Supporting Statement A

Stem Cell Therapeutic Outcomes Database

OMB Control No. 0915-0310

Terms of Clearance: None.

A. JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The Health Resources and Services Administration (HRSA) is requesting that the Office of Management and Budget continue 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 (CWBYCTP). The information collection activities described in this submission are reauthorized by the Stem Cell Therapeutic and Research Reauthorization Act of 2015, Public Law 114–104, which was signed into law on December 18, 2015 (legislation attached). 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 (CWBYCTP). The SCTOD is required to collect data for all allogeneic[1] hematopoietic stem cell transplantation (HSCT) for reconstitution using cells from either donors not related to the patient or donors related to the patient, and the

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

instruments contained in this information collection request provide the data elements required to fulfill the contractual requirements of the SCTOD. 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 HSCT, both related and unrelated, where either the donor or the recipient resides in the U.S.

HRSA is responsible for establishing and maintaining a standardized database (SCTOD) of allogeneic (related and unrelated donor) marrow and cord blood transplants performed in the United States. The Stem Cell Act requires that transplant centers performing these transplants provide patient outcomes data to this national system. Data collection on patient outcomes is required in order to be in compliance with the requirements of the Act and is critical to the successful implementation and maintenance of the CWBYCTP. Collected data are used to understand transplant activity including trends in numbers of transplantations and emerging uses of cells, report outcomes, and for research use, as outlined in the Stem Cell Act.

In this submission of the information collection request, no new forms are being added. Existing instruments have been revised to reflect changes in transplant practice over time, and the need to accommodate these changes in reports and analyses of the data. Specifically the Post-TED form (used at 100-days, six months, and annually) is being revised in this submission. The portion of the Product Form related to confirmation of Human Leukocyte Antigen (HLA) typing has minor changes to the identification and date fields to allow this form to more flexibly capture HLA typing data. The amount of time required to complete this form is unchanged. The Pre-TED form remains unchanged from the previously approved OMB submission.

2. Purpose and Use of Information

The overall purpose of the data collection is to fulfill the legislative mandate to establish and maintain a standardized database of allogeneic (related and unrelated donor) marrow and cord blood transplants performed in the United States or using a donor from the United States. The data collected also meets the requirements of the Act to provide relevant scientific information not containing individually identifiable information available to the public in the form of summaries and data sets. The data will be made available to encourage medical research and to provide information to transplant programs, physicians, patients, and entities awarded a contract under section 379 donor registries, and cord blood banks. Further, the data collected will also provide information for the required annual report on blood stem cell transplantation to the HHS Secretary.

The data collection is conducted regularly from an estimated 200 U.S transplant centers to collect data on approximately 9,600 patients annually who underwent allogeneic transplant. The data collection instruments included in this package are the *Pre-TED* (Transplant Essential Data*), Disease Classification*, *Post-TED* (100-day, 6 month, 1 year, and annual) 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. Graft characteristic data for cord blood units and unrelated donor grafts facilitated by the CWBYCTP are collected within fourteen days of HSCT on the *Product Form*. This form includes 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* 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 CWBYCTP.

3. Use of Improved Information Technology

The system for the outcomes database is electronic. Implementation of the data collection instruments includes reporting forms that can be downloaded or can be submitted electronically using the Web-based interface, called FormsNet 3.0. All U.S. HCT centers provide their data through the electronic system. Data collection instruments are accompanied by an instructions manual. HRSA is acutely aware of the need to minimize the burden of data collection for transplant centers, and the electronic system is designed to streamline data submission wherever possible through smart navigation tools, electronic validation and autopopulation of previously submitted fields. Transplant centers collect, store, and report information using a variety of mechanisms ranging from paper forms and electronic software packages to Web interfaces.

FormsNet 3.0 allows for remote data entry of all transplant baseline and follow-up data by the transplant centers. This system is 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; and
- tools for monitoring accuracy and processes.

The system includes automated validation checks within and between forms; automatically generated error reports; field-level saving and field-level audit trails; review functions for center supervisors; forms due reporting; and the flexibility to add additional features. FormsNet 3.0 is 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.*

4. Efforts to Identify Duplication

HHS is the primary federal entity authorized to oversee the national system of blood stem cell transplantation. Within HHS, HRSA DoT is responsible for administering the CWBYCTP. To the best of our knowledge, no other entity within the federal government has implemented or will implement a system used for data collection within the United States for HCT. For purposes of this database, all data collection for the HCT outcomes is collected using a single set of instruments that encompasses all allogeneic transplants performed in the United States, including umbilical cord blood transplantation. No other known organization in the United States currently collects these data in a systematic way that would represent a duplication of effort.

5. Impact on Small Businesses or Other Small Entities

No small businesses will be involved in the data collection.

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, as amended by the Stem Cell Therapeutic and Research Reauthorization Act of 2015, Public Law 114–104 (the Act). The Act mandates the collection of data for the outcomes database. The data that are 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 regarding data that would be essential to understand the broad requirements of the CWBYCTP. These requirements include numbers of transplants facilitated by the CWBYCTP, 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. A representative forum of U.S. HCT centers, scientists, patients, and payers participates in discussion and revision of data elements needed to support the center specific analysis every other year.

HRSA will continue to collect data from HCT centers on the following schedule: baseline, 100 days after HCT, six months after HCT, one year after HCT, annually for six years after HCT and biennially thereafter, and, if the patient dies, cause of death data. Baseline data are collected within 30 days of the HCT and includes patient demographics, disease characteristics, and status,

co-morbidities, HCT procedure characteristics including preparative regimen and GVHD prophylaxis, graft source, donor type and degree of HLA matching and graft manipulation. Graft characteristic data for cord blood units, including infused cell dose, are collected within 60 days of HCT. These data are collected on the *Pre-TED, Disease Classification, and Product* forms. Data collected at 100 days and beyond include hematopoietic recovery and engraftment[2], serious complications including Graft-Versus-Host-Disease (GVHD) and second cancers, disease status, survival status, and cause of death. Subsequent procedures are collected on HCT recipients. These data are due within 60 days of achieving the milestone date. These data are collected on the *Post-TED* form (the *Post-TED* form will be completed for all time points at or beyond 100-days after transplantation).

These requirements are well established in U.S. transplant centers and represent a balance between collecting sufficient data to analyze HCT outcomes and minimizing the data submission burden.

Collecting less information than what is contained 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

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.

outcomes at various time points 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 CWBYCTP;
- what types of transplants are being performed in the United States and for what clinical indications, and the outcomes of those transplants; and
- outcomes of blood stem cell transplantation across transplant centers.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The request fully complies with the regulation.

8. Comments in Response to the Federal Register Notice/Outside Consultation

Section 8A:

The 60-day notice required in 5 CFR 1320.8(d) was published in the *Federal Register* on March 7, 2019 (Volume 84, Number 45, pages 8334-8335). No comments were received.

Section 8B:

Data collection instruments are reviewed on an established timeline, at least every three years, to ensure that the most relevant data are being collected. Broad stakeholder participation in this process is accomplished through the Working Committees established by the SCTOD contractor, cord blood banks, other CWBYCTP contractors, and collaborative relationships with other relevant organizations including: Eurocord, EBMT, WBMT, ASTCT, and FACT. Similarly, transplant centers are represented in the form revision process, especially to meet the needs of the Transplant Center-Specific Survival Analysis. Data collection instruments are accompanied by a detailed data dictionary that is updated regularly.

In December 2007, the SCTOD contractor implemented a standard dataset developed in collaboration with national and international partners. The contractor subsequently worked with the American Society for Blood and Marrow Transplantation (ASBMT) Quality Outcomes Committee and experts in the HCT community to refine this dataset to better allow assessment of HCT outcomes across transplant centers (center-specific outcomes), such as including data on pre-HCT co-morbidities. This standard data set comprises the current OMB-approved TED forms and is collected on all patients. Collection of data captured on TED forms is a requirement for HCT center accreditation by the Foundation for the Accreditation of Cellular Therapy (FACT) and its European counterpart, the Joint Accreditation Committee of the International Society for Cellular Therapy and the EBMT (JACIE).

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 CWBYCTP. Since initially arriving at the standard dataset

described above, the SCTOD contractor has continued to work with the national and international community to maintain those standards. These data elements are represented on the *Pre-TED* (baseline data), *Disease Classification*, *Post-TED* (outcomes data), and *Product Forms* that are being submitted for continued OMB approval.

The effort is underway to promote international harmonization of HCT data standards and participates in the annual data standards review of the European Group for Blood and Marrow Transplantation (EBMT) and the Worldwide Network for Blood and Marrow Transplantation (WBMT) Transplant Center Committee. Broad acceptance of standards facilitates acquisition of data regarding HCTs done outside the U.S. with U.S. products. The SCTOD contractor will continue to work with ASBMT, EBMT, WBMT, the Clinical Working Group of the World Marrow Donor Association (WMDA), cord blood banks (using the Cord Blood Data Working Group), and other CWBYCTP members. This collaboration will allow the SCTOD contractor to achieve consensus on any revisions to the standard dataset and to ensure it meets the needs of the CWBYCTP to fulfill its contractual requirements. These requirements include disseminating data, performing center-specific analyses, creating cord blood inventory and adult donor registry models, and capturing data elements critical for understanding HCT outcomes while minimizing the data submission burden for HCT centers. The SCTOD contractor will continue to work with the Single Point of Access – Coordinating Center (SPA-CC) and The National Marrow Donor Program (NMDP) Histocompatibility Advisory Group to ensure that HLA data reflect current HLA matching algorithms.

9. Explanation of any Payment/Gift to Respondents

Respondents will not receive any payments or gifts associated with completing these forms for the CWBYCTP.

10. Assurance of Confidentiality Provided to Respondents

The data collection instruments used for the SCTOD do not require information that could be used to identify transplant recipients directly. The SCTOD contractor utilizes 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 exists within an isolated server and uses 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 is used by the transplant center and other CWBYCTP 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 exists within the context of the designation of the SCTOD contractor, Medical College of Wisconsin's Center for International Blood and Marrow Transplant Research (CIBMTR), as a public health authority for purposes of the Health Insurance Portability and Accountability Act (HIPAA) as determined by the HHS Office of General Counsel and Office of Civil Rights (OCR) in fulfillment of the contract requirements (PHA letter attached). The Office of the General Counsel has determined, and OCR concurs, that the SCTOD contractor 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 SCTOD contractor the individually identifiable health information

collected by the SCTOD 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 do not request direct identifiers, by the nature of reporting transplant outcomes required for the SCTOD contract, they request birth dates, procedure dates, complication and event dates, and death dates. These data are housed in secure electronic data systems, which exist with certification and accreditation from HRSA OIT.

Data will be kept private to the extent allowed by law. A Certificate of Confidentiality covers this data collection from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify a patient in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless the patient has consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except if there is a federal, state, or local law that requires disclosure. Laws of this nature include those designed to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings (see below); if the patient has consented to the disclosure, including for medical treatment; or if it is used for other scientific research as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or

program evaluation by Health Resources and Services Administration (HRSA) or National Institutes of Health (NIH) which is funding this project or for information that must be disclosed in order to meet the requirements of the Food and Drug Administration (FDA).

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

11. Justification for Sensitive Questions

There are no questions of a sensitive nature, except for race and ethnicity. These questions are required to support analysis of demographic subgroups. 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. However, as detailed above, these data are maintained in secure and protected systems. Only aggregate data summarizing transplant activity and outcomes are included in reports published by the SCTOD.

12. Estimates of Annualized Hour and Cost Burden

The estimate of average hour burden to complete data collection instruments is shown in 12A. SCTOD collects transplant data from an estimated 200 U.S. transplant centers using these 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. Over time there is an expected increase in the number of recipients for whom data are reported as an increasing number of transplants are performed annually and survivorship after transplantation improves. 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. The overall burden for this data collection has decreased due to streamlining of response options on the Post-TED form.

12A.

Estimated Annualized Burden Hours

Type of Respondent	Form Name	No. of Respondents	No. Responses per Respondent	Average Burden per Response (in hours)	Total Burden Hours
Data Manager	**Disease Classification**	200	48	0.43[3]	4,160
Data Manager	**Baseline Pre-TED (Transplant Essential Data)**	200	48	0.68[2]	6,560
Data Manager	**Product Form (includes Infusion, HLA, and Infectious Disease Marker inserts)**	200	45	1.00	9,000
Data Manager	**100-Day Post-TED**	200	48	0.85	8,160
Data Manager	**6-Month Post-TED**	200	43	0.85	7,310
Data Manager	**1-year Post-TED**	200	40	0.65	5,200
Data Manager	**2-year Post-TED**	200	34	0.65	4,420
Data Manager	**3+ years Post-TED**	200	172	0.52[4]	17,773
	Total*	**200**			**62,583**

*The total of 200 is the number of centers completing the form. The same group of 200 centers completes each of the forms.

[2] The decimal is rounded down, and the actual number is .683333333.

[3] The decimal is rounded down, and the actual number is .433333333.

[4] The decimal is rounded up, and the actual number is .516667.

12B.

Estimated Annualized Burden Costs

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs

Data Manager	62,583	$18.25	$1,142,140
Total	62,583		$1,142,140

Hourly Wage Rate based on the United States Department of Labor, Bureau of Labor Statistics: (https://www.bls.gov/news.release/archives/ecec_06082018.htm)

13. Estimates of other Total Annual Cost Burden to Respondents or Recordkeepers/Capital Costs

Other than their time, there is no cost to respondents.

14. Annualized Cost to the Federal Government

The cost of the study for government personnel is estimated at five years for an estimated annualized cost per year of $57,662 (30 percent full-time equivalent at per year; GS-14 Step-5 salary level with 48% fringe benefit included [https://www.opm.gov/policy-data-oversight/pay-leave/salaries-wages/salary-tables/18Tables/html/DCB.aspx]). The annual estimated government cost for a contract to carry out this study is approximately $4 million to be spent on all aspects of the contract for the operation of the Stem Cell Therapeutic Outcomes Database.

15. Explanation of Program Changes or Adjustments

This is a revised collection of information with a reduction in the overall hour burden inventory from 68,660 hours to 62,583 hours due to the proposed revisions to the forms.

16. Plans for Tabulation, Publication, and Project Time Schedule

Publication: The data collected using the instruments outlined above populate a database for the SCTOD and are used for numerous analyses, reports, and publications. Data collected for the SCTOD are shared with other components of the CWBYCTP in fulfillment of the goals and

statutory charge of the CWBYCTP. The data collected is shared to HRSA and reports from the data are shared to umbilical cord blood banks and the transplant programs. The outcomes database is also used to prepare reports about the CWBYCTP for the Secretary, the Advisory Council on Blood Stem Cell Transplantation, HRSA, and the public. One of the main reports produced under SCTOD is the Transplant Center-Specific Survival Report, which outlines 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 makes relevant scientific information that does not contain individually identifiable information available to the public. This information is 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. The Transplant-Center Specific Survival Report and the U.S. Transplant Activity Report are available on the HRSA website, and the de-identified dataset is available upon request.

Analysis Plan: The report will provide tabulations at the national level, and for relevant subpopulations, including age groups, gender, racial and ethnic groups, and broad disease group. It will include an executive summary along with detailed findings of factors related to center specific survival and/or transplant activity that occurred in the United States. This information collection will not use statistical methods such as sampling, imputation, or other statistical estimation techniques.

Time Schedule: The center-specific survival analysis report is delivered to HRSA annually in the fall and made available to the public each December. The data collection is ongoing, and the maximum number of years for clearance (3 years) is requested.

17. Reason(s) Display of Expiration Date is Inappropriate

The OMB number and Expiration date will be displayed on every page of every form/instrument.

18. Exceptions to Certifications for Paperwork Reduction Act Submissions

There are no exceptions to the certification.