CRITIQUE 3:

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 1
Environment: 1

Overall Impact:
Strengths:

- Growth of the program since the last application with a significant increase in number of studies and publications
- Improvements in process of data collection from the site, improvements in accuracy of reports, and improvements in software , training
- Addressing new areas, such as health outcomes research and patient reported outcomes
- Direct contact method for assessment of long term survivors
- Addition of other cellular based therapies
- Significance of published research from CIBMTR studies which has facilitated change in practice patterns and improved patient outcomes
- Improving interface with other databases
- Formation of executive committee to outline goals and objectives, new system to prioritize studies

Weaknesses:

- None apparent. Resources may be stretched with additional projects.

1. Significance:
Strengths:

- The CIBMTR provides a unique resource to the medical community for the collection of data from transplant centers around the world for a wide range of diseases including malignant and non-malignant conditions. This organization has provided statistical analysis of data for quality improvement, biomedical research, and now for health outcomes research. The size of the database has facilitated retrospective studies which have enlightened the academic community with regard to transplant donor matching, conditioning regimens, and specific outcomes for rare subsets of patients which would not be studied in single or even multi-institutional settings. Utilization of the database and resources of the Center has been extensive, as is evidenced by their recent statistics: 89 study proposals, 245 studies, 207 peer-reviewed publications, 337 institutions represented as authors on papers. The number of papers and studies has doubled since the last application.
- The size of the database
- Linkage of registry data with a biorepository of samples from transplant donors and recipients, which has facilitated biomedical research to improve outcomes for transplant recipients.
- Initiatives to assist with long term follow up of transplant recipients, an effort which would not be funded by other organizations
- Assistance with clinical trials by close collaboration with the Bone Marrow Transplant CTN
- Recent initiation of health outcomes research program
- Improvement in data management systems to provide a more user-friendly linkage with data from other registries, such as EBMT and to improve data collection thru FormsNet and interface programs.

Weaknesses:

- None

2. Investigator(s):
Strengths:

- Dr. Horowitz has provided outstanding leadership in her role as the director of the registry. Dr Klein has been highly productive as the chief biostatistician.
- The team that Drs Horowitz and Klein have assembled is highly qualified to carry out the mission of the Registry.

Weaknesses:

- With the additional responsibilities, more staffing may be required.

3. Innovation:
Strengths:

- The applicants propose to use existing data and additional planned analyses to develop an algorithm for donor selection. This effort, if successful, will greatly facilitate the process of donor selection for individual centers and will standardize an approach to this process.
- The applicants propose to include additional cellular therapies under the umbrella of the CIMBTR, including cellular regeneration procedures and cellular therapies which are being developed for the treatment of lymphomas, such as the use of modified T-cells. This effort augments the recent initiative to focus research efforts on the use of transplant for nonmalignant disorders and will enhance the available as well as providing a "registry" for these novel therapies.
- The applicants propose to improve their existing methodologies for acquiring data, including providing support for the AGNIS format. This effort has been ongoing since the last renewal of the center grant, and vendors are developing software to support this platform. The AGNIS platform will also address the issue of data flow from other institutional databases into FormsNET, which remains a significant problem for some institutions.
- The application proposes to improve the facility of data flow from the European registry (EBMT) into the CIBMTR registry. Improving these methodologies would be highly significant for the mission of the Registry.
- FormsNET will be further improved so that sites will be able to enter data more easily. A new version will be released this year.
- The Registry is evaluating procedures to capture patient reported outcomes.

Weaknesses:

- The applicant recognizes that interface with existing institutional systems and electronic medical record systems remains on ongoing challenge.

4. Approach:
Strengths:

- Organizational: the Registry has formed an External Advisory Board to outlines goals and objectives. The applicants have reviewed the goals and progress toward addressing each.
- Research: the Registry has continued to provide mentorship to junior investigators by providing close collaboration with biostatisticians and other members of the Center. In response to criticism that there were many studies which took too long to complete, a committee structure has been outlined to triage trials for the most clinically significant questions and to track the completion of the research as well as the publication.
- The Registry has initiated a study for MDS patients to assist with Medicare reimbursement for this population.
- Long term survivors are being followed by direct contact and internet tools.
- The CIBMTR has provided data management and reports for Cord Blood banks, thus facilitating their licensing procedures.

- Patient interface: the Registry has expanded its patient interface by improving its website and by expanding available information for patients.
- Interactions with Centers: the Registry has enhanced its Center Back function for centers to review their data online. The ongoing training program has been enhanced and training manuals have been updated. The Registry has addressed the issue of missing data by auditing centers and establishing a 3% rule; in the most recent audit, the average was 2%.
- The website has been improved to include a portal for collaboration between investigators who wish to share data. This has been used by the Immunobiology Committee and the Leukemia Committee.
- Collaboration with other organizations: the Registry has an ongoing collaboration with SCTOD.

Weaknesses:

- How will the Health Outcomes research group interface with other groups and collaborative efforts?
- Follow up on long term survivor contact initiative should include a backup plan if there is not significant patient compliance.

5. Environment:
Strengths:

- The environment is excellent and is able to support the proposed studies.

Weaknesses:

- May need additional resources with addition of other Regenerative cellular therapies

Protections for Human Subjects: Acceptable

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only): Acceptable

Inclusion of Women, Minorities and Children: Well outlined in the proposal, acceptable

Vertebrate Animals: N/A

Biohazards: N/A

Renewal: The applicant has responded appropriately to the previous review and has made significant progress as outlined above.

Budget and Period of Support:

Recommended budget modifications or possible overlap identified: Acceptable

CRITIQUE 4:

Significance:	1
Investigator(s):	1
Innovation:	1
Approach:	1
Environment:	1

Overall Impact: This application is a renewal for a program to support the operation of the Center for International Blood and Marrow Transplant Research (CIBMTR), an on-going registry of patients. CIBMTR is focused on developing and utilization of resources.

Strengths:

- The CIBMTR plays a very important role to provide data and statistical support hematopoietic cell transplantation (HCT) investigators.
- There are complex and comprehensive approaches applied to the registry. This resource has a significant impact on HCT research.
- The Biostat Team has done exceptionally well in developing new methodologies. The Team is commended for their efforts.

Weaknesses:

- None.

1. Significance:

Strengths:

- There have been a significant number of studies/papers (published or in press) in the previous funding cycle (Table 2).
- Data from the CIBMTR are critical to advance outcomes in the hematopoietic transplant field. This resource has a significant impact on HCT research.

Weaknesses:

- None.

2. Investigator(s):

Strengths:

- The Principal Investigator, Dr. Mary Horowitz, has been a pioneer in blood and marrow transplant research and has been conducting this type of research for over 20 years.
- The Principal Investigator has also collaborated with Dr. Klein and colleagues to advance novel statistical techniques for registry designs.
- Dr. Mary Horowitz has been providing effective leadership for this project since 1991.
- The project teams in both Milwaukee and Minneapolis are well trained and bring complementary skills to the project.
- Dr. John Klein is a well-respected biostatistician with strong methodology in statistics for analyzing HCT data.
- The other senior staff members have been with the Center and its predecessor for years and also have strong publication records.
- The Principal Investigator and her team of investigators are well qualified.

Weaknesses:

- None.

3. Innovation:

Strengths:

- The investigators have done a good job innovatively overcoming many logistical challenges to run this international registry.
- Dr. John Klein is well recognized for his work in statistical methods for analyzing longitudinal data.
- The implementation of CDE-compliant data forms and the AGNIS security and transmission overlay on the ca-GRID concept have been innovative for NCI-wide initiatives to conduct multi-institutional clinical trials.

Weaknesses:

- There are no concerns.

4. Approach:
Strengths:

- The methodology and approach used are well thought out and appropriate for analyzing the proposed specific aims.
- The statistical and study design issues are well thought out, such as randomized sampling for the comprehensive cases, validated data entry, edit checks and novel statistical analysis techniques and are appropriate.
- There are complex and comprehensive approaches applied to the registry.
- The Biostat Team has done exceptionally well in developing new methodologies.

Weaknesses:

- There are no concerns.

5. Environment:
Strengths:

- The CIBMTR is located at both the Medical College of Wisconsin (MCW) and the University of Minnesota (NMDP site).
- The physical and IT facilities are excellent to support the project.
- There are epidemiologists in the medical school or school of public health that are engaged in the analysis of large observational data sets.
- Collaborations with experts working in the area of clinical effectiveness are beneficial.
- Computing facilities and administrative support all appear to be adequate.

Weaknesses:

- None

Protections for Human Subjects: Federal requirements and IRB policies of all institutions involved appear to be met. The CIBMTR appears to have gotten the necessary legal clearance to protect the privacy of study enrollees. There are no concerns regarding inclusion of women, minorities, or children in this database; all consecutive HCT recipients are enrolled.

Renewal: Dr. Mary M Horowitz and her team of investigators have addressed most of issues raised by the reviewers in previous funding cycle.

Resource Sharing Plans: This appears to be adequately addressed by the investigators. The resources available for sharing data are specifically tailored for this purpose.

Budget and Period of Support:

Recommended budget modifications or possible overlap identified: The budget for this resource seems appropriate for the scope of work being proposed. The budget is recommended as requested.

CRITIQUE 5:

Significance:	1
Investigator(s):	1
Innovation:	1
Approach:	1
Environment:	1

Overall Impact: In this application, the investigators propose that the current Center for International Blood and Marrow Transplant Research (CIBMTR) continue to provide a unique resource to the research community with its collection and analysis of data on patients who have undergone hematopoietic cell transplantation (HCT). The Resource Development Program is addressing the future needs of researchers, physicians and patients through several initiatives to ensure resources are used for the most important issues. This registry is a unique resource and its' scientific importance are demonstrated by the extensive number of publications that have resulted as well as the number of investigators and institutions involved. The investigators should be commended for their strong commitment not only to the development and maintenance of this database, but the creative initiatives developed to give back information to the patients, physicians and investigators. The likelihood for the Resource to continue to exert a sustained, powerful influence on the HCT research is extremely high.

1. Significance:
Strengths:

- The investigators propose that the current Center for International Blood and Marrow Transplant Research (CIBMTR) continue to provide a unique resource to the research community with its collection and analysis of data on more than 300,000 patients who have undergone hematopoietic cell transplantation (HCT). Data are included from more than 300 HCT centers worldwide including almost all of the US HCT centers. HCT is used to treat a wide range of diseases.
- The large observational CIBMTR database is ideal (and has been used very extensively) for retrospective studies, with appropriate limitations noted, and for the design of future clinical trials.
- It is especially useful to address scientific questions in a reasonable time period which would otherwise be difficult and sometimes impossible (rare diseases as one example) to address within single centers or even multiple centers.
- Generally, the specific aims are to a) further enhance the Resource from a technological perspective and to expand this Resource by collecting other sources of data including patient-reported outcomes and health services research data and b) increase the utility of the Resource through improved processes for access to support as well as prioritization of studies.
- The Resource Development Program is addressing the future needs of researchers, physicians and patients through several initiatives including, but not limited to, expanding data collection for quality of life, late effects of HCT and health services research as well as web-based initiatives to enhance community outreach and communication.
- To increase the value of the Resource the investigators continue to expand data types collected, develop methods to obtain long term follow-up data, develop programs aimed at increasing investigators involvement, especially junior investigators, and improve processes for evaluating the overall research agenda to ensure resources are used for the most important issues.
- The continued improvement in the infrastructure and IT are extremely important as these will improve the efficiency of data collection and quality control procedures, as well as

communication; these improvements are essential as the number of patients in data base, in particular in long term follow-up, continues to grow.
- This registry is a unique resource and its' scientific importance are demonstrated by the extensive number of publications that have resulted as well as the number of investigators and institutions involved. The impact of the CIBMTR studies on HCT science and practice is further demonstrated with the H-index of 83 for all CIBMTR studies (the H-index is a measure of impact of body of work based on median number of citations) and the number and type of studies which would have otherwise been difficult or impossible to do without this Resource.

Weaknesses:
- None perceived

2. Investigator(s):
Strengths:
- Principal investigator, Mary Horowitz, MD,MS, has been the Scientific Director of the CIBMTR since 1991 and has worked with the Statistical center since 1986. She has provided exceptional overall leadership to the CIBMTR for optimal functioning of the CIBMTR. She is ideally suited for this project as a MD with a Master's in biostatistics.
- John Klein, PhD has been the CIBMTR Statistical Director since 1993. He has developed and evaluated innovative statistical methods for HCT studies and therefore, provides excellent biostatistical expertise for this project. He is well qualified for this project.
- J Douglas Rizzo, MD,MS serves as the Associated Scientific Director for the Data Operations of the CIBMTR and has worked with the CIBMTR since 1998. He has the primary responsibility of supervising data collection and quality control activities and staff at both MCW and the National Marrow Donor Program (NMDP). He has experience in the medical informatics and development of electronic systems and is well qualified for this project.
- These three leaders (Drs. Horowitz, Klein and Rizzo) along with the Associate and Assistant Scientific Directors and the working committees bring complementary and integrated expertise to the Resource and provide outstanding leadership to enable optimal scientific progress in the CIBMTR.
- The remaining investigators are well qualified and excellent for their respective roles.
- The modifications to the Working Committee and Advisory Committee processes based on the 2009 External Review (specifically to rank the projects with additional Advisory Committee review) should help to ensure that the resources are used to address the most important scientific questions.

Weaknesses:
- None

3. Innovation:
Strengths:
- The approaches, methodologies and direction proposed for the collection, use and publication of the transplant data are innovative.
- The investigators recognize the challenges and limitations from a practical and technical perspective, and have addressed these methodically with reasonable, practical and well thought out, innovative solutions.
- The electronic data capture system was successfully deployed with a new version with enhancement features planned in 2012.
- The multiple approaches to allow for data to flow into the CIBMTR are important as it reduces the burden on the centers.
- The web-based tools will enhance communication with the community (Public Website) as well as between CIBMTR staff and members (Portal and Collaborative Web spaces).

- Planned interventions to enhance data quality are appropriate and well explained and include continued comprehensive update of forms and expansion of online manuals; process changes to improve data flow and accuracy and efficient long term follow-up collection and expansion of current static specimen inventory reports to real-time interactive reports.
- Several other important, innovative initiatives include, but not limited to, collection of patient-reported outcomes; expansion of data available in data back to center application; standardize reports for centers; enhanced data collection and analysis of rare HCT indications (including hemoglobinopathies, autoimmune diseases) and non-HCT MDS patients; health policy and services initiative; linkage of the CIBMTR and the NMDP's biorepository; immunologic determinants of the HCT outcome; quality of life and late effects study and HCT for MDS study to allow coverage by Medicare.

Weaknesses:

- None

4. Approach:

Strengths:

- The HCT data in this registry have been collected using two different approaches (hard copy and electronic) and two levels of detail (transplant essential data and comprehensive report form). The transplant essential data (TED) contains a limited number of fields focusing on critical HCT variables. Participating centers must submit data TED data for all consecutive patients.
- Due to the amount and cost of collection of the information the comprehensive report form (CRF), the statistical center developed a weighted-randomization algorithm to select cases for CRF submission. It aims to provide adequately sized representative subsets of patients for studies requiring detailed level data. For example, for rare diseases all patients would be selected whereas for unrelated donor HCTs about 50% of patients are selected and for most common autologous HCT in myeloma about 20% are selected. The factors to be considered and the weights applied in the selection algorithm are reviewed annually by the CIBMTR leadership. This approach seems reasonable and well thought out.
- Currently, about 40% of cases are selected for comprehensive data acquisition on report forms.
- The two data collection approaches, historically, are hard-copy and electronic.
- The new web based electronic data submission system (FormsNetv2) was launched since the last review. A new version is planned for activation in 2012.
- Currently more than 95% of the data collected in the registry is submitted electronically, representing a successful deployment of the system. Submission of data via hard copy is still allowed if needed because of local technology limitations or regulatory issues (approximately 20 centers still use hard copy). Some information (such as pathology reports) still must be submitted on paper and stored as images, however, an upgrade to import these directly into FormsNet is planned.
- The FormsNet system contains real time validations, control of data flow, error handling and messaging, and smart navigations to move between fields.
- Processes are in place to ensure data quality, specifically processes to ensure consecutive reporting of patients, uniform reporting, timely reporting as well as online validation and online audit processes.
- Other applications were developed to facilitate HCT and statistical center operations.
- Data can flow from other databases into the CIBMTR database through an application called AGNIS. This is a very useful application which results in reduced work for the HCT sites.
- The future plans for expansion of data resources, and the IT to support are well explained and reasonable.
- The CIBMTR provides biostatistical expertise on the projects and this group has been very productive with direct impact on the HCT literature. During the current funding period, the PhD

statisticians have developed and expanded several novel techniques for the analysis of HCT data with the corresponding SAS and R functions. Based on their track record, it is anticipated that this will continue.

- The Statistical Center's methods work had an impact on research outside of the HCT community as the work has been cited in over 200 non-CIBMTR statistical methods papers and more than 80 non HCT research papers.
- To enhance the value of the Resource, the CIBMTR investigators have launched several initiatives.
- An application was released in 2009 called Data Back to Centers which enabled sites to download TED-level data since December 2007. This application has been utilized with 284 downloads by 81 centers since May 2011. Centers can also request custom datasets specific to a project.
- The CIBMTR web site was enhanced and provides better access to HCT information for both scientific researchers and the public, training and support for HCT centers, and a shared communication site for the statistical center staff, Working Committee and study teams. The recently hired training specialist will enhance the web-based training modules.
- The CIBMTR collaborates with other organizations including other data collection initiatives (SCTOD, Immune Deficiency Network, Cellular Deficiency Networks, Cellular Therapy for Regenerative Medicine, International Networks) and other research organizations (International Histocompatability Working Group, EBMT).
- There is evidence for meaningful collaborative initiatives to enhance linkage to relevant clinical entities.
- The CIBMTR operation and oversight committees appear appropriate in terms of responsibilities and are designed to obtain broad input into the scientific agenda and ensure that the resources meet the needs and priorities of the scientific communities.
- These committees include Advisory, Executive, Nominating and Assembly Committees, the 19 Working Committees, Consumer Advocacy Committee as well as others.
- The Working Committees have biostatistcal representation.
- Based on 2009 External Review Panel recommendations, the CIBMTR developed a system for examining the overall research agenda whereby the Working Committee Chairs score proposals to assist in prioritization (40 studies were dropped in 2011) and the Advisory Committee reviews the master list of proposals 3 times per year to assess the overall scientific agenda (30 studies identified as low potential impact in 2011).
- In addition a Task Force led by Dr. Martin was established to assess the function of the Working Committees.
- Therefore, the CIBMTR is well structured for prioritization of research problems that can be addressed by observational studies. The processes are well defined and appropriate for the approval, completion and timely publication of results.

Weaknesses:

- None noted

5. Environment:

Strengths:

- The infrastructure (physical and IT) are sufficient for this project.
- From IT perspective, a back-up system is in place as well as disaster recovery and outage plan. Security is well described and sufficient (eg. biometric, electronic key, video surveillance).
- Both the NDMP and the MCW campuses provide strong institutional support to the projects. The environments of both campuses are optimal for the goals of Resource Utilization Program with respect to integration with other relevant programs and activities in the general field of hematopoietic stem cell transplant.

- This group has demonstrated ability to adapt the IT infrastructure required and therefore, it is expected that would continue as need arises in the collection and sharing of the data.

Weaknesses:

- None noted

Protections for Human Subjects:

- Federal requirements and IRB policies of all institutions involved appear to be met.
- As of February 2011, the NMDP Institutional Review Board has primary oversight for the CIBMTR observational database protocol. All domestic transplant centers are required to have Federal Wide Assurance with Office for Human Research Protection and obtain local IRB approval for the CIBMTR observational database protocol as part of the Data Transmission Agreement with the CIBMTR. International centers follow the human subject protection regulations of their country; compliance with these rules is a stipulation of the Data Transmission Agreement.
- To fulfill the CIBMTR's SCTOD statutory obligations, the Office for Civil Rights and the Office of the General Counsel, U.S. Department of Health and Human Services designated the CIBMTR as a Public Health Authority under the HIPAA Privacy Rule. Therefore, transplant centers, regardless of their HIPAA covered entity status, are allowed to disclose PHI to the CIBMTR without an individual's written consent or authorization. Only transplant essential data (TED) are collected on those recipients who do not provide written consent to participate in the CIBMTR observational database. These non-consenting recipients are excluded from CIBMTR research activities and their data are only included in program reports required by the SCTOD contract, such as the transplant center-specific analyses.
- Security mechanisms for the database appear to be sufficient. The FormsNet application is compliant with U.S. database security requirements as established by the HRSA Office of Information Technology. HRSA security audits are performed annually; the most recent audit was August 2011. In March 2012 CIBMTR requested an independent assessment of the FormsNet application to confirm the application's compliance with FDA 21 CFR 11 regulations for electronic systems. The assessment identified modest enhancements that were anticipated by CIBMTR IT staff and are already prioritized and approved for implementation within the next FormsNet upgrade (to be released by the end of 2012).

Inclusion of Women, Minorities and Children: This is considered adequate.

Renewal: The investigators continue to make substantial progress for Resource Development and Utilization of the registry as reflected by the large number of publications, investigators and institutions involved (H-index measured was high as well). They have utilized their External Review Panel, last convened in 2009, to critically review the progress of the program (which was quite favorable) and have implemented the 9 recommendations of this panel. In the last funding period, the electronic capture system (FormsNet) was successfully deployed; interventions were implemented to enhance data quality; collection of patient directed outcomes and health policy and rare indications data were expanded or implemented; web-based access to information, including lay summaries of reports, were further improved; and procedures were modified to tackle the difficult task of long term follow-up. Statistical methods were developed and published which are specific to observational and registry data. In addition, enhanced processes were developed to ensure that the resources are being used to address the most important issues.

Resource Sharing Plans: A process is in place for applications to be submitted, reviewed, prioritized and resources allocated as appropriate. Shared resources include statistical support as well as data.

Budget and Period of Support:

Recommended budget modifications or possible overlap identified: None

CRITIQUE 6:

Significance:	1
Investigator(s):	1
Innovation:	1
Approach:	1
Environment:	1

2. Investigator(s):
Strengths:

- Dr. Mary Horowitz is an outstanding Principal Investigator with an extraordinary track record of bringing the CIBMTR to its current level of performance. There is no question of her ability to direct and manage the organization.

Weaknesses:

- At the same time, this strength is also a potential weakness. There should be an investigator who should be groomed to step into Dr. Horowitz place if for some reason Dr. Horowitz is not able to perform her duties.

Renewal: The applicants have clearly addressed each and every one of the points raised in the previous critique to the review panel's satisfaction.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE, G1A

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE, M1A

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE, M1A

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html.
The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review

meeting or calculated into the overall impact score. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

National Cancer Institute Special Emphasis Panel
NATIONAL CANCER INSTITUTE
A Data Resource for Analyzing Blood and Marrow Transplants
ZCA1 SRLB-V (J1) R
October 10, 2012

CHAIRPERSON

LUM, LAWRENCE G, DSC, MD
DIRECTOR OF IMMUNOTHERAPY, STEM CELL
LABORATORY & TRANSLATIONAL RESEARCH
PROFESSOR OF IMMUNOLOGY AND MICROBIOLOGY
SCIENTIFIC DIRECTOR OF IMMUNOTHERAPY AND BMT
BARBARA ANN KARMANOS CANCER INSTITUTE
DETROIT, MI 48201

MEMBERS

FOSS, FRANCINE M, MD
PROFESSOR
DEPARTMENT OF ONCOLOGY/DERMATOLOGY
YALE UNIVERSITY
NEW HAVEN, CT 06520

GORDON, LEO I., MD
DIRECTOR AND PROFESSOR
DEPARTMENT OF MED, HEMATOLOGY ONCOLOGY DIVISION
NORTHWESTERN UNIVERSITY FEINBERG SCHOO OF MED
CHICAGO, IL 60611

LEISENRING, WENDY M, SCD
FULL MEMBER
DEPARTMENT OF CLINICAL STATISTICS
FRED HUTCHINSON CANCER RESEARCH CENTER
SEATTLE, WA 98109

SINGH, KARAN P., PHD
PROFESSOR AND DIRECTOR - BBSF
DEPARTMENT OF MEDICINE
DIVISION OF PREVENTIVE MEDICINE
UNIVERSITY OF ALABAMA AT BIRMINGHAM
BIRMINGHAM, AL 352944410

WELLER, EDIE A, PHD
SENIOR RESEARCH SCIENTIST
DEPARTMENT OF BIOSTATISTICS& COMPUTATIONAL BIOLOGY
DANA-FARBER CANCER INSTITUTE
HARVARD SCHOOL OF PUBLIC HEALTH
BOSTON, MA 02215

SCIENTIFIC REVIEW ADMINISTRATOR

SOLDATENKOV, VIATCHESLAV A, MD, PHD
SCIENTIFIC REVIEW OFFICER
SPECIAL REVIEW AND LOGISTICS BRANCH
DIVISION OF EXTRAMURAL ACTIVITIES
NATIONAL CANCER INSTITUTE
BETHESDA, MD 208928329

GRANTS TECHNICAL ASSISTANT

ABEBE, ETSEGENET
EXTRAMURAL SUPPORT ASSISTANT
SPECIAL REVIEW & LOGISTICS BRANCH
DIVISION OF EXTRAMURAL ACTIVITIES
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 208928329

PROGRAM REPRESENTATIVE

MERRITT, WILLIAM D., PHD
PROGRAM DIRECTOR
CLINICAL GRANTS AND CONTRACTS BRANCH, CTEP
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

資料説明－4：NIH への中間報告書

5 年間のプロジェクトとはいえ中間報告書（Progress Report）は毎年提出する。
全 105 頁中頭書の 68 頁を掲載した。一年間の業績の喧伝の仕方は徹底している。

A. OVERALL COVER PAGE

Project Title: A Data Resource for Analyzing Blood and Marrow Transplants	
Grant Number: 5U24CA076518-18	**Project/Grant Period:** 03/01/1998 - 02/28/2018
Reporting Period: 03/01/2014 - 02/28/2015	**Requested Budget Period:** 03/01/2015 - 02/29/2016
Report Term Frequency: Annual	**Date Submitted:**
Program Director/Principal Investigator Information: MARY MARESCA HOROWITZ , MD MS **Phone number:** (414) 456-8325 **Email:** marymh@mcw.edu	**Recipient Organization:** MEDICAL COLLEGE OF WISCONSIN MEDICAL COLLEGE OF WISCONSIN 8701 WATERTOWN PLANK RD MILWAUKEE, WI 532263548 **DUNS:** 937639060 **EIN:** 1390806261A3 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: APRIL A HAVERTY Medical College of Wisconsin Office of Grants & Contracts 8701 Watertown Plank Road Milwaukee, WI 53226 **Phone number:** 414-955-4844 **Email:** grants@mcw.edu	**Signing Official:** DAVID MATTSON 8701 Watertown Plank Road Milwaukee, WI 532263548 **Phone number:** 414-955-4844 **Email:** aor@mcw.edu
Human Subjects: Yes HS Exempt: Yes Exemption Number: E4 Phase III Clinical Trial:	**Vertebrate Animals:** No
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

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

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

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

The specific aims of this project are:

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

Resource Utilization: Increase use of data and statistical resources maintained by the CIBMTR to support studies with important clinical and policy implications, and enhance Working and Advisory Committee and Coordinating Center processes to prioritize and complete these studies.

The CIBMTR has defined the following Research Strategy to attain these goals:

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

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

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: U24.CIBMTR.B2.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

File uploaded: U24.CIBMTR.B4.pdf

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

The CIBMTR disseminates research results utilizing numerous methods, including at the BMT Tandem Meetings, which we co-sponsor each year; through scientific presentations at national and international conferences; and via documents, such as reports and newsletters, which are distributed in printed and electronic media.

B.5.1 BMT TANDEM MEETINGS

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

B.5.2 PRESENTATIONS

In 2014, 43 CIBMTR study investigators presented results at national and international conferences. At the BMT Tandem Meetings, 16 investigators presented 13 oral presentations and 3 posters. At the EBMT annual meeting, one investigator presented a poster. At the American Society of Clinical Oncology annual meeting, three investigators presented posters. At the American Society of Hematology annual meeting, 23 investigators presented 15 oral presentations and 8 posters.

B.5.3 DOCUMENT DISTRIBUTION AND WEBSITES

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

B.5.3.a Report of Survival Statistics for BMT
The CIBMTR publishes a detailed report on survival statistics describing the use and outcome of autoHCT and alloHCT in the 350 transplant centers that participate and provide data to the CIBMTR.

B.5.3.b Transplant Data by US Center Report
Annually, as part of the HRSA contract, the CIBMTR reports HCT volumes and demographic data to transplant centers. The information is made available to patients and the public via the C.W. Bill Young Cell Transplantation Program website (bloodcell.tranpslant.hrsa.gov).

B.5.3.c Annual Report on Transplant Center Survival Rates
A center-specific survival analysis comparing the one-year survival rates among US centers, this report contains outcomes for transplants using both related and unrelated donors. The purpose of the report is to provide potential HCT recipients, their families and the general public a comparison of survival rates among the centers in the C.W. Bill Young Cell Transplantation Program network. Transplant centers may use these reports for quality improvement initiatives. Results are published on the Program website (bloodcell.transplant.hrsa.gov).

B.5.3.d Summary Slides
Using information from the Research Database, the CIBMTR annually prepares and distributes charts and figures summarizing current uses and outcomes of alloHCT and autoHCT. These slides are developed in conjunction with the BMT Tandem Meetings, and they are available on the CIBMTR website as well as through the Information Request Service.

B.5.3.e Summary of Accomplishments
Produced annually, this trifold document provides a high level summary of CIBMTR fiscal year accomplishments and high impact publications. In addition to being posted on the CIBMTR website, this document is distributed via social media, mailings to supporters, at national and international conferences, and in a variety of meetings.

B.5.3.f Study Summaries for Patients
The CIBMTR publishes summaries of research articles for patients and their caregivers on the CIBMTR website. Research articles are selected by the members of the Consumer Advocacy Committee and are developed as a collaborative effort among the CIBMTR Medical Writer, first author of the publication, Consumer Advocacy Committee members, and NMDP Patient and Health Professional Services. The summaries are written in plain language at a high school reading level. They incorporate an outcomes-focused title and important points in addition to the full summary. This allows readers to learn from the study even if they do not read the entire summary. Three summaries were published this year:
• Allo Transplant Helps Some Children with Neuroblastoma
• Allo Transplant Helps Some Older Patients with AML
• Very Few Donors have Severe Side Effects from Donation: Blood Stem Cell Donors have Fewer than Bone Marrow Donors
During their September 2014 meeting, the Consumer Advocacy Committee discussed opportunities for further dissemination of the patient summaries. The CIBMTR will continue to explore opportunities for dissemination of these summaries during the next reporting period.

B.5.3.g Newsletters
The CIBMTR publishes two newsletters:
• CIBMTR Newsletter. This newsletter is published at least twice per year. In addition to being posted on the CIBMTR website, it is distributed to the CIBMTR network of approximately 5,000 physicians, data managers, pharmacists, IT professionals, and other personnel. Previously, printed editions of the newsletter were distributed by mail and at various meetings and conferences. This year the CIBMTR implemented an electronic distribution system through Campaign Monitor. Newsletter articles feature updates on Working Committees, the SCTOD, data management and collection, and noteworthy events in the HCT community.
• Data Matters Training Newsletter. The Data Matters Training Newsletter is published monthly via email and contains updates on projects, announces training opportunities and manual updates, and provides answers to frequently asked questions. Newsletter content is developed as a collaborative effort among several internal departments.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

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

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

• Implement key data validations in FormsNet, close to the point of data capture. As part of quality data, key data fields, minimally required for research, that today are validated up to a month after they are captured and when they are loaded to the Research Database, will be implemented further upstream near the point of capture, either within FormsNet or as part of the Data Warehouse. The CIBMTR began redesigning where the validations will be completed and will continue this work well into the next calendar year.

• Centralize management of metadata throughout the organization into a single Metadata Mart. Traceability of metadata along the CIBMTR Research Data Life Cycle is critical to preserving scientific logical and conceptual meaning of data as changes are made to reflect the evolution and dynamism of medicine. Centralized management of data from end to end also increases efficiencies and minimizes the potential for error. The CIBMTR plans to enhance the existing Metadata Mart to include metadata used in the existing Research Database to allow traceability between common data elements on data capture forms and fields used in research retrievals.

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

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

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

Risk management and IT security will be ensured through oversight of all hardware and software, effective management of user accounts and information sharing as well as event management.

The CIBMTR represents a large network of 350 participating transplant centers that submit transplant-related data for patients. The CIBMTR Coordinating Center, staffed by approximately 170 employees, provides data management and statistical support for analyses of these data. The Chief Scientific Director is responsible for all administrative and scientific operations. Senior and Associate Scientific Directors assist Senior Operational leadership in overseeing operation aspects of the Coordinating Center. The CIBMTR committees

provide input and advice to the leadership team, ensuring the continued support of both the needs and priorities of its scientific and medical communities.

During the next reporting period, the goals under the Scientific Resource Utilization Program will continue to focus on the review and refinement of current organizational practices, including:

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

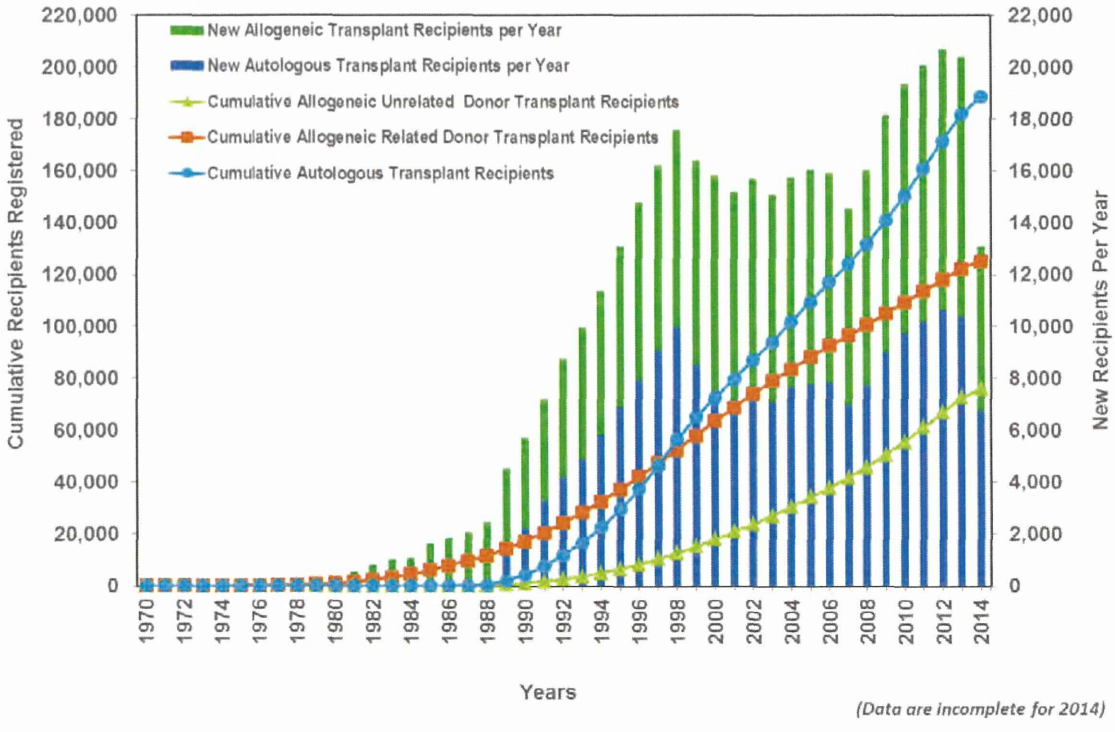
B.2 ACCOMPLISHMENTS

B.2.1 Resource Development Plan

B.2.1.1 OPTIMIZE AND ENHANCE THE QUALITY AND SCOPE OF THE DATABASE

The CIBMTR collects data for approximately 20,500 new transplant recipients annually as well as a continually increasing volume of follow-up data on previously reported recipients and donors. **Figure B.2.A** shows cumulative accession of transplants since 1970 when the IBMTR began collecting these data.

Figure B.2.A. Accession of Transplant Recipients Registered with the CIBMTR



B.2.1.1.a Stem Cell Therapeutic Outcomes Database (SCTOD)

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

- Collecting, analyzing and reporting outcomes data for all allogeneic transplants and other therapeutic uses of blood stem cells;
- Publicizing information about HCT available to patients, families, health care professionals, and the public;