For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Human Subjects Protection and Inclusion Guidelines.

Inclusion of Women, Minorities, and Children

When the proposed Resource involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the Human Subjects Protection and Inclusion Guidelines.

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

Not Applicable.

Renewals

For Renewals, the committee will consider the progress made in the last funding period.

Revisions

Not Applicable.

Additional Review Considerations - Overall

As applicable for the Resource proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact/priority score.

Applications from Foreign Organizations

Not Applicable.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms; and 3) Genome Wide Association Studies (GWAS).

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to

the proposed research.

2. Review and Selection Process

Application will be evaluated for scientific and technical merit by a Scientific Review Panel convened by the NCI, in accordance with NIH peer review policy and procedures, using the stated review criteria. Review assignments will be shown in the eRA Commons.

As part of the scientific peer review, application submitted in response to this FOA will receive a written critique.

Appeals of initial peer review will not be accepted for the application submitted in response to this FOA.

Applicationwill be assigned on the basis of established PHS referral guidelines to the appropriate NIH Institute or Center and will compete for available funds with all other recommended applications submitted in response to this FOA. Following initial peer review, recommended application will receive a second level of review by the National Cancer Advisory Board. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.

3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD(s)/PI(s) will be able to access his or her Summary Statement (written critique) via the eRA Commons.

Information regarding the disposition of applications is available in the *NIH Grants Policy Statement*.

Section VI. Award Administration Information

1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the *NIH Grants Policy Statement*.

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to the DUNS, CCR Registration, and Transparency Act requirements as noted on the Award Conditions and Information for NIH Grants website.

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement* as part of the NoA. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities. More information is provided at Award Conditions and Information for NIH Grants.

Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, U.S. Department of Health and Human Services (HHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other DHHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement (U24), an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

- Defining the overall goals for CIBMTR and overseeing the execution of the program as a whole;
- Ensuring optimal operation of the resource related to data management and statistical analyses;
- Coordinating the activities of CIBMTR organizational components, including the Advisory Committee, the Executive Committee and topical Scientific Working Committees;

- Seeking opportunities for collaborations with other investigators outside of the CIBMTR in order to enhance and extend the utility of the CIBMTR database;
- Assuring that the CIBMTR establishes and implements mechanisms to ensure that data collection and management procedures are adequate for quality control and analysis and patient and donor privacy;
- Ensuring compliance of the Resource with the mandatory regulations, including compliance with the assurance program of the Federal Office of Human Research Protection;
- Interacting with NIH staff members involved and ensuring their access to Resource data if needed;
- Cooperating with the NIH staff members in the periodic evaluation of the Program and its specific aspects;
- Providing NIH with information relevant to such evaluations or other purposes as needed when such information is requested by the participating ICs; and
- Administratively managing the award.

The main responsibilities of the CIBMTR as the awardee will include:

- Maintaining a resource of data and statistical expertise available to the broad community for clinical research in blood and marrow transplantation in the areas identified in this FOA;
- Optimizing and enhancing the quality and scope of the database in aspects relevant to the mission of the particpating institutes;
- Participation in new research and analyses using the CIBMTR data in areas relevant to the priorities of the participating ICs as stated in this FOA, including efforts to ensure timely publication of such studies in peer reviewed biomedical journals. *Although initiating new research and analyses is not the main role of the CIBMTR, investigators involved in CIBMTR are expected and encouraged to actively engage in such efforts, e.g., through collaborations within the CIBMTR Working Committees.*

To perform its functions, the CIBMTR must maintain an appropriate organizational and administrative structure. This structure is expected to include the Advisory Committee, the Executive Committee, and several Scientific Working Committees.

Expected activities of the Executive Committee include:

1) providing advice to the overall PD(s)/PI(s) for scientific activities and policy decisions;

2) establishing priorities for scientific studies after obtaining input from the Working Committees;

3) reviewing results of audits and recommending measures to correct deficiencies; and

4) reviewing and assisting in preparation of the agenda for annual Advisory Committee meetings.

Expected Activities and Responsibilities of the Scientific Working Committees include:

1) designing and conducting studies relevant to their subject area and involving CIBMTR data, statistical resources, networks, and/or centers;

2) considering proposals to use CIBMTR data for studies pertinent to their subject area;

3) periodically assessing and revising relevant sections of the CIBMTR data collections forms; and

4) planning and conducting workshops at CIBMTR meetings.

The activities of the Working Committees are expected to be based on the voluntary service and expertise by hundreds of physicians, basic scientists, and clinical research associates. The CIBMTR plays a central role in these activities as well as in coordinating data collection and management and providing statistical and administrative support for studies involving use of data in the CIBMTR database.

Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies.

NIH staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

A designated NCI Program Director, acting as a Project Scientist, will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards. NCI Project Scientist will not attend peer review meetings of renewal and/or supplemental applications. If such participation is essential, this individual will seek NCI waiver according to the NCI procedures for management of conflict of interest. Other NCI staff members as well as staff members from the participating ICs may also become substantially involved. Those individuals will not attend peer review meetings of renewal and/or supplemental applications (or will seek waiver). The activities of all NIH representatives involved in this cooperative agreement will be internally (within NIH) coordinated by the NCI Project Scientist.

In addition, an NCI Program Director acting as the Program Official will be responsible for the normal scientific and programmatic stewardship of the award, and will be named in the award notice. If the same individual serves as both Project Scientist and Program Official, he/she will not attend peer review meetings of renewal and/or supplemental applications or will seek NCI waiver if such participation is essential.

The responsibilities of substantially involved NIH staff members representing the NCI and other participating ICs will

include, but will not not limited to, the following activities:

1) Monitoring CIBMTR progress and coordinating periodic external reviews.

2) Serving as ex officio member(s) of the of the CIBMTR Advisory Committee.

3) Serving as a resource with respect to other ongoing NCI, NHLBI, and NIAID activities that may be relevant to the CIBMTR research efforts.

4) Reviewing mechanisms for data analysis and review, when appropriate.

5) Participating in appropriate CIBMTR committee meetings and conference calls.

6) *Review of Progress:* Performance of the CIBMTR will be reviewed as requested, and at least annually. For example, the NCI Project Scientist, in consultation with NIH staff members from NHLBI and NIAID, will review mechanisms established by CIBMTR for data management and analysis, when appropriate. Also evaluated will be progress in areas specific to the interests of participating ICs, including resulting publications (based on IC-specific reports from CIBMTR). In case of insufficient progress, or noncompliance with the terms of award, the NCI and other participating ICs reserve the right to reduce the award budget, withhold support, suspend or terminate the award.

7) NIH staff members will coordinate with Health Resources and Services Administration/DHHS on activities in stem cell transplant outcomes data collection for the C. W. Bill Young Cell Transplantation Program especially to eliminate and avoid duplication in data collection and harmonizing computer systems.

Access to Data: The NCI and other participating ICs will have access to all data collected under this cooperative agreement and may periodically review the data. The awardee will retain custody and primary rights to the data consistent with current HHS, PHS, and NIH policies.

Areas of Joint Responsibility include the following:

Advisory Committee consisting of CIBMTR representatives and NIH staff members is expected to provide oversight for all CIBMTR policies, agendas and long-term mission. Respresentatives of the NIH (NCI and other participating ICs) serve on the Advisory Committee as non-voting ex officio members.

Collective responsibilities of the members of the Advisory Committee include:

1) reviewing policies for use of CIBMTR data;

3) assisting in grant application preparation and other fund-raising activities; and

4) reviewing all research reports and manuscripts that describe results of CIBMTR-linked studies.

The Advisory Committeee is expected to meet annually, with additional teleconferences, as needed.

The CIBMTR and NIH staff members will jointly develop methods to make this resource accessible to other investigators. This joint development may occur through strategy meetings, development of datasets for publication on the Internet, and other mechanisms, as deemed appropriate.

The CIBMTR and NIH staff will jointly coordinate activities to eliminate and avoid duplication in data collection and harmonizing computer systems.

Dispute Resolution

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between the award recipient and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel composed of three members will be convened: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardees right to appeal an adverse action that is otherwise appealable in accordance with PHS regulations 42 CFR Part 50, Subpart D and HHS regulations 45 CFR Part 16.

3. Reporting

When multiple years are involved, awardees will be required to submit the Non-Competing Continuation Grant Progress Report (PHS 2590) annually and financial statements as required in the *NIH Grants Policy Statement*. In addition to the standard annual PHS 2590 report, the participating ICs may request, as needed, interim reports on progress in areas specific to their interests.

A final progress report, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement*.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over $25,000. See the *NIH Grants Policy Statement* for additional information on this reporting requirement.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

GrantsInfo (Questions regarding application instructions and process, finding NIH grant resources)
Telephone 301-435-0714
TTY 301-451-5936
Email: GrantsInfo@nih.gov

eRA Commons Help Desk(Questions regarding eRA Commons registration, tracking application status, post submission issues)
Phone: 301-402-7469 or 866-504-9552 (Toll Free)
TTY: 301-451-5939
Email: commons@od.nih.gov

Scientific/Research Contact(s)

For NCI:

William D. Merritt, Ph.D.
Clinical Grants and Contracts Branch
Cancer Therapy and Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
6130 Executive Blvd, EPN Room 7009, MSC 7432
Bethesda, MD 20892-7432 (for U.S. Postal Service regular or express mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: 301-496-8866
Email: merrittw@mail.nih.gov

For NHLBI:

Nancy L. DiFronzo, Ph.D.
Transfusion Medicine and Cellular Therapeutics Branch
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, MSC 7950
Bethesda, Maryland 20892-7950
Telephone: 301-435-0065
Fax: 301-480-1046
E-mail: difronzon@nhlbi.nih.gov

For NIAID:

Linda M. Griffith, M.D., Ph.D.
Autoimmune and Primary Immunodeficiency Diseases Section
Autoimmunity and Mucosal Immunology Branch
Division of Allergy, Immunology and Transplantation
National Institute of of Allergy and Infectious Diseases
6610 Rockledge Drive, Room 6716, MSC 6601
Bethesda, MD 20892-6601 (for U.S. Postal Service regular or express mail)
Bethesda, MD 20817 (for non-USPS delivery)
Telephone: 301-496-7104
Fax: 301-480-1450
Email: LGriffith@niaid.nih.gov

Peer Review Contact(s)

Referral Officer
Division of Extramural Activities
National Cancer Institute (NCI)
6116 Executive Blvd, Room 8041, MSC 8329
Bethesda, MD 20892-8329 (for US Postal Express or regular mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: (301) 496-3428
Fax: (301) 402-0275
Email: ncirefof@dea.nci.nih.gov

Financial/Grants Management Contact(s)

Romy M. Reis
National Cancer Institute
Office of Grants Administration
6120 Executive Boulevard, EPS Room 243
Bethesda, MD 20892-7150 (for US Postal Express or regular mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: 301-496-2834
FAX: 301-496-8601
Email: reisr@mail.nih.gov

Section VIII. Other Information

Recently issued trans-NIH policy notices may affect your application submission. A full list of policy notices published by NIH is provided in the *NIH Guide for Grants and Contracts*. All awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement*.

Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Parts 74 and 92.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, Audio or Video files, see Help Downloading Files.

添付資料－２：CIBMTR から NIH への研究申請書

これは先の要請に基づき CIBMTR から NIH へ提出された 5 年間約 18 億円の研究申請書の全 222 頁中冒頭 4 頁である。この研究費は研究者計 18 人の給与の一部を含む。

Form Approved Through 6/30/2012 OMB No. 0925-0001

Department of Health and Human Services
Public Health Services

Grant Application

Do not exceed character length restrictions indicated.

LEAVE BLANK—FOR PHS USE ONLY.		
Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT *(Do not exceed 81 characters, including spaces and punctuation.)*
A Data Resource for Analyzing Blood and Marrow Transplants

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT OR SOLICITATION ☐ NO ☒ YES
(If "Yes," state number and title)
Number: CA-12-503 Title: A Data Resource for Analyzing Blood and Marrow Transplants

3. PROGRAM DIRECTOR/PRINCIPAL INVESTIGATOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3h. eRA Commons User Name
Horowitz, Mary M	M.D., M.S.	marymh

3c. POSITION TITLE
Professor of Medicine, Scientific Director

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Medicine

3f. MAJOR SUBDIVISION
Center for International Blood and Marrow Transplant

3d. MAILING ADDRESS *(Street, city, state, zip code)*
Medical College of Wisconsin
9200 W. Wisconsin Avenue
CLCC Suite C5500
Milwaukee, WI 53226

3g. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 414-805-0700 FAX: 414-805-0714

E-MAIL ADDRESS:
marymh@mcw.edu

4. HUMAN SUBJECTS RESEARCH	4a. Research Exempt	If "Yes," Exemption No.
☐ No ☒ Yes	☒ No ☐ Yes	

4b. Federal-Wide Assurance No.	4c. Clinical Trial	4d. NIH-defined Phase III Clinical Trial
FWA00000820	☒ No ☐ Yes	☒ No ☐ Yes

5. VERTEBRATE ANIMALS	5a. Animal Welfare Assurance No
☒ No ☐ Yes	

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
03/01/13	02/28/18	$3,013,612	$3,620,000	$15,068,060	$18,100,000

9. APPLICANT ORGANIZATION
Name Medical College of Wisconsin
Address
8701 Watertown Plank Road
Milwaukee, WI 53226-0509

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☐ State ☐ Local
Private: → ☒ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
1390806261A3
DUNS NO.93-763-9060 Cong. District WI-005

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name April A. Haverty, JK
Title Director, Grants and Contracts
Address 8701 Watertown Plank Road
Milwaukee, WI 53226-0509
Tel: 414-456-4844 FAX: 414-456-6555
E-Mail: grants@mcw.edu

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name
Title
Address 8701 Watertown Plank Road
Milwaukee, WI 53226-0509
Tel: FAX:
E-Mail:

14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Services terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.	SIGNATURE OF OFFICIAL NAMED IN 13. *(In ink. "Per" signature not acceptable.)*	DATE

PROJECT SUMMARY (See instructions):

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a clinical research program dedicated to addressing important issues in the field of hematopoietic cell transplantation (HCT). CIBMTR maintains a large outcomes registry with information for >330,000 HCT recipients in >300 centers and provides statistical support for analyzing those data. A separately funded Research Repository of donor-recipient specimens linked to these clinical data is available for a large subset of patients. Use of this Resource by hundreds of investigators around the world during the current and previous funding cycles have contributed to >700 publications on important issues and to improved global collaboration in data exchange and HCT research. With continuation of U24-CA76518, CIBMTR will continue to build on the infrastructure made possible by this support to facilitate in-depth exploration of clinical, immunogenetic, quality of life, and health services issues related to HCT. This application proposed to enhance this Resource and to advance its utility through the following Specific Aims:

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 Statistical Center processes to prioritize and complete these studies.

RELEVANCE (See instructions):

The CIBMTR continues to play a unique and important role in facilitating clinical research in HCT. It is committed to developing its research database and statistical capabilities to meet the needs of investigators in a rapidly evolving field. It will build on the infrastructure made possible by support from U24-CA76518 and its partnerships to better serve the research and medical community and address important issues in HCT.

PROJECT/PERFORMANCE SITE(S) (if additional space is needed, use Project/Performance Site Format Page)

Project/Performance Site Primary Location		
Organizational Name: Medical College of Wisconsin		
DUNS: 93-763-9060		
Street 1: 8701 Watertown Plank Road	Street 2:	
City: Milwaukee	County: Milwaukee	State: WI
Province:	Country: USA	Zip/Postal Code: 53226
Project/Performance Site Congressional Districts: WI-005		

Additional Project/Performance Site Location		
Organizational Name: National Marrow Donor Program, Inc.		
DUNS: 623225737		
Street 1: 3001 Broadway St. N.E.	Street 2: Suite 100	
City: Minneapolis	County: Hennepin	State: MN
Province:	Country: USA	Zip/Postal Code: 55413-1753
Project/Performance Site Congressional Districts: MN-05		

Program Director Principal Investigator (Last, First, Middle): r t ar

SCIENTI IC KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s) Principal Investigator(s). List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
r t ar	ar	a	Pr a t at r
a ar	P	a	t at r
ar Para ara	ar	a	t at r
Pa ar	Pa	a	t at r
a		a	t at r
a r a	a r	a	t at r
		a	t at r
a		a	tat t a
a		a	tat t a
ra a a ta		a	tat t a

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project
r	at a arr r Pr ra	Pr t r t r
r a	at a arr r Pr ra	r ar r
a a a t	at a arr r Pr ra	ta t t r t r
a t	at a arr r Pr ra	r r
ar	tt a r t r	ta t t r t r
t a	r t a r ar t	ta t t r t r
r ra ta	at a arr r Pr ra	ta t t r t r
r t	r t ta	ta t
r t	r t a t r	ta t

Human Embryonic Stem Cells ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research registry/eligibilityCriteria.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

The name of the program director/principal investigator must be provided at the top of each printed page and each continuation page.

RESEARCH GRANT

TABLE OF CONTENTS

* Follow the page limits for these sections indicated in the application instructions, unless the Funding Opportunity Announcement specifies otherwise.

資料説明－3：NIH からの審査結果

この評価は略満点に近いものであり、CIBMTR といえども、この様なことは稀であるとのことであった。

SUMMARY STATEMENT

PROGRAM CONTACT:
WILLIAM MERRITT
301-496-8866
merrittw@mail.nih.gov

(Privileged Communication) *Release Date:* 10/22/2012

Application Number: 2 U24 CA076518-16

Principal Investigator

HOROWITZ, MARY M MD

Applicant Organization: MEDICAL COLLEGE OF WISCONSIN

Review Group: ZCA1 SRLB-V (J1)
National Cancer Institute Special Emphasis Panel
A Data Resource for Analyzing Blood and Marrow Transplants

Meeting Date: 10/10/2012
Council: JAN 2013
Requested Start: 03/01/2013

RFA/PA: CA12-503
PCC: W6CL
Dual PCC: BBRR N
Dual IC(s): HL, AI

Project Title: A Data Resource for Analyzing Blood and Marrow Transplants

SRG Action: Impact Score: 10
Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 1A-Both Children and Adults, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
16	2,711,271	3,603,525
17	2,725,669	3,622,662
18	2,727,131	3,624,605
19	2,727,130	3,624,603
20	2,727,131	3,624,605
TOTAL	13,618,332	18,100,000

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

2U24CA076518-16 HOROWITZ, MARY

RESUME AND SUMMARY OF DISCUSSION: This is a renewal application from Dr. Mary Horowitz of the Medical College of Wisconsin. The applicant requests continued support for operation of the Center for International Blood and Marrow Transplant Research (CIBMTR). Dr. Horowitz, the Principal Investigator, has provided effective leadership for the International Blood and Marrow Transplant Registry (IBMTR) since 1991, and then of the CIBMTR after its creation in 2004. Her hematology/oncology training coupled with her MS in biostatistics, her leadership and organizational skills make Dr. Horowitz ideally suited to be the Principal Investigator of the program. Dr. Horowitz's leadership remains an important strength of this application, and the strong statistical team adds to the overall strength of the investigative team. The CIBMTR serves as a data coordinating center for hematopoietic transplantation studies and data analyses and its operation have lead to shifts in clinical treatment paradigms and specific clinical trials addressing critical issues in stem cell transplantation. The extensive utilization of this registry by the hematopoietic cell transplantation (HCT) community speaks to the significance it has among investigators in the field of HCT. The proposed approaches to the specific aims of Resource Development and Resource Utilization are clearly outlined and are feasible and achievable. The methods of data collection, data retrieval, and the infrastructure to support the collection are well developed, well integrated and appropriate for the goals of the resource. The strengths of this application include: experienced and well qualified research team; highly-organized program that provides data quality assurance; development of a new electronic system (FormsNet) for data submission, a network information system (AGNIS), initiatives to assist with long term follow up of transplant recipients; new system to prioritize studies; new statistical methodology specifically targeting problems related to the analysis of HCT data; and formation of executive committee to outline goals and objectives. Both the Medical College of Wisconsin and the University of Minnesota (National Marrow Donor Program site) provide strong institutional support to this resource and the environments are appropriate. The applicant and co-investigators have been highly responsive to concerns raised by the prior review and have addressed them in detail. They have taken advantage of their impressive External Advisory Board for critical input and have implemented suggestions that have strengthened the program. These elements have resulted in a highly productive program as reflected by the large number of publications with high clinical impact on the field that would not have been possible without the CIBMTR. The plan for information transfer and data sharing plan are adequately addressed. A minor concern was raised during the discussion if Dr. Horowitz had enough effort to also serve as Division Chief and who would take over if Dr. Horowitz were unable to perform her duties as Scientific Director. It would be important to identify a succession plan to the leadership of such a program. Overall, this is a highly significant and innovative application with a number of strengths and essentially no weaknesses. The enthusiasm for this application was very high that merited a rating of "exceptional".

DESCRIPTION (provided by applicant): The Center for International Blood and Marrow Transplant Research (CIBMTR) is a clinical research program dedicated to addressing important issues in the field of hematopoietic cell transplantation (HCT). CIBMTR maintains a large outcomes registry with information for more than 330,000 HCT recipients in over 300 centers and provides statistical support for analyzing those data. A separately funded Research Repository of donor-recipient specimens linked to these clinical data is available for a large subset of patients. Use of this Resource by hundreds of investigators around the world during the current and previous funding cycles have contributed to >700 publications on important issues and to improved global collaboration in data exchange and HCT research. With continuation of U24-CA76518, CIBMTR will continue to build on the infrastructure made possible by this support to facilitate in-depth exploration of clinical, immunogenetic, quality of life, and health services issues related to HCT. This application proposes to enhance this Resource and to advance its utility through the following Specific Aims: 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 disseminating 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 Statistical Center processes to prioritize and complete these studies. RELEVANCE: The CIBMTR continues to play a unique and important role in facilitating clinical research in HCT. It is committed to developing its research database and statistical capabilities to meet the needs of investigators in a rapidly evolving field. It will build on the infrastructure made possible by support from U24-CA76518 and its partnerships to better serve the research and medical community and address important issues in HCT.

CRITIQUE 1:

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

Overall Impact:
Strengths:

- The strengths of this application in the last funding period include the development of a new electronic system (FormsNet™) of data submission so that >95% of TED and CRF data are now submitted electronically. This includes real time data validations, control of data entry flow and error handling and measuring.
- Complementary to this, the Resource has developed a network information system (AGNIS) that allows data flow from other databases into FormsNet™ and vice versa.
- These developments will greatly enhance the utility of this invaluable resource for the HCT research community and for HCT patients. These developments will greatly enhance the ability of this resource to serve the needs of the HCT investigators and will enable continued utilization of this highly successful resource.
- The overall impact of the CIBMTR has been huge, allowing for numerous important and impactful publications in HCT that would otherwise not have been feasible, given the nature of HCT research.

Weaknesses:

- Weaknesses are negligible and include the usual challenges of maintaining privacy in databases and the usual limitation of registry based research. However, these are minimal because investigators in general and the applicant in particular recognize and indeed have helped to define these limitations and have not attempted to use registry based research for any purpose other than what is within the limits of that research.

1. Significance:
Strengths:

- This resource addresses a critical problem in HCT research by providing a well-constructed, reliable and non-biased database (over 17,000 new HCT recipients annually are entered into the database) that is available to any investigator who is interested in conducting HCT research. If the Specific Aims, which are simply stated in the application as Resource Development and Resource Utilization, are met, then scientific knowledge and technical capability will be enhanced and will result in improvement in clinical practice.

- The recent publication of overall guidelines for the care of the HCT patient are examples of how treatments and preventive interventions are codified by data generated by for the most part registry based research and how the CIBMTR facilitates this.
- This registry has been the major vehicle for this type of research for the past 40 years and based on this renewal application, it is likely that it will be able to meet challenges of data collection, patient privacy and data analysis for the next grant period.

Weaknesses:

- None

2. Investigator(s):

Strengths:

- Dr. Mary Horowitz, the Principal Investigator, has been the director of this registry since 1991 and she has the skills and qualifications to continue to provide leadership through this renewal application period. She has done an exceptional job in developing the CIBMTR and her leadership remains an important strength of this application.
- The other major investigators, Associate Director Eapen, Assistant Director Hari, Associate Scientific Director Rizzo and Pasquini, all appear to have clear roles and enhance the scientific mission of the registry.
- Further, the strong statistical team (Klein, Ahn, Brazaukas, Perez, Carreras, Wang, Zhong, and programmer Liu and Jacquot) adds to the overall strength of the investigative team.
- The senior investigators has a strong track record of publication in their respective areas of expertise and the more junior investigators are similarly well on their way towards independent careers.

Weaknesses:

- A minor concern is the new role that Dr. Horowitz will play in the Division of Hematology/Oncology at MCW as since 2010 she has taken on the role of Division Chief. It is not clear how this will impact her role in CIBMTR.

3. Innovation:

Strengths:

- The major innovation in the concepts and approaches to this field of registry research is the novel electronic data submission process initiated in the last funding period with plans to refine it in the current one. The use of the FormsNet™ database and the ability to enter data from other databases in two directions is innovative and allows for rapid data accumulation which in turn allows for more relevant and impactful registry studies. Further, the development of working groups (19 working groups are described in Appendix E1), each with national leaders in their respective fields, with administrative and statistical support from CIBMTR, allows for collaborative research and facilitates asking and answering relevant questions in diseases as diverse as lymphoma/leukemia, to auto immune disease and congenital immune deficiency states. The applicant has described very well the system whereby the working groups pose questions and arrive at answers in rapid time frames.
- The administrative structure (Assembly, Advisory (Appendix E2), Executive (Appendix E3) and Nominating Committees (Appendix E4) allows for equitable governance of this registry and are well described in the application. Other committees (NMDP Histocompatibility Advisory Group (Appendix E5), the Consumer Advocacy Committee 9Appendix E6) and the Clinical Trials Advisory Committee (Appendix E7) help to facilitate novel, innovative studies in CIBMTR.
- The data are validated by an innovative model of onsite audits and online validation
- The public website, launched in 2010, expand content to a wider audience and make the data more accessible
- A novel "Collaborate" web site is now open to facilitate collaborative studies among investigators, and examples include the Kir ligand studies now extant in choice of donors for allogeneic stem cell transplant in AML.

- The "Portal" site houses custom application and is another example of innovative database development and utilization that enhances this registry.
- QOL information is now collected

Weaknesses:

- None. There is very little that this group has not done to develop innovative registry studies in HCT

4. Approach:

Strengths:

- Extremely well organized
- High volume data collection and analysis (17,000 new cases/year)
- Well codified
- Web tools are provided to aid in community outreach and communication
- Use of drop down menus
- 19 working groups among related disease entities to ask questions of the database
- Training program for masters level statistician
- Collection of TED and CRF data

Weaknesses:

- None

5. Environment:

Strengths:

- Superb environment at MCW and University of Minnesota

Weaknesses:

- Risk of division of the 2 campuses, but this has not been an issue to date

Protections for Human Subjects:

- Plans for protection of human subjects are in place

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only): N/A

Inclusion of Women, Minorities and Children:

- G1A
- M1A; Inclusion of minorities are addressed
- C1A

Vertebrate Animals: N/A

Biohazards: N/A

Renewal: Excellent progress and preliminary data in this application

Select Agents Research: N/A

Resource Sharing Plans: Acceptable

Budget and Period of Support:

Recommended budget modifications or possible overlap identified: None

Additional Comments to Applicant (Optional): None

CRITIQUE 2:

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

Overall Impact:
Strengths:

- The CIBMTR continues to provide a unique and powerful resource that has a significant impact on the state of HCT research throughout the world. Specific details regarding areas of significance and innovation are noted below, but simply stated, this is an exceptional resource for the HCT research community.
- The investigators should be commended for consistently and efficiently working to improve this resource to make it a truly world class resource. In particular, their efforts to improve and increase data capture via multiple electronic and other routes are innovative and comprehensive.
- The investigators are to be commended for their continued ability to leverage different sources of funding to enhance and build on this resource.

1. Significance:
Strengths:

- CIBMTR provides comprehensive data capture of 100% allogeneic transplants in U.S. and over 80% of autologous transplants from over 200 U.S. centers proving HCT.
- International data is also available from more than 100 centers enrolled.
- Data collected from a total of ~17,000 new HCT recipients annually as well as follow-up data on previously reported transplants.
- Innovative prioritizing of data collection due to limited resources to distinguish **Registration** from **Research** Centers. All centers provide basic sets of data on all allogeneic and/or autologous HCT recipients. Research centers provide a more comprehensive data set on a subset of patients selected based on disease, type of donor/graft, age of recipient and aspects of the treatment regimen. In particular oversampling is carried out for rare diseases and other patient groups for which adequate subsets of subjects are needed and would otherwise be hard to achieve. Careful statistical thought has been given to appropriate sampling taking into account the above criteria, illustrating the strong communication and collaboration between the statistical team and clinical researchers.
- Comprehensive electronic data submission system, FormsNet was launched during this funding period. Over 95% of data is collected electronically.
- The CIBMTR data has facilitated an increasingly growing number of publications. Since inception as IBMTR in 1972, CIBMTR data and statistical support has resulted in over 700 publications, of which about 400 were since 1993, and of those, over 200 during the current funding period.
- Similarly, the overall number of investigators involved in CIBMTR research has dramatically increased over the past funding period (approximately doubled).

Weaknesses:

- None noted.

2. Investigator(s):
Strengths:

- Dr Mary Horowitz has provided exceptional leadership to this project since 1991 and plans to continue in this role. Her combined MD and masters in biostatistics make her especially well suited for this project.
- Dr. John Klein is a highly productive biostatistician with a clear focus of research on methods for analyzing HCT data. He has provided excellent leadership for the statistical areas of the CIBMTR and is also well qualified and suited to this project.
- The remaining investigators are excellent and well qualified to carry out their respective roles.

Weaknesses:

- None noted.

3. Innovation:
Strengths:

- One major innovation over the current award period was developing software so that data from HCT at over100 European centers will be available from EBMTR.
- Comprehensive electronic data submission system, FormsNet, includes the advantage of real-time data validation.
- Established program for providing data back to Centers, using FormsNet data provided since December 2007.
- Enhanced web presence established during the current funding period with public sections and password protected workspaces (**Portal** and **Collaborate**) to facilitate collaboration and information dissemination.
- Further development of new statistical methodology specifically targeting problems related to the analysis of HCT data. Papers published during the current grant award period included those on a variety of topics including: 1) quality adjusted mean survival time, 2) comparing treatments with crossing survival curves, 3) computing the best cut point to discretize continuous covariates in a GEE analysis, 4) adjusting for associations between subjects using marginal models,5) comparing current disease-free survival curves and 6) determining center-specific outcomes based on pseudo-observations computed using the 1-year survival function. The group has continued to build on their strong body of research working on competing risks methodology, both providing publications aimed at statisticians as well as the medical professionals. Drs Klein and Zhang continue to be leaders in the statistical analysis of HCT data, having provided editorship for a recent issue of *Lifetime Data Analysis* on the topic.
- The statistical leadership has proposed to build further on their work in pseudo-values to extend the methods to left-truncated and interval censored data. They also propose what should be very useful work to further explore optimizing selection and analysis of matched pairs data (or more generally, case/control data). These are relevant and interesting topics for development that will serve to allow for more efficient utilization of the resource.
- Recognition that a key barrier to HCT centers' submission of electronic data is mapping their data to the AGNIS data format has led the CIBMTR to explore development of new open-source tools. This, along with other approaches to make this task more easily attained, is an excellent goal that should serve the resource and the research community well.
- Implementation of self-service "Data Back to Centers" is an efficiency that will serve to both increase the accessibility of the data set to more investigators while reducing the drain on the CIBMTR staff to carry out complex data requests.

Weaknesses:

- None noted.

4. Approach:
Strengths:

- The investigators have described successful activities and proposed to continue building on a successful framework for their **Resource Development Program**, as requested in the FOA. It is clear that the investigators have taken great pains to both solicit diverse outside expertise to prioritize and utilize their own experiences and talents to improve their systems. For example, a pilot study is underway to evaluate collection of Patient Reported Outcomes
- One priority of the CIBMTR that is more challenging includes maintaining long-term follow-up for collection of later occurring adverse events. Innovative approaches utilizing internet based methods, cost sharing with external sources and general perseverance in working with HCT centers and IRBs are being implemented with documented success.
- As requested in the FOA, the investigators have described their **Resource Utilization Program** and illustrated that they have developed carefully conceived and rigorously executed plan for increasing the utilization of the resource, both in number of diverse interactions as well as in quality of those interactions that are prioritized.

Weaknesses:

- None noted.

5. Environment:
Strengths:

- Both MCW and NMDP provide strong institutional support to this resource and the environments are appropriate.
- The move to a larger facility in the past funding period has further enhanced the capacity for growth within the group.
- Other aspects of the environment such as computing facilities and administrative support all appear to be adequate.

Weaknesses:

- The usual issues of communication being a little more difficult between two campuses could be a weakness, but the success of the resource to date indicates that the procedures in place for facilitating communication seem to be working well.

Protections for Human Subjects: Exceptional care appears to be taken to ensure the protection of human subjects, as would be expected for such a large international data collection entity. All federal requirements and IRB policies of all institutions involved appear to be met. Staff is trained in these policies and they maintain certification.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only): N/A

Inclusion of Women, Minorities and Children: There are no concerns regarding inclusion of women, minorities or children in this database; all consecutive HCT recipients are enrolled.

Vertebrate Animals: N/A

Biohazards: N/A

Renewal: As noted above and detailed in Significance, Innovation and Approach, exceptional progress and achievement has been made during the previous funding period.