STEM CELL THERAPEUTIC OUTCOMES DATABASE
SUPPORTING STATEMENT

A. JUSTIFICATION

1. Circumstances of Information Collection

The Health Resources and Services Administration (HRSA) is requesting Office of Management and Budget approval of the data collection instruments for the Stem Cell Therapeutic Outcomes Database (SCTOD), a component of the C.W. Bill Young Cell Transplantation Program (the Program). These instruments are intended to provide the data elements required to fulfill the contractual requirements of the SCTOD, as outlined below. They were developed by the Center for International Blood and Marrow Transplant Research at the Medical College of Wisconsin, in collaboration with hematopoietic cell transplantation experts in the United States and the international arena.

The Stem Cell Therapeutic and Research Act of 2005

The information collection activities described in this submission are authorized by the Stem Cell Therapeutic and Research Act of 2005 (Public Law 109-129) which was signed into law on December 20, 2005. Section 379A of the Public Health Service (PHS) Act (42 U.S.C. 274l) is amended to require the Secretary, acting through the Administrator of HRSA, to establish and maintain the C.W. Bill Young Cell Transplantation Program.

The Stem Cell Therapeutic Outcomes Database

Congress has legislated that outcomes data must be collected on all patients "who have been recipients of a stem cell therapeutics product (including bone marrow, cord blood, or other such product) from a donor." This includes allogeneic transplants, both related and unrelated, where either the donor or the recipient resides in the U.S. The Center for International Blood and Marrow Transplant Research (CIBMTR) at the Medical College of Wisconsin was awarded the contract for the outcomes database in September 2006. As the recipient of this contract, the CIBMTR is responsible, with HRSA oversight, for the administration of this activity and the collection and analysis of the data.

The CIBMTR is a research partnership formed through an affiliation between the International Bone Marrow Transplant Registry (IBMTR) and Autologous Blood and Marrow Transplant Registry (ABMTR) of the Medical College of Wisconsin and the National Marrow Donor Program (NMDP). Transplant centers have long collaborated with the CIBMTR and the NMDP and have substantial experience with providing data in voluntary partnerships and networks. The Act establishes federal oversight of a new standardized electronic system, and the CIBMTR is in a unique position to collect the required data due to their substantial experience and proven methods in collecting transplant data.

The CIBMTR is a voluntary organization involving more than 400 transplant centers in 47 countries that have collaborated to share patient data and conduct scientific studies since 1972. This organization has collected retrospective outcomes data provided voluntarily (without HRSA oversight) by transplant centers worldwide on both allogeneic and autologous (patient's own cells) hematopoietic stem cell transplants (HCT). Hematopoietic stem cells are the cells responsible for continual regeneration of circulating blood cells throughout life; they are not embryonic stem cells. The CIBMTR has made these data available to investigators and physicians worldwide, providing physicians, scientists, policy makers and patients with the information they need to make the best possible clinical decisions and to advance the field.

The NMDP is a non-profit organization that works through an extensive network of U.S. and international organizations to facilitate marrow and blood stem cell transplants for patients who need an unrelated donor transplant. The NMDP coordinates hematopoietic cell transplants by managing a worldwide network of affiliated organizations. These organizations have established relationships with the NMDP and work together to arrange the collection and transfer of donated bone marrow (or cord blood). The CIBMTR is subcontracting with the NMDP to help fulfill the contract requirements. The scope of data collection under this contract includes:

1. allogeneic[1] transplantation for hematopoietic reconstitution using cells from donors <u>not related</u> to the patient;
2. allogeneic transplantation for hematopoietic reconstitution using cells from donors who are <u>related</u> to the patient; and
3. emerging clinical applications of cells derived from bone marrow, peripheral blood, and umbilical cord blood. (Defined as therapeutic applications of cells derived from the bone marrow, peripheral blood, or umbilical cord blood for purposes other than hematopoietic reconstitution.)

HRSA is responsible for establishing and maintaining a standardized database of allogeneic (related and unrelated donor) marrow and cord blood transplants performed in the United States. The Act requires that transplant centers performing these transplants provide patient outcomes data to this new national system. Data collection on patient outcomes is required to be in compliance with the requirements of the Act and is critical to the successful implementation of the Program.

2. Purpose and Use of Information

The data collection instruments proposed to HRSA by the CIBMTR are the *Pre-TED* (Transplant Essential Data), *Post-TED* and the *Product Form*. The *Product Form* consists of the Infusion Insert, Infectious Disease Marker Insert and the Human Leukocyte Antigen or HLA Typing Insert. These instruments contain the data elements necessary to fulfill the broad requirements of the SCTOD as established in the authorizing legislation for all allogeneic transplants occurring in the United States or using a donor from the United States.

[1] In an allogeneic transplant, a patient receives blood stem cells collected from a sibling or other related donor, or from an unrelated donor.

The requirements for data submission using the *Pre-TED* and the *Post-TED* have substantial overlap with existing CIBMTR procedures and are familiar to most transplant centers. The CIBMTR has a long history of collecting similar data from transplant centers. The balance between collecting sufficient data to analyze patient outcomes versus minimizing the reporting burden on transplant centers to collect and submit such data has been carefully considered.

Graft characteristic data for cord blood units and unrelated donor grafts facilitated by the Program will be collected within fourteen days of HCT on the *Product Form*. This form will include critical details of: procedures to facilitate stem cell collection; product collection, handling, transport, manipulation and storage; graft content including essential cell counts for engraftment; infectious contamination of cellular products; infusion timing and adverse events; and demographic information about the donor (includes the donor mother's information for cord blood units). The HLA or tissue type and infectious disease marker sections of the *Product Form* will collect information regarding degree and resolution of HLA-matching between donor and recipient, as well as the relevant infectious disease testing of the donor. These graft data, along with the outcomes data collected on the *Pre-TED* and *Post-TED* are essential data elements for the Program.

The data collected using these instruments will meet the requirements of the Act in establishing a scientific database and providing information for the required annual report on blood stem cell transplantation to the Secretary.

3. Use of Improved Information Technology

The system for the outcomes database is electronic. Implementation of the data collection instruments will include reporting forms that can be downloaded as well as an electronic, Web-based interface, called FormsNet 2.0. Data collection instruments will be accompanied by an instructions manual. The CIBMTR is acutely aware of the need to minimize the burden of data collection for transplant centers. Transplant centers currently collect, store and report information using a variety of mechanisms ranging from paper forms and electronic software packages to Web interfaces.

FormsNet 2.0 will allow for remote data entry of transplant baseline and follow-up data by the transplant centers. This system will be a single Web-based application for data entry, viewing, and auditing of recipient forms. Important features included in the system are:

- 24/7 accessibility
- create/edit forms and inserts
- create/edit all CIBMTR specific inserts
- create/edit confirmation of HLA typing and product forms
- audit trail and user interface
- data entry and form reconciliation
- tools for monitoring accuracy and processes

The system will also include automated validation checks within and between forms; automatically generated error reports; field-level audit trails; review functions for center

supervisors; electronic signatures; forms due reporting; and the flexibility to add additional features. FormsNet 2.0 will be fully compliant with Federal database security requirements as established by HRSA's Office of Information Technology (OIT) and the Food and Drug Administration (FDA) *21 CFR Part 11; Electronic Records; Electronic Signatures Maintenance of Electronic Records* and *Computerized Systems Used in Clinical Trials.*

FormsNet 2.0 will be available online for data entry following approval from OMB.

4. Efforts to Identify Duplication

The CIBMTR has established a system for data collection within the United States for HCT that is not duplicated, to any significant degree, by any other U.S. entity. The CIBMTR and the NMDP have worked together to develop the systems that will capture the required outcomes reporting. For purposes of this database, all data collection for the HCT outcomes will be collected using a single set of instruments that will encompass all allogeneic transplants performed in the United States, including umbilical cord blood transplantation. No other organization in the United States currently collects these data in a systematic way that would represent a duplication of effort.

5. Involvement of Small Entities

This information collection does not include small businesses or other small entities.

6. Consequences If Information Collected Less Frequently

The information collection activity outlined in this request is required under the Stem Cell Therapeutic and Research Act of 2005. The Act mandates the collection of data for the outcomes database. The data that are to be collected have been carefully considered by the broad transplant community. These data, and the time points for data collection, represent a parsimonious solution to the trade-offs of data collection and reporting burden to those providing data and the need to have comprehensive data to fulfill the requirements of the SCTOD. The data reporting schedule and the proposed instruments represent the consensus of the transplant community for data that would be essential to understand the broad requirements of the Program. These requirements include numbers of transplants facilitated by the Program, numbers of transplants performed annually in the United States, outcomes of those transplant procedures, long-term outcomes of blood stem cell transplantation, effective use of cord blood units for transplantation, and alternative uses of cells derived from bone marrow and cord blood. Additionally, these requirements include annual transplant center specific survival reports to be made available to patients, physicians, and the general public.

The CIBMTR will collect outcomes data on allogeneic transplants according to the following schedule: at baseline, 100-days after HCT, 6-months after HCT, 1-year after HCT, and annually thereafter.

Baseline data will be collected within 10-days of the blood stem cell transplant and will include patient demographics before transplantation, disease characteristics and status, co-morbidities,

transplant procedure characteristics including preparative regimen and graft versus host disease prophylaxis, graft source, donor type and degree of HLA matching, and graft manipulation. These data will be collected on the *Pre-TED* forms.

Data collected at 100-days and beyond will include hematopoietic recovery and engraftment[2], serious complications including GVHD and second cancers, disease status, survival status, and cause of death, if applicable. Subsequent procedures, including additional transplants or cellular therapies, will also be collected. These data will be due within 30-days of achieving the milestone. These data will be collected on the *Post-TED* form (the *Post-TED* form will be completed for all time points at or beyond 100-days after transplantation).

Collecting less information than that proposed in the submitted data collection instruments threatens the ability to understand the type of transplant, the comorbid conditions of the patients who undergo transplantation, and the short-term and long-term results of the transplant procedures. Much of the data collected is essential to understanding and reporting differences in transplant outcomes across U.S. transplant centers in an equitable fashion, using data already proven, or commonly believed to affect outcomes by transplant experts and accrediting organizations. Collecting data at the proposed time points is not only essential to understand outcomes at various waypoints in the transplant process, but represent standard time points of assessment for allogeneic transplant recipients. These time points are also meant to reinforce the importance of follow-up assessments by transplant centers to avoid losing contact with transplant recipients in a system where recipients gradually become more remote from the tertiary care centers where allogeneic transplantation is performed.

If the information required in Section 379A(c) is not collected, HRSA will not be in compliance with the authorizing legislation. This information is required by the Secretary to report the following:

- whether program funds for the SCTOD are fulfilling the mission of the C.W. Bill Young Cell Transplantation Program;
- what types of transplants are being performed in the United States and for what clinical indications, and the outcomes of those transplants;
- outcomes of blood stem cell transplantation across transplant centers.

7. Consistency with the Guidelines in 5 CFR 1320.5(d) (2)

The data will be collected in a manner fully consistent with the guidelines in 5 CFR 1320.5.

8. Consultation Outside the Agency

The 60-day notice required in 5 CFR 1320.8(d) was published in the *Federal Register* on September 22, 2006 (Volume 71, Number 184, Pages 55493-55494). No comments were received.

[2] The process in which transplanted hematopoietic cells begin to grow in the bone marrow of the host and to produce new white blood cells, red blood cells and platelets.

The CIBMTR and NMDP have extensive experience and collaborative relationships to facilitate collecting transplant outcomes data in performance of contracts and grants establishing existing observational databases. These current databases have been used extensively in the last few decades to advance knowledge regarding HCT outcomes. However, in order to provide data instruments for collection of the data elements required by the Program, the CIBMTR has consulted extensively with U.S. and international transplant centers, accrediting bodies, professional societies representing the transplant community, international outcomes registries, and representatives of cord blood banks. These consultations include discussions with the American Society for Blood and Marrow Transplantation (ASBMT) and its Quality Outcomes Committee on establishing the data elements necessary to perform fair and representative center-specific outcomes reporting. Additionally, transplant center directors nominated by the ASBMT participated in numerous conference calls and in-person meetings to provide input regarding data items essential for understanding transplant outcomes and perspective regarding the burden of data reporting.

Consistent with the requirements of the contract for operation of the SCTOD, the CIBMTR established a Data Working Group for the Program. The Data Working Group is comprised of representatives from the CIBMTR, NMDP, HRSA, and umbilical cord blood banks. The Data Working Group meets approximately monthly to explore the technical aspects of communications and data flow among and between Program participants and ways to reach feasible solutions to challenges and to enhance the overall efficiency of the Program.

In addition to the Data Working Group, the CIBMTR has established a Data Advisory Group with a much broader constituency. In addition to the categories represented by the Data Working Group, the Advisory Group includes broader representation from the transplant community including representatives from U.S. and international transplant centers, representatives from professional associations, and representatives from other Federal agencies (e.g., National Institutes of Health). The Data Advisory Group first met in December 2006. At that time a number of sub-groups were formed to work more closely on specific aspects of the data collection instruments. The entire Data Advisory Group convened a second time in February 2007 to review the work performed by the sub-groups.

The CIBMTR worked with the Foundation for the Accreditation of Cellular Therapy (FACT), the U.S. organization which provides HCT center accreditation, as well as it European counterpart, Joint Accreditation Committee of the International Society for Cellular Therapy (JACIE), to assure that the data elements captured on the forms meet the SCTOD requirements. The CIBMTR has worked closely with its counterpart observational database in Europe, the European Group for Blood and Marrow Transplant (EBMT) to develop the forms. This collaboration ensures that data collection efforts in the U.S. are also consistent with international efforts to collect data essential to understanding transplant outcomes and to facilitate data submission to CIBMTR for U.S. cellular therapy products facilitated by the Program that occur in international transplant facilities.

Discussions also have involved the Asian-Pacific Blood and Marrow Transplant Group and Australia-New Zealand Outcomes Registry. The CIBMTR has worked diligently with the umbilical cord blood banks to develop a set of data and data exchange mechanisms that will

provide the data necessary to fulfill the requirements of this Program. These requirements include understanding the characteristics of cord blood grafts that affect outcomes and providing information regarding adverse events that are needed to meet FDA regulatory requirements. These efforts have resulted in the *Product Form* (includes the Infusion Insert, HLA Typing Insert, and Infectious Disease Markers Insert) which will be collected for every unrelated adult donor or cord blood transplant that is facilitated by the C.W. Bill Young Cell Transplantation Program. Finally, the CIBMTR has collaborated with donor registries, including the World Marrow Donor Association, to assure that data collected regarding outcomes of transplantation will fulfill the needs of the donor registries using the same data collection instruments.

These extensive discussions have led to international consensus on a set of common data elements that should be collected to understand outcomes of transplantation in general, and to meet the requirements of the Program. These data elements are represented on the *Pre-TED* (baseline data), *Post-TED* (outcomes data) and *Product Forms* that are being submitted for OMB approval.

9. Remuneration of Respondents

Respondents will not be remunerated.

10. Assurance of Confidentiality

The data collection instruments proposed for the SCTOD do not require information that could be used to directly identify transplant recipients. The CIBMTR's subcontractor, the NMDP, will utilize a unique identification (ID) registration system for transplant recipients to avoid redundant reporting of transplant recipients across transplant centers and across time. This unique ID registration system will exist within an isolated server and will use identifying information about transplant recipients provided by the transplant center to assign a unique ID number that does not contain personal identifiers. Subsequently, this unique number will be used by the transplant center and other Program components to exchange data regarding transplant recipients for purposes of reporting outcomes to the Government.

The ID registration system and the exchange of data between entities will exist within the context of the designation of the CIBMTR as a public health authority for purposes of the Health Insurance Portability and Accountability Act (HIPAA) as determined by the Office of General Counsel and Office of Civil Rights (OCR) in fulfillment of the contract requirements (HIPAA letter attached). The Office of the General Counsel has determined, and OCR concurs, that the CIBMTR meets the Privacy Rule's definition of a public health authority and is authorized by law to collect the information necessary for the SCTOD to fulfill its statutory purpose and functions. Under this analysis, transplant centers that are covered entities may disclose to the CIBMTR the individually identifiable health information collected by the SCTOD in order for the Database to comply with its statutory purposes. Additionally, the electronic systems used to create and maintain the unique ID system exist under the auspices of HRSA's Office of Information Technology (OIT) Certification and Accreditation system.

Although the data collection instruments will not request direct identifiers, by virtue of the

nature of reporting transplant outcomes required for the SCTOD contract, they will request birth dates, procedure dates, complication and event dates, and death dates. These data will be housed in secure electronic data systems which will exist with certification and accreditation from HRSA OIT.

All reports and tabulated data released to the general public will be in the form of aggregate summaries of information across patients and transplant centers.

11. Questions of a Sensitive Nature

There are no questions of a sensitive nature collected on the *TED* and *Product Forms*. The only patient-level identifying information is birth date, procedure and complication dates, and death dates. These are required for outcomes reporting for the SCTOD for HRSA. However, as detailed above, these data will be maintained in secure and protected systems. Only aggregate data summarizing transplant activity and outcomes will be included in reports published by the SCTOD on behalf of HRSA.

12. Estimates of Annualized Hour Burden

The estimate of average hour burden to complete data collection instruments is shown in Table 1. As Table 1 shows, an estimated 225 respondent transplant centers will report transplant data to the CIBMTR using the proposed reporting instruments. Reporting of transplant outcomes is required with greater frequency during the first year post-transplant. Subsequent transplant follow-up reporting is conducted annually. The cumulative number of annual *Post-TED* forms submitted by any given transplant center will increase in subsequent years. Burden of data collection and reporting will vary by transplant center, as there is a large variation in the number of allogeneic transplants performed at transplant centers across the United States.

Table 1. Estimates of Average Annualized Hour Burden

Form	Number of Respondents	Responses per Respondent	Total Responses	Hours per Response	Total Burden Hours
Baseline Pre-TED (Transplant Essential Data)	225	32	7,200	0.85	6,120
Product Form (includes Infusion, HLA, and Infectious Disease Marker inserts)	225	14	3,150	1.5	4,725
100-Day Post-TED	225	32	7,200	0.85	6,120
6-Month Post-TED	225	23	5,175	1.00	5,175
12-Month Post-TED	225	20	4,500	1.00	4,500
Annual Post-TED	225	16	3,600	1.50	5,400
Total	**225**		**30,825**		**32,040**

The Pre-TED, Product Form, 100-Day Post-TED, 6-Month Post-TED, and 12-Month Post-TED will be collected on all patients during their first year of transplant. In subsequent years, patient outcomes will be reported on the Annual Post-TED form. There will be a gradual increase in the cumulative reporting burden over time commensurate with the number of survivors for

which transplant centers must submit an Annual Post-TED.

13. Estimates of Annualized Cost Burden to Respondents

There are no direct costs to respondent transplant centers other than their time spent completing the data collection instruments. There are no capital or start-up costs for respondents related to this effort. Web-based electronic data entry mechanisms and instructions on use of the applications will be available free of charge to transplant centers by the CIBMTR.

14. Estimate of Annualized Cost to the Federal Government

HRSA has planned and allocated resources for the efficient and effective management and use of the information to be collected, including the processing of the information in a manner that shall enhance the utility of information to agencies and the public. HRSA estimates an annual investment of approximately $3.5 million to be spent on all aspects of the contract for the operation of the Stem Cell Therapeutic Outcomes Database, including data collection, maintenance of Web based data collection systems, ongoing training for entities submitting data, data analysis, and preparation of reports.

15. Changes in Burden

This is a new collection of information.

16. Time Schedule, Publication, and Analysis Plans

The data collected using the instruments outlined above will populate a database for the SCTOD and will be used for numerous analyses, reports, and publications.

Data collected for the SCTOD will be shared with other components of the C.W. Bill Young Cell Transplantation Program in fulfillment of the goals and statutory charge of the Program. The electronic systems being implemented by the CIBMTR will be used to provide outcomes data to HRSA, the umbilical cord blood banks, and the transplant programs themselves. The system will accommodate pre-programmed queries for outcomes reporting and allow transplant centers and other appropriate entities to generate customized reports. Applications are being built to disseminate data regarding the quality characteristics of transplanted stem cell products to and from transplant centers, collection facilities, and cord blood banks.

The outcomes database will also be used to prepare reports about the C.W. Bill Young Cell Transplantation Program for the Secretary, the Advisory Council on Blood Stem Cell Transplantation, HRSA, and the public.

The CIBMTR will prepare an annual Transplant Center Specific Outcomes Report for the Program outlining the specific survival rates for all transplant centers in the U.S. This is an extremely important report for patients and physicians, both for improving quality of care at transplant centers and for helping patients and their physicians make well informed choices about which transplant centers are most appropriate for each patient.

In addition, as required in section 379A(d) of the Act, the outcomes database shall make relevant scientific information that does not contain individually identifiable information available to the public. This information will be provided by CIBMTR in the form of summaries and data sets to encourage medical research and to provide information to transplant programs, physicians, patients, and cord blood banks.

17. Exemption for Display of Expiration Date

The expiration date will be displayed.

18. Certifications

This information collection fully complies with 5 CFR 1329.9. The certifications are included with the package.

List of Acronyms

ASBMT	American Society for Blood and Marrow Transplantation
CIBMTR	Center for International Blood and Marrow Transplant Research
EBMT	European group for Blood and Marrow Transplantation
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	U.S. Food and Drug Administration
HCT	Hematopoietic cell transplantation (i.e., bone marrow or cord blood transplantation or blood stem cell transplantation)
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human Leukocyte Antigen
HRSA	U.S. Health Resources and Services Administration
JACIE	Joint Accreditation Committee of the International Society for Cellular Therapy
NMDP	National Marrow Donor Program
OCR	Office of Civil Rights
OIT	HRSA's Office of Information and Technology
OMB	U.S. Office of Management and Budget
Program	C.W. Bill Young Cell Transplantation Program
SCTOD	Stem Cell Therapeutic Outcomes Database
TED	Transplant Essential Data