2.4 Stem Cell Therapeutic Outcomes Database

The Stem Cell Therapeutic Outcomes Database (SCTOD) is the fourth component of the C.W. Bill Young Cell Transplantation Program. It is administered by the Center for International Blood and Marrow Transplant Research (CIBMTR) at the Medical College of Wisconsin. The goal of the SCTOD is to collect, store and analyze data about bone marrow, peripheral blood stem cells (PBSC) and cord blood transplants and provide information for research to help improve outcomes for patients.

2.4.1 Background and Purpose

The purpose of the SCTOD is to collect data on all allogeneic (related and unrelated donor) hematopoietic stem cell transplants (HCTs) done in the United States to advance the field. It also collects information on all HCTs done with products received through the C.W. Bill Young Cell Transplantation Program but performed outside the United States.

Another part of the SCTOD contract with HRSA requires establishing a related donor-recipient sample repository in addition to the existing repository for unrelated donor-recipient samples. This new feature was launched in December 2007 along with the FormsNetTM 2.0 electronic data collection system.

2.4.2 Responsibilities

In its role as SCTOD contractor, CIBMTR:

- Provides an electronic database of scientific information about outcomes of allogeneic bone marrow, PBSC and cord blood transplants, to be used by researchers and health care professionals.
- Establishes a quality control program for the database functions including:
  - Quality assurance of data
  - Performance monitoring
  - Training and assistance to data contributors
- Collects and analyzes information about:
  - Medical diagnoses for which transplant may be a treatment option
  - Transplant preparation and procedures
  - Patient outcomes
  - Patients' quality of life
  - New uses for cells found in bone marrow, peripheral blood, and umbilical cord blood
- Works with transplant centers to reduce the burden of data reporting.
- Reports information about:
  - The need for donors and CBUs to policymakers, based on data from the Program.
  - Cost-benefit analyses of the size, composition and growth rate of the NCBI and Adult Donor Registry, in order to provide specific recommendations for recruitment activities, and determine the probability that patients of specific racial/ethnic groups will find suitable HLA-matched cells.
  - Annual patient outcomes for each transplant center.
  - Transplant research to the public, researchers, and health care professionals.
- Stores blood samples from donors and patients that will be used for transplant research.

2.4.3 What is the Center for International Blood and Marrow Transplant Research (CIBMTR)?

The CIBMTR was created to collaborate with the worldwide scientific community, to advance the fields of hematopoietic (blood) stem cell transplantation (HCT) and cellular therapy research. As a combined research program of the Medical College of Wisconsin (MCW) in Milwaukee and

the National Marrow Donor Program (NMDP) in Minneapolis, the CIBMTR facilitates important clinical research to increase survival and enrich the quality of life for thousands of HCT patients.

The CIBMTR is a unique resource of data and statistical expertise. Its services are available to the scientific community for addressing important issues in HCT. It is made up of two parts: a network of more than 450 transplant centers that share data on HCT outcomes, and a Statistical Center that maintains a clinical database with information about more than 300,000 transplants (as of the end of 2009). This database and the analytic support provided by the Statistical Center have led to successful completion of hundreds of studies that have had an important impact on clinical practice.

The CIBMTR has campuses in Milwaukee and Minneapolis, with staff consisting of more than 135 medical, statistical, clinical research and administrative personnel, including 13 MD Scientific Directors with advanced training in biostatistics and related fields, 15 Masters-level biostatisticians, and seven PhD statisticians.

CIBMTR has a system of committees that was designed to obtain a broad range of input, to ensure that its activities match the priorities of the scientific community it serves. As of December 2009, there were 225 observational research studies in progress using the CIBMTR databases. The research agenda of CIBMTR is accomplished within the framework of 19 Working Committees that are responsible for:

- Designing and conducting studies relevant to their subject area and involving CIBMTR data, statistical resources, networks and/or centers;
- Considering proposals to use CIBMTR data for studies pertinent to their subject area;
- Periodically assessing and revising relevant sections of CIBMTR data collection forms;
- Planning and conducting workshops at CIBMTR meetings; and
- Setting priorities for future CIBMTR studies.

CIBMTR serves the public and the biomedical community in diverse and evolving ways. One is through its historic role of providing estimates about how well HCT will work for a particular condition by analyzing the information on past transplants from many centers. It also determines the potential benefits and adverse effects of emerging technologies and identifies uncommon events that may occur in long-term transplant survivors. Statistical Center personnel have a strong record of expert, innovative analyses of these and other data. CIBMTR Working Committees include representatives from hundreds of HCT centers around the globe. CIBMTR data and statistical resources are sought and used by scientists, clinicians, health policy-makers and the public.

2.4.4 What is Hematopoietic Stem Cell Transplantation (HCT)?

Hematopoietic (blood) cell transplants are widely used to treat several malignant and non-malignant diseases. They include hematologic malignancies (e.g. leukemia, lymphoma, multiple myeloma and others), neuroblastoma, ovarian and testicular cancer, myelodysplasia (MDS), aplastic anemia, congenital immune deficiencies, inborn errors of metabolism and recently, autoimmune diseases.

HCT may use cells from a related or unrelated donor (allogeneic transplants) or from patients themselves (autologous transplants). The cells may be collected from bone marrow, peripheral (circulating) blood or umbilical cord blood. Before the cells are infused into the recipient, chemotherapy and/or radiation (conditioning) is used to suppress the recipient's immune system so that the donor cells will engraft (become a working part of the recipient's body) and/or eradicate the malignant disease.

Conditioning processes (therapy given to prepare the recipient for transplantation) vary and are evolving rapidly, as are the strategies for collecting donor cells. New techniques are also being

developed for treating graft-versus-host disease (GVHD, a common complication of transplantation) and for treating patients after their HCT. New technologies hold promise for decreasing the toxicity of chemotherapy, while maintaining or even enhancing the anti-tumor effects of the transplant. This has led to wider use of HCT for treating more patients. HCT can be life-saving in that it cures at least some patients who are considered incurable with other therapies.

HCT is also intensive, costly and carries high risks of morbidity (side effects) and mortality (death). Risks early in the process include infection, mucositis (painful inflammation of the lining of the digestive tract), non-engraftment (failure of the cells to grow in the recipient), acute GVHD and organ toxicity. Transplant-related mortality ranges from 3 percent to greater than 50 percent, depending on the underlying disease, the recipient's age and medical status and the type of graft. Most transplant-related deaths occur in the first year after the HCT.

HCT is also associated with a risk for long-term negative physical, psychological and psychosocial effects. Some of the potential later complications include chronic (ongoing) GVHD, infection, respiratory diseases, cataracts, bone degeneration, endocrine disturbances, cognitive difficulties, relapse and therapy-related cancers. These late effects lead to persistently high death rates for HCT recipients and may negatively affect their performance of daily activities, interpersonal relationships and sense of well-being.

The challenge for physicians is to identify the patients who are most likely to benefit from HCT and to select the treatment strategies most likely to lead to good outcomes. The challenge for clinical scientists is to pursue the most promising avenues for improving outcomes in the most efficient manner. The CIBMTR plays a vital role in providing the information they need to meet these challenges.

2.4.5 What is Outcomes Analysis?

Assessing HCT outcomes is challenging for many reasons, including the following:

- The diseases treated with HCT are uncommon, so statistical analysis is difficult.
- New HCT technologies are being rapidly developed, so the results of some clinical (investigational) trials may be obsolete before they are even published.
- Some important HCT issues cannot be tested with randomized trials. These include the influences of HLA matches or how gene profiles affect the success of a transplant.
- Most clinical trials focus on short- and intermediate-term outcomes (1-5 years). Yet, HCT may have important effects, such as therapy-related cancers, that occur many years after transplantation.

A database that includes the results of research from many centers (observational database), such as the one managed by CIBMTR for the SCTOD, helps scientists understand HCT outcomes by addressing questions that cannot be studied through randomized trials or single transplant center studies. These include:

- Describing HCT results for particular diseases and patient groups;
- Determining what factors are most important in a patient's prognosis;
- Defining what will vary between centers as far as diagnosis and practice, and how that may affect outcomes;
- Evaluating long-term outcomes, including quality of life (QOL); and
- Developing analytic approaches to evaluating HCT outcomes.

An observational database can be an asset in planning clinical trials. It helps by: 1) identifying the most promising questions (hypothesis generation); 2) providing realistic estimates of baseline outcomes and whether enough patients in the appropriate groups might be available for the study (eligibility criteria); and 3) allowing different statistical designs to be simulated. An

observational database can also be used to study whether the results of one study can be generalized to other patient groups who did not participate in that study.

Analyzing HCT outcomes poses challenges that cannot be met by standard statistical methods. They include:

- The complexity of creating statistical models for the post-HCT period, when patients are transitioning between numerous states of health, including episodes of engraftment, GVHD, relapse, and a variety of post-HCT therapies.
- Competing risks that must be accounted for in the statistical analysis. These result when the occurrence of one outcome (e.g., death from regimen toxicity), prevents the occurrence of another (e.g., relapse).
- Secondary variables, such as GVHD or immune suppressive treatment, which may change over time and affect the outcomes at different times.
- Treatments started at varying stages in the disease for different patients.
- Potential effects and biases in treatment assignment from one center to another (center effects).
- Patients for whom HCT was intended but not delivered because of intervening medical problems.

These statistical problems require development or extension of new statistical tools by investigators with expertise in both the clinical and statistical challenges of HCT.

2.4.6 CIBMTR Data Collection

Data collected for the SCTOD includes:

- Allogeneic HCTs performed in the United States using related or unrelated donors;
- Allogeneic HCTs using U.S. donors, whether the transplant is performed in the United States or elsewhere; and
- Use of allogeneic hematopoietic stem cells for emerging clinical applications other than hematopoietic cell recovery.

2.4.6 1 Privacy and Confidentiality

CIBMTR is fully committed to and appreciates the importance of maintaining the privacy and confidentiality of all patients and donors. CIBMTR and NMDP are fully compliant with Federal Regulations regarding privacy and confidentiality, including the Common Rule and the Privacy Rule.

The SCTOD contract authorized CIBMTR as a Public Health Authority to collect the information needed by the SCTOD. HCT centers, regardless of their status as a “covered entity,” are allowed to disclose protected health information to CIBMTR without an individual’s written consent or authorization, to allow CIBMTR to fulfill its statutory obligations as a Public Health Authority.

In addition to reporting to the government about the C.W. Bill Young Cell Transplantation Program, CIBMTR is also expected to use the data collected for the Program, whenever possible, for research to advance the field. All observational studies use existing data from the records of patients treated in participating CIBMTR institutions. The CIBMTR does not direct or suggest how patients in participating institutions are treated. The observational database of the CIBMTR and the studies performed using this database have been reviewed and approved annually by the Institutional Review Board (IRB) of MCW since 1987, in compliance with the Common Rule for the protection of human subjects.

Physical and technical security measures at CIBMTR comply with federal security standards defined by the SCTOD contract. The CIBMTR information network infrastructure is completely segregated from other departments at MCW. A systems security plan was developed, and in December 2008, CIBMTR achieved HRSA Office of Information Technology Authority to Operate based on documentation provided since October 2006.

2.4.6.2 Data Collection Standards

Basic information is collected for all allogeneic and autologous HCTs on a form called the Transplant Essential Data (TED) form. TED forms were developed by CIBMTR in collaboration with the European Group for Blood and Marrow Transplantation (EBMT). This minimizes work for centers that participate in both organizations (approximately 30 percent of CIBMTR centers) and allows for better collaboration between the two organizations. The TED forms were revised to accommodate the needs of the SCTOD with input from representatives of the EBMT, Asian-Pacific Blood and Marrow Transplant Group, Australia-New Zealand Registry, the ASBMT, FACT, and other national and international HCT organizations. TED forms represent international consensus on a basic data set for all HCT recipients.

The data collection forms required by the SCTOD include:

- Pre-Transplant Essential Data Form
- Post-Transplant Essential Data Form
- Unique ID Assignment Form
- Recipient Death Form

The following forms are also required in some cases, including cord blood and related donor transplants:

- Infectious Disease Markers
- Confirmation of HLA Typing
- Hematopoietic Stem Cell Transplant (HCT) Infusion

CIBMTR data collection forms can be found at:
http://www.cibmtr.org/DataManagement/DataCollectionForms/index.html.

An electronic data collection system, FormsNet™ 2.0 (a Web-based application designed specifically for the SCTOD), is used to provide a single electronic platform to collect all data requested by the CIBMTR. FormsNet2 is available to all U.S. transplant centers and non-U.S. CIBMTR transplant centers to help them submit the outcomes data required by the Stem Cell Therapeutic and Research Act of 2005.

FormsNet2 allows bi-directional communication between centers, including handling notifications for expected or missing data. It includes automated validation checks within and between forms, and it automatically generates error reports. In the future, FormsNet2 will make pre-programmed queries available to transplant centers for several of the outcomes reports and will allow customized reports to be produced.

2.4.6.3 Data Collection Efforts of CIBMTR

The CIBMTR collects data on large numbers of transplant recipients every year, including information on new patients and follow-up information on previously reported patients. In the past, the data came from two sources: CIBMTR centers, which voluntarily registered consecutive transplant recipients; and NMDP transplant centers that were required to provide comprehensive outcome data on all transplants facilitated by NMDP.

Now, all U.S. transplant centers are required to submit outcomes data on allogeneic transplants to a single national registry: CIBMTR. CIBMTR continues to receive voluntarily submitted data from its international centers and from centers performing autologous transplants not covered by the new law. Collection of this new level of data (SCTOD pre- and post-Transplant Essential Data) began on December 3, 2007. The system was not available to 100 percent of U.S. centers until early 2008, so data received via the new electronic system was not fully representative of all contributing centers until then.

A list of institutions that are reporting data to CIBMTR is in Appendices B and C. CIBMTR estimates that it now collects data on nearly all allogeneic HCTs done in the United States. It also receives data on about 25 percent of allogeneic transplants done elsewhere and about 60 percent of autologous HCTs done in North and South America through the end of 2008. With the launch of the C.W. Bill Young Cell Transplantation Program, CIBMTR began collecting data on all allogeneic HCTs in the United States in 2008.

Figure 19 shows the number of allogeneic transplants done per year since data collection began in 1970, and autologous transplants done since data collection began in 1990.

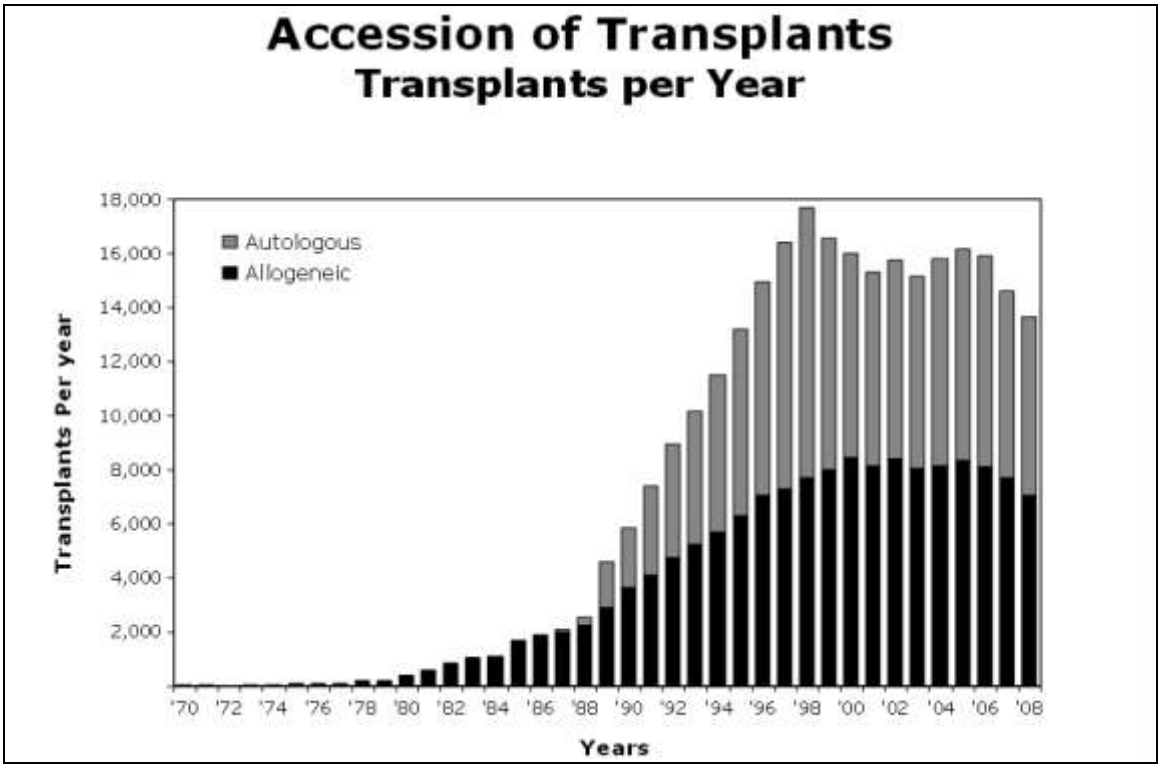

Figure 19. Number of transplants per year registered with the CIBMTR since it began collecting allogeneic transplant data in 1970

Figure 20 shows cumulative information on related donor transplants, autologous transplants, and unrelated donor transplants facilitated through NMDP since 1987.

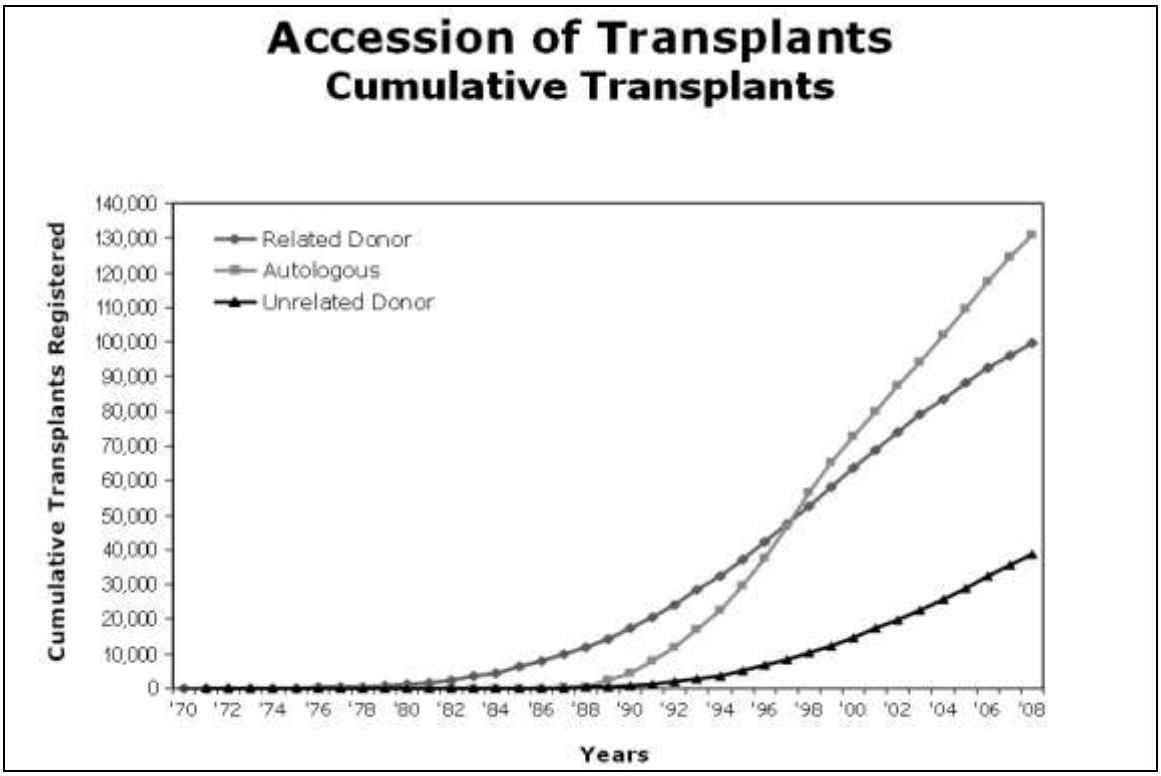

Figure 20. Cumulative totals for registered transplants

2.4.6.4 Overall Data Collection

The following tables summarize the distribution of HCT by disease for which data was collected and the quantity of data collected by CIBMTR. Along with Figures 19 and 20 in the previous section, they include information about allogeneic transplants since 1970 and autologous transplants done since 1989.

Table 9 shows the distribution of transplants worldwide by disease available in the CIBMTR Research Database.

Disease	2008-2009 Allogeneic[a]	2008-2009 Autologous	Cumulative Allogeneic	Cumulative Autologous
Acute lymphoblastic leukemia	3,293	32	27,059	1,549
Acute myelogenous leukemia	6,032	403	42,594	7,552
Chronic myelogenous leukemia	1,859	1	26,996	730
Chronic lymphocytic leukemia	650	10	3,067	607
Hodgkin disease	87	1,626	1,182	15,733
Non-Hodgkin lymphoma	1,446	3,795	10,650	37,565
Plasma cell disorders	165	6,150	3,100	34,791

[a] Includes allogeneic transplants [IBMTR] since 1970, allogeneic and autologous transplants [ABMTR] since 1989, NMDP since 1987; registration began in 1991 and comprehensive data collection in 1992; data for 1989-90 were collected retrospectively.

Disease	2008-2009 Allogeneic[a]	2008-2009 Autologous	Cumulative Allogeneic	Cumulative Autologous
Breast cancer	(12)	83	181	23,289
Neuroblastoma	9	418	183	3,411
Ovarian cancer	1	20	23	1,708
Melanoma	-	-	48	59
Lung cancer	-	5	10	231
Sarcoma (soft tissue, bone and other)	(1)	5	37	703
Ewing sarcoma	4	10	75	813
Wilm tumor	-	34	7	307
Myelodysplastic syndromes	2,170	7	12,871	251
Other leukemia	394	6	2,085	394
Medulloblastoma	-	138	5	826
Germ cell tumor	2	67	12	690
Brain tumors	(1)	80	4	1,184
Testicular cancer	1	122	9	1,410
Other malignancies[b]	26	198	1,085	1,498
Autoimmune diseases[c]	10	40	69	388
Severe aplastic anemia	1,461	2	10,143	17
Inherited erythrocyte abnormalities	29	(1)	4,865	4
SCID and other immunodeficiencies[d]	390	2	3,768	6
Inherited disorders of metabolism	218	-	1,884	4
Histiocytic disorders	181	1	818	8
Other non-malignancies	50	12	380	333
TOTAL	**18,464**	**13,266**	**153,210**	**136,061**

Table 9. Distribution of transplants worldwide by disease available in the CIBMTR Research Database through 2009 (Data continue to accrue in this reporting period)

Table 10 shows the number of transplants worldwide for which data were submitted to CIBMTR.

Type of Transplant	2008	2009	Life-to-Date*
Allogeneic	8,749	9,169	178,841
Autologous	7,836	8,501	149,759
TOTAL	**16,585**	**17,670**	**328,600**

Table 10. Number of transplants worldwide for which data were submitted to CIBMTR by year

b Includes retinoblastoma, head and neck tumors, mediastinal neoplasms, GI tract tumors, pancreatic cancer, hepatobiliary, kidney and urinary tract tumors, prostate cancer, cervical, uterine cancer, vaginal cancer and thymoma

c Includes multiple sclerosis (n=150), systemic sclerosis (n=91), systemic lupus erythematosis (n=75), rheumatoid arthritis (n=15), ITP (N=10), Crohn's disease (n=12) and other (n=104) in registration data

d SCID=Severe Combined Immune Deficiency