.
Symyx
* Teva Pharmaceutical Industries
The Marrow Foundation
† THERAKOS, Inc.
† Vidas Care Corporation
† Vion Pharmaceuticals, Inc.
† ViroPharma, Inc.
† Wellpoint, Inc.
* Corporate Member

† CIBMTR Executive Committee members

This newsletter has been published for and on behalf of the CIBMTR by:

Feldmar, NHLBI
DiFronzo, NHLBI
Nancy Bunin, MD, HRSA
Robert Baitty, MPP, Imperial College London, London, England
Jane Liesveld, MD, Medical Director, Puget Sound Blood Center
†Daniel Weisdorf, MD, Mayo Clinic, Rochester, MN
†Carmen Maria Sales-Bonfim, MD, Hospital Nossa Senhora das Graças, Brazil
†Jeffrey Szer, MD, Royal Melbourne Hosp., Parkville, Victoria, Australia
†Shelley Tims, MPh
†Marcelle Tomblyn, MD, MS, University of Minnesota, Minneapolis, MN
†Donna Wall
†Daniel Weisdorf, MD, University of Minnesota, Minneapolis, MN
†Roy Wu, PhD, NO