- Defining better processes for identifying unrelated matched marrow donors, peripheral blood stem cell (PBSC) donors, and cord blood units through one electronic system;
- Increasing availability of unrelated adult volunteer donors and cord blood units;
- Expanding research to improve patient outcomes.

Annually, the CIBMTR publishes HCT volumes and demographic data by transplant center and provides public access to this information available on the Program website (http://bloodcell.transplant.hrsa.gov).

As part of the contract to operate the SCTOD, the CIBMTR is required each year to perform a center-specific survival analysis comparing the one-year survival rates among US centers. The report contains transplants from both related and unrelated donors. The most recent report was finalized in November 2014 and contains information on all first allogeneic transplants performed in US centers from January 1, 2010, through December 31, 2012.

The CIBMTR has conducted four Center Outcomes Forum meetings to engage relevant stakeholders in the center specific outcomes reporting process. The most recent meeting was held in June 2014.

In addition, the Cellular Therapies for Regenerative Medicine (CTRM) data repository is an SCTOD requirement that tracks alternate uses of stem cells. The SCTOD contract mandates the collection of data on new uses of cells found in the bone marrow, peripheral blood, and umbilical cord blood for alternative therapeutic applications including regenerative medicine. CTRM is the use of cells for the treatment of diseases without the intention of replacing the recipient's hematopoietic function. These therapies are not considered BMT and include, but are not limited to: treatment of infectious, cardiovascular, rheumatologic, neurologic, musculoskeletal, and endocrinologic diseases with the intent to improve organ function without rescuing or replacing the recipient's bone marrow function. The CIBMTR anticipates that the expansion of cellular therapy field with use of not only hematopoietic derived cells, but also cells form other tissues, will only increase. The CIBMTR currently tracks CTRM cases and is expanding the capability and flexibility of data collection in this area.

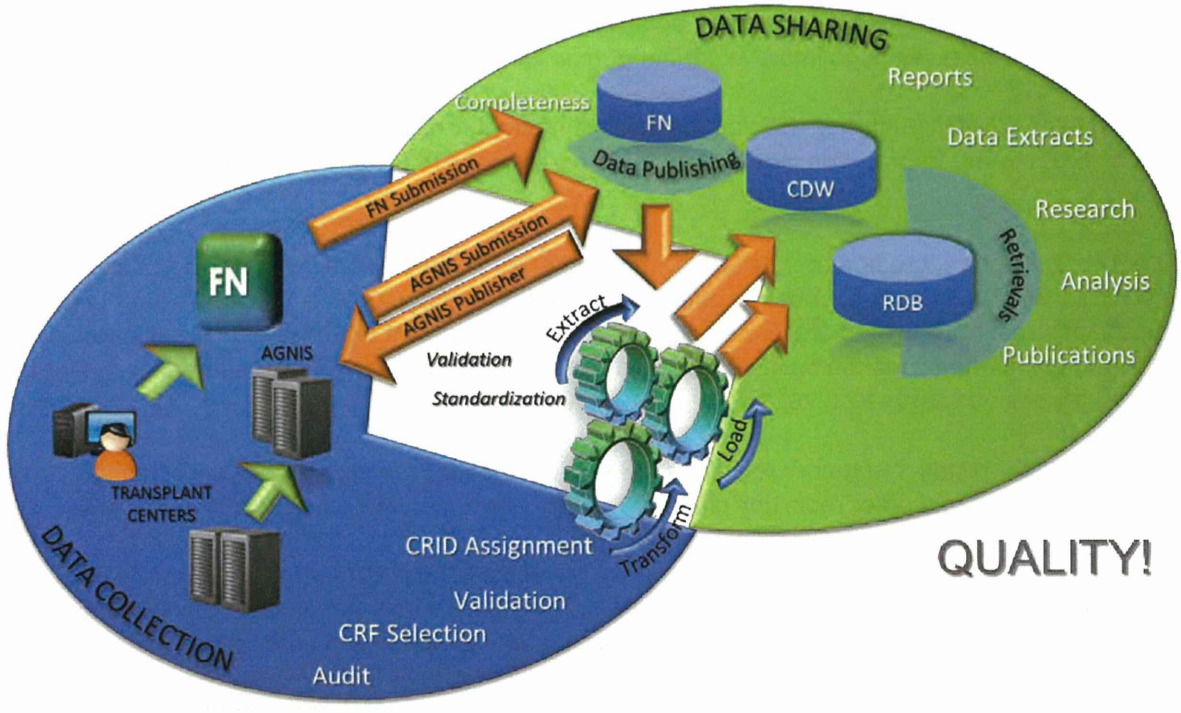
Two working groups provide oversight specific to SCTOD:

- **Cord Blood Data Working Group**. This group reviews and makes content suggestions for the cord blood outcomes reports which, utilizing CIBMTR data, help banks meet regulatory requirements and understand product quality.
- **HRSA Blood Cell Transplant Website Working Group**. This group reviews and makes content suggestions for the C.W. Bill Young Cell Transplantation website (http://bloodcell.transplant.hrsa.gov). The CIBMTR provides the HCT data for this website.

B.2.1.1.b Research Data Life Cycle

The Research Data Life Cycle (**Figure B.2.B**) describes the journey that data makes in its transformation along the CIBMTR value chain to information and knowledge from the point of capture to its ultimate use in analysis. Solutions along the Research Data Life Cycle are grouped in three general areas according to their primary function: Data Collection; Extraction, Transformation, and Load; and Data Sharing.

Figure B.2.B. Research Data Life Cycle



Research data begins at data collection when transplant centers enter the data in one of the solutions we offer to enable electronic data capture. Most centers will enter data in FormsNet, a web application now in its third generation. Centers that have implemented local or third party systems can also capture and submit data using AGNIS (A Growable Network Information System) Service. An overriding goal of these solutions is to ease data capture burden on the centers.

The CIBMTR collects data at two levels: a Transplant Essential Data (TED) level and a Comprehensive Report Form (CRF) level. The TED data set is an internationally accepted standard data set that contains a limited number of key variables for all consecutive transplant recipients. The CRF captures additional patient, disease, and treatment-related data. TED-level data, with some additional details of donor and graft characteristics, comprise the obligatory data to be submitted to the SCTOD.

Following data collection, data are pulled four times per month from FormsNet via "the Pipeline" to an Oracle staging environment that starts an Extraction, Transformation, and Load (ETL) program. During ETL, data are transformed from a native vertical schema to a horizontal, relational schema to make transformation and loading easier to manage. Data are also more rigorously validated for consistency, completeness, and uniqueness using custom logic and then further standardized and encoded for optimal statistical analysis. ETL culminates in the loading of validated data to the Research Database.

Data Sharing completes the cycle, providing data for analysis that we have collected and curated to generate research value. Depending on the need, these data are extracted from the Research Database in periodic retrievals to serve a range of research and stakeholder needs.

B.2.1.1.c FormsNet

FormsNet is the CIBMTR's web-based application for electronic submission of transplant outcomes data. The application was updated in 2014 to support the new CIBMTR colors and branding in addition to key enhancements supporting operational efficiencies. Monthly form maintenance releases began in January 2014 to update key form validations, which save time as well as improve user experience and accuracy for CIBMTR staff and FormsNet users. Additional improvements to FormsNet in 2014 include:

- **Upgrades**. The Donor module was upgraded to the FormsNet3 platform to provide autopopulation, improved navigation / validation, and overall improved user experience.
- **Enhancements**. Recipient, Donor, Clinical Trials, Audit, Forms Definition Manager, and Monitoring applications were enhanced to provide improved support and operational efficiencies.
- **Auditing support**. Enhancements were made to the applications for auditing FormsNet data against source documents at centers.
- **Monitoring support**. The Monitoring application was enhanced to provide monitoring support for an additional clinical trial.
- **Research support**. Support was provided for several prospective studies:
    - Evaluated the activity, safety, and feasibility of administration of moxetumomab pasudotox in the pre-alloHCT setting to patients with B-lineage acute lymphocytic leukemia who have pre-transplant minimal residual disease.
    - Began the process of implementing a "call tracking" package tool for the Survey Research Group to contact study subjects and collect survey data. This new tool will automate processes, saving time in the group's daily activities as well as the time needed to add new studies.
    - Aided a Health Services Research Program study funded by the Patient Centered Outcome Research Institute to develop standard care plans by utilizing call tracking.

B.2.1.1.c.1 Continuous Process Improvement (CPI)

CPI ensures timeliness and completeness of data forms submissions. Transplant centers receive CPI reports three times per year (January, May, and September), listing the number of follow-up forms that were due in the previous trimester and the number and percentage of each submitted within the trimester. A form is not officially submitted until all errors are resolved and all applicable information is submitted and approved.

To be compliant, centers must submit at least 90% of forms due for the trimester, for all unrelated donor transplants and for related donor transplants that have occurred since December 3, 2007 (**Table B.2.A**). As of September 1, 2014, 95% of US transplant centers were in compliance. The few remaining non-compliant centers enter a forms-due remediation procedure. If a center does not have current Institutional Review Board (IRB) approval information on file with the CIBMTR, it will not pass CPI even if the forms submission requirements are met.

Table B.2.A. CPI Form Submission		
Form	**Due Date**	**90% Submitted Within**
Pre-TED or Form 2000, required disease forms and/or Infection Forms	HCT date	60 days
Post-TED or Form 2100, required disease forms and/or Infection Forms	Day 100 post HCT	60 days
Post-TED or Form 2200, required disease forms and/or Infection Forms	6 months, 1 year, and 2 years on HCT anniversary	90 days
Post-TED or Form 2300, required disease forms and/or Infection Forms	Starting at year 3, annually on HCT anniversary	45 days

In addition to the CPI *recipient* forms program, there are CPI regulations for *donor* forms. The Donor Data Management Team oversees submission of these forms from NMDP donor, collection, and apheresis centers. Donor CPI reports are generated four times per year (January, April, July, and October). To be compliant, centers must submit 100% of the forms required for that CPI period.

B.2.1.1.d Research Database

Table B.2.B. Distribution of Patients in the CIBMTR Research Database (alloHCT since 1970, autoHCT since 1989)				
	Allogeneic		**Autologous**	
	TED	**CRF**	**TED**	**CRF**
Disease				
Acute myelogenous leukemia	36,196	26,012	5,707	2,412
Acute lymphoblastic leukemia	19,374	15,771	1,083	475
Chronic myelogenous leukemia	13,572	14,751	417	287
MDS / mucopolysaccharidosis	11,458	9,250	186	89
Plasma cell disorder	1,922	1,360	52,100	10,883
Lymphoma	10,137	5,991	60,224	13,068
Other malignant diseases[1]	5,551	3,527	28,201	12,171
Severe aplastic anemia	5,667	6,403	13	8
Immune deficiencies	2,197	2,711	0	0
Inherited erythrocyte disorders[2]	5,687	6,673	691	175
Graft Source				
Bone Marrow	44,705	55,183	9,931	5,925
Peripheral Blood	53,814	26,561	127,492	32,113
Cord Blood	4,336	7,124	15	10
TOTAL	**111,761**	**92,449**	**148,622**	**39,568**

1. Includes other leukemias (n=8,629) and solid tumors (n=40,821).
2. Includes inherited erythrocyte disorders (n=8,078), inborn errors of metabolism (n=2,348), histiocytic disorders (n=1,321), autoimmune disease (n=606), and other non-malignant diseases (n=873).

Once collected in FormsNet, submitted data goes through computerized completeness and quality checks before being added to the CIBMTR Research Database. The latter now contains information on more than 390,000 transplant recipients going back to transplants performed in 1968. The distribution of patients in the database is displayed in **Table B.2.B** Mandatory submission of outcomes data for alloHCTs in the US ensures we capture almost all US transplants. We have made notable progress in transferring data from the European Group for Blood and Marrow Transplantation (EBMT), increasing our capture of transplant outcome data worldwide. (For more information, see **Section B.2.1.2.c Examples of Data Sharing**.)

In July 2014, the CIBMTR completed integration of Part I Forms Revision changes to the Research Database, including changes to pre-TED, baseline, product, and pre- and post-transplant disease forms for five major diseases that went live in FormsNet in October 2013. The scope of this effort encompassed the integration of 211 forms pages and more than 2,875 FormsNet field changes in the Research Database, ETL program, and SAS data retrievals that support CIBMTR research.

- **SAS Retrieval**. CIBMTR biostatisticians perform most analyses using third-party SAS software applications for clinical data analysis and reporting. To simplify study datasets, the CIBMTR creates SAS datasets of the most commonly analyzed data fields and the most commonly used computed variables. The data are extracted from the Research Database and formatted to be SAS-compatible. Four different datasets are created eight times per year, as shown in **Table B.2.C**.

Table B.2.C. Study Datasets

Dataset	Description	Number of Variables	Number of Cases
TED	All patients and transplants, regardless of reporting track	1,743	446,303
Research: Allogeneic	All patients on CRF track who had an allogeneic transplant and a follow-up form was submitted	15,984	105,713
Research: Autologous	All patients on CRF track who had an autologous transplant and a follow-up form was submitted	11,676	42,690
Study	All patients in studies not funded by the NIH grant	16,208	14,535

B.2.1.1.e Improve Data Quality

In 2014, a Data Quality Team was formed to focus on data quality. The team coordinates data requests to the network, identifies opportunities for training or enhancing the manual, and suggests form or validation changes to improve the quality of data collected. The need for the team was identified in the LEAN process review of generating the Transplant Center Specific Analysis dataset.

Data operations product owners of FormsNet have been trained on the AGILE framework and, using the framework, support the product owners' prioritization of items that improve the quality of data collected.

B.2.1.1.e.1 Verification and Validation

When data are entered into FormsNet, a series of entry level validation checks takes place to ensure the data are valid. This process flags certain errors at the time of entry and allows the center data manager to correct them immediately while source documents are readily available. If a data field does not pass the following validation checks, an error comment is generated on the electronic data field that the entry has not passed the validation rule. In addition, if any errors are present at completion of the form, the data manager is navigated to an error review page to review, resolve, or override the unresolved errors. Lastly, an error report is generated that lists any unresolved errors as well as errors that have been overridden. FormsNet validation checks include:

- **Mandatory field validation**. Certain fields on the forms must be completed for all recipients (e.g., primary questions that lead into secondary questions). Other fields must be completed depending on how a primary question is answered (e.g., 'yes' to 'developed acute graft vs host disease (GVHD)' makes all acute GVHD questions mandatory). The validation process checks that all mandatory fields are completed.
- **Range validation**. The validation process checks all laboratory values, drug doses, heights, and weights against established upper and lower limits. Additionally, the validation process ensures dates fall within an appropriate time frame.
- **Cross form consistency**. For certain data fields, the validation process checks for consistency between data reported on the current form and related data reported on a previous form. For example, on all forms, the contact date is validated against the HCT date.
- **Within form consistency**. The validation process also checks each form for consistency between related data reported on the same form. For example, all dates are validated against the 'date of last contact' or 'date of actual contact'.
- **Core field validations**. The validation process checks against certain core data fields. For example, some questions are optional for international centers and required for domestic centers, so based on the location of the transplant center, a question may be optional or required.

Data extracted from FormsNet and loaded to the Research Database each month undergoes even more comprehensive validation and verification via an Extraction, Transformation & Load (ETL) process. During ETL, data is transformed from a native vertical schema to a horizontal, row-based relational schema to make query and validation more manageable. These data are then more rigorously validated for consistency, completeness, and uniqueness using business rules created in custom logic for the following categories:

- **Fields that cannot be null**. Nearly 30 business rules conduct structural validations to ensure data is complete and to limit the level of missing values in the data that may compromise its research utility.
- **Cross form consistency**. An additional 20 rules are applied ensure consistency across forms for a given patient on unique identifiers, key dates, and key values. This ensures the patient is uniquely defined across the database and there is no double counting.
- **Longitudinal consistency**. Several data specific rules are applied to ensure data is associated with the correct transplant records, especially for patients who receive multiple lines of therapy.
- **Logical relationships**. These rules ensure that logical dependencies between data are enforced. For example, currently the date of transplants must occur after the patient's date of birth.

Rules across these categories were updated and tested as part of the recent Forms Revision. Currently, the rate of form rejection is less than 2%, which owes to transplant center education as well as to validations built in at the point of capture to FormsNet.

B.2.1.1.e.2 On-Site Data Audit Program

On-going data audits are performed at all CIBMTR participating transplant centers as part of the CIBMTR's overall data quality assurance program. The audit compares data in source documents maintained at the transplant center with data contained in the CIBMTR Research Database. Currently, six Clinical Research Associates perform the on-site transplant center audits, spending 3-4 days at each center reviewing original source documents. The overall audit process is as follows:

- **Audit cycle**. Each domestic and international center that has submitted data for at least 20 HCTs is audited once within the 4-year audit cycle.
- **Recipient selection and eligibility requirements**. If a center has performed more than 20 HCTs during the audit period, recipient records are randomly selected for audit.
- **Forms and data fields**. All TED and CRF data are subject to data audit, and essential critical data fields are audited for each recipient.
- **Methodology**. Auditors compare the data submitted to the CIBMTR Research Database with the data in the source documents. Errors are reviewed with the data coordinator. CIBMTR auditors make all data corrections to the database, and the transplant center is provided with a record of all changes made to the TED forms and/or CRFs.
- **Audit analysis, reports, and corrective action**. Transplant centers receive a detailed audit report evaluating the results of their audit. Centers are required to submit a Corrective Action Plan following the audit in response to a critical field error rate above 3%, any systemic errors, consent issues requiring correction, or outstanding missing documentation issues.

In calendar year 2014, 51 centers were scheduled for audit (47 domestic, 4 international). As of December 1, 2014, 40 centers have been notified of their final audit results, including requested corrective action follow-up. Of those centers that have been sent reports, 80% passed with fewer than 3% critical field errors. Of the eight centers that did not pass the audit, four have completed all required corrective action, so their audits were closed out; the remaining four centers are in the process of completing requested corrective action.

In addition to its CPI and audit programs, the CIBMTR monitors transplant center regulatory compliance, including submission of data transmission agreements. At year end, 98% of active US centers and 90% of international centers had returned a data transmission agreement, and all active US centers had IRB approval in place.

B.2.1.1.f Transplant Center Visits

The CIBMTR continued a program of transplant center visits in 2014 with the goal of providing better data sharing solutions focusing on consolidating data from disparate data sources, reducing time, and improving access to and delivery of data. Fifteen visits were conducted in 2014; the business needs gathered during these site visits will be incorporated into future enhancements to data sharing capabilities.

B.2.1.1.g Information Security and Data Privacy

The SCTOD federal contract requires appropriate risk management in the form of minimum security controls, policies, and standards. The CIBMTR's data systems are maintained in accordance with the Federal Information Systems Management Act of 2002, with information security guidance provided by the National Institute of Standards and Technology (http://www.nist.gov). In accordance with National Institute of Standards and Technology Special Publication 800-18(http://csrc.nist.gov/publications/PubsSPs.html), and supervised by HRSA's Office of Information Technology, the CIBMTR maintains a System Security Plan to address information security by implementing measures including management, operational, and technical controls. The CIBMTR must ensure the following:

- Ongoing maintenance of hardware and software inventories;
- Ongoing management of user accounts and privileges;
- Ongoing incident event management;
- Monthly incident reporting to the HRSA Office of Information Technology;
- Monthly vulnerability scans and patching;
- Monthly Plan of Action and Milestones reporting;
- Quarterly Configuration Management Review Board meetings;
- Annual Contingency Plan testing;
- Annual Incident Response testing;
- Annual Risk Assessment;
- Annual System Security Plan Assessment;
- Annual Privacy Impact Assessment;
- Annual Product Accessibility Template Assessment;
- Annual review and update of Federal Information Systems Management Act documents;
- Annual Security Awareness training.

Since December 2008, the CIBMTR holds an Authority to Operate from the Chief Information Officer of HRSA. The certification was renewed in December 2011, and annual security audits were performed in 2012, 2013, and 2014 to ensure compliance. The NMDP also holds an Authority to Operate from HRSA; ensuring similar standards of information security are applied to all CIBMTR and NMDP systems, including the FormsNet data collection system. These controls maintained by the CIBMTR and NMDP represent robust information security risk management beyond those outlined by HIPAA.

B.2.1.2 PROVIDE STATE OF THE ART TECHNOLOGY SOLUTIONS AND DEVELOP COLLABORATIVE AGREEMENTS TO SHARE DATA FOR RESEARCH

The CIBMTR leverages its federal funding to support a broad array of research programs in a cost-effective manner through its expert staff of physicians, statisticians, immunologists, and clinical research and information technology (IT) professionals. The organization has become a respected leader in HCT research by providing a unique resource of information and expertise to the medical and scientific communities. CIBMTR studies have changed clinical practice and helped to improve survival and quality of life for patients undergoing or being considered for this complex procedure.

B.2.1.2.a Data Sharing Initiative

In 2014, the CIBMTR formalized its commitment to data sharing by creating a program to coordinate activities and effort to provide quality research data, information, and knowledge to meet the diverse needs of its stakeholders. The CIBMTR collaborated with external partners on developing a BRIDG physical database to facilitate optimized data sharing by transplant partners. Additionally, the CIBMTR launched and completed a Data Sharing Assessment to evaluate the CIBMTR's current IT resources and capabilities for data sharing, document the business needs and data uses of our stakeholders, and develop a roadmap for the future that leverages CIBMTR strengths as well as industry best practices. The Data Sharing Roadmap provides an evolutionary approach to create a unified Data Warehouse that leverages the existing work and design of the CIBMTR Data Warehouse as a foundation and is further expanded with the domain intelligence that already exists in the Research Database.

B.2.1.2.b Applications for Sharing Data

B.2.1.2.b.1 A Growable Network Information System (AGNIS)

To assist transplant centers in collecting data for internal research, patient care requirements, and reporting purposes, the CIBMTR and NMDP BioInformatics created AGNIS. AGNIS supports secure data sharing across diverse database systems. It is an open-source web service developed with tools from the National Cancer Institute (NCI) caBIG® effort and other well-established projects, such as the Globus Toolkit. AGNIS software, distributed under a public license at www.agnis.net, is available to any interested center.

AGNIS allows participating centers to collect and share data with the CIBMTR as well as others who link to AGNIS. Data are entered once and then distributed and synchronized among databases. Data elements transmitted via AGNIS are curated using the metadata repository operated by the NCI Center for Biomedical Informatics and Information Technology, known as the Cancer Data Standards Registry and Repository (caDSR). This repository is compliant with government standards for electronic data transmission.

In the caDSR, common data elements for FormsNet database fields are compiled into Form Builder reports, which convert CIBMTR format into caDSR format and which centers use to submit data automatically to FormsNet via AGNIS. To date, common data elements have been created for more than 14,235 FormsNet database fields. This represents those database fields associated with 99% of the forms submitted via FormsNet. In addition, 28 Form Builder reports have been released in the caDSR. An additional 49 Form Builder reports have been created and are pending quality assurance testing and release in AGNIS. Between January 1 and December 1, 2014, a total of 18,109 forms were submitted through AGNIS.

The CIBMTR worked with the EBMT and others to standardize data collection for TED and MED-A forms, establishing data collection benchmarks that are now used for most collaborative studies.

B.2.1.2.b.2 Data Back to Center (DBtC)

The DBtC application provides users the ability to download CIBMTR TED level data variables. The data has been validated and processed in the CIBMTR Research Database and can be downloaded in a comma-separated value format. These data are reviewed and refreshed quarterly. A data dictionary is

provided for each field and value in the datasets. Legacy IBMTR data is available for download as far back as 1964, and some legacy NMDP data is available as far back as 1987. These data can be downloaded by authorized users of a transplant center in a comma-separated value format. Between January 1 and December 1, 2014, 951 unique, non-CIBMTR visitors viewed 2,332 DBtC pages and downloaded data 486 times.

- In June 2013, DBtC access was extended to two cooperative registry groups (Asia-Pacific Blood and Marrow Transplant Group & Canadian Blood and Marrow Transplant Group) to obtain data submitted to the CIBMTR by their transplant center members. Access to a transplant center's data is only provided in cases in which the transplant center has signed a data transmission / sharing agreement form with their respective registry. In 2014, the CIBMTR continued discussion with other international registries to put in place formal agreements to use CIBMTR data as their primary data source.
- In July 2014, DBtC underwent major enhancement to include all pre-TED and post-TED form version 4 changes introduced in FormsNet3 during the Forms Revision release in October 2013.

B.2.1.2.b.3 Center Volumes Report

The Center Volumes Report allows centers to preview; correct, if necessary; and approve center volume data published annually to the HRSA Blood Cell Transplant website (http://bloodcell.transplant.hrsa.gov). Under contract to HRSA as part of the C.W. Bill Young Transplantation Program, the CIBMTR provides information regarding transplants performed at US transplant centers.

The CIBMTR uses the portal site to give centers access to Center Volumes Report and to display and download the previous five years (2009-2013) of volume data as well as the current year under review (2013). For 2013, 59 of 215 centers have submitted approval to publish their center volume data. The review of the Center Volumes Report will be ongoing through December 2014, and we anticipate the number of centers that agree to have their data published will increase significantly. During 2014, there were 5,081 pages viewed by 707 unique, external visitors to the portal site, and, of those, 1,668 views were of Center Volumes Report. As the Center Volumes Report review process is ongoing at the time of this report, we anticipate the number of pages and unique visitors to the portal site will increase.

B.2.1.2.b.4 Patient One-Year Survival Calculator – Allogeneic Transplants

In July 2014, the CIBMTR launched the Patient One-Year Survival Calculator for Allogeneic Transplants by deploying the calculator to the portal site for access by medical directors. This calculator represents the first of other online application tools planned by the CIBMTR that leverage data submitted by centers to support decision-making and research. The intent of this online survival calculator is to provide centers with a tool to predict one year survival for individual allogeneic HCT recipients. Data taken from the CIBMTR Center-Specific Survival Report for 2013 is used to calculate the "expected" probability of one-year survival for individual recipients of first allogeneic HCT in the US. Patient, disease, and transplant characteristics of allogeneic HCT recipients at US HCT centers between 2009 and 2011 are used to generate these estimates. The calculator will be updated annually to reflect new information contained in the center outcomes analysis.

B.2.1.2.b.5 Disease Risk Index Assignment Tool

By the end of December 2014, the CIBMTR plans to launch a Disease Risk Index Assignment Tool, which is based on peer-reviewed literature and intended to be used by clinicians and researchers. The aim of

the Disease Risk Index is to provide a robust and flexible tool that can be used for prognostication and the analysis and interpretation of retrospective data, whether conducted in single-center, multi-center, or registry settings, or within the context of the federally mandated center outcome reporting. The Disease Risk Index can also be used for the stratification of patients entering prospective HCT clinical trials. The Disease Risk Index was developed for the primary outcome of overall survival after HCT. At present, this index applies only to adult patients with hematologic malignancies. It is NOT intended to give an accurate prognosis for individual patients.

B.2.1.2.c Examples of Data Sharing

B.2.1.2.c.1 EBMT Electronic Data Exchange

The EBMT began sharing data for European centers with a data sharing agreement with the CIBMTR utilizing a data pipeline through AGNIS in February 2012. Since then, the CIBMTR has received more than 23,000 new production forms from 50 EBMT centers. Currently, the following forms are being submitted via the AGNIS connection: CIBMTR Recipient ID, Pre-TED, Post-TED-Day 100, Post-TED-6 month, and Infusion; these represent the basic data set of information that is the core requirement for all participating CIBMTR centers. This data exchange is important not only because it increases the volume and geographical spread of data submitted to the CIBMTR, but it will help facilitate the provision of data regarding the outcomes of cord blood HCTs to US cord banks that provide units to European centers.

B.2.1.2.c.2 Clinical Outcomes Research

Thousands of hours of voluntary efforts from physicians and scientists spent using data from the Research Database to address important issues in HCT and other cancer treatments validate the need for this unique resource. The inclusive nature of the CIBMTR Working Committees and data access policies make these research data available to many. During 2014, the CIBMTR data access and data use policies were reviewed and updated for clarity regarding expectations as well as obligations of users of CIBMTR data. While the Data Sharing Initiative is specifically focused on providing fast, easy, and flexible access to quality data, patient privacy and protection is our primary concern. The CIBMTR Coordinating Center, by providing data and analytic support, helps to advance research and clinical practice for the benefit of thousands of patients. In 2014, the CIBMTR supported the research of 44 principal investigators by providing datasets from the Research Database for analysis.

B.2.1.2.c.3 Non-Transplant Therapies Data Expansion

With the consensus and support of its Advisory Committee, the CIBMTR is committed to collecting data on non-transplanted patient populations. A follow-up study to the ongoing Centers for Medicare and Medicaid Services study of HCT outcomes is now collecting comparison data for a cohort of patients receiving non-HCT therapy for myelodysplastic syndrome (MDS). The CIBMTR is combining its resources with those of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) to do this in a cost-effective manner. Similarly, the CIBMTR is working collaboratively with the Primary Immune Deficiency Disease Consortium to add transplant outcomes data to data on non-transplant therapy collected by the Consortium. Additionally, the CIBMTR is amending its registration of cases to more easily accommodate data collection for cellular and other therapies that do not involve transplantation.

B.2.2 Scientific Resource Utilization Program

B.2.2.1 ENHANCE PROCESSES FOR REVIEW, PRIORITIZATION, AND IMPLEMENTATION OF PROPOSED STUDIES

The CIBMTR provides many opportunities to conduct research in HCT and cellular therapy and encourages both senior and junior investigators to participate. Scientific Working Committees provide an opportunity for investigators to collaborate with leaders in the field and leverage the unique resources of the Research Database. The CIBMTR ensures that data from the Research Database are used for scientifically and clinically relevant research by engaging the scientific community and providing investigators with the statistical and scientific support necessary to perform studies that adhere to rigorous methodological standards.

To ensure Working Committee studies have notable impact on the field and effectively utilize CIBMTR resources, a number of processes took place in 2014:

- **Advisory Committee Oversight**. The CIBMTR Advisory Committee reviewed Working Committee work plans and progress in February (before the BMT Tandem Meetings), March (after the BMT Tandem Meetings), and July.
- **Communication Plan**. The CIBMTR developed and distributed a communication plan for Working Committee leadership in November. This plan articulated best practices for communication among the collaborating parties in their respective roles: principal investigators, writing committee members, Working Committee Chairs, MS statisticians, and Scientific Directors.
- **Working Committee Chair Meeting**. The CIBMTR conducted a meeting for all Working Committee Chairs at the BMT Tandem Meetings in February to discuss best practices and the role of an active Working Committee Chair.
- **Working Committee Scientific Directors Meetings**. Working Committee Scientific Directors met bi-monthly to discuss best practices.
- **Working Committee Leadership Meetings**. Each Working Committee's leadership team conducted monthly phone conferences to monitor study progress, discuss new proposals, prioritize activities, and refine study goals.
- **Statistical Team Meetings**. All MS statisticians met monthly to discuss best practices and implement enhanced collaboration tools across the statistical team.
- **MS Statistician Meetings**. The Associate Statistical Directors met with each MS statistician individually on a regular basis to assist with task prioritization and ensure work plan goals were met.

In 2014, CIBMTR Clinical Outcomes Research resulted in the following milestone accomplishments:

- **Studies**. Among the 15 Scientific Working Committees, 209 studies were in progress at the end of December.
- **Proposals**. The following proposals were submitted to Working Committees to be considered for presentation at their meetings, which occur during the BMT Tandem Meetings:
    - For the 2014 Working Committee meetings, the CIBMTR received 156 study proposals; 88 were presented, and 40 were accepted.
    - For the 2015 Working Committee meetings, the CIBMTR received 150 study proposals.

- **Publications**. In 2014, 37 CIBMTR clinical outcomes research papers were published in peer-reviewed journals, including early electronic publications and printed publications. As of December 1, 2014, an additional 15 were submitted for publication and are under review.
- **Presentations**. Clinical outcomes investigators presented the following abstracts at annual scientific meetings:
    - At the 2014 BMT Tandem Meetings, 16 abstracts (13 oral and 3 posters) were presented.
    - At the 2014 American Society of Hematology Annual Meeting, 16 abstracts (9 oral and 7 posters) were presented.

B.2.2.2 OPTIMIZE THE TIMELINE FOR MOVING A STUDY PROPOSAL TO PUBLICATION

Efficiently moving a study proposal to publication is a multi-faceted effort. In 2014, the following groups accomplished the specified activities.

Working Committee Chairs:

- Limited the number of studies in progress, emphasizing making greater progress on fewer studies.
    - Investigators submitted 156 proposals to be implemented in 2014; 88 were presented during the Working Committee meetings at the 2014 BMT Tandem Meetings, and 40 were accepted by Working Committee Chairs for implementation.
- Assigned studies to a particular Chair so that the Chair could follow-up with the principal investigator to ensure the study is progressing.

Coordinating Center Staff Members:

- Reviewed studies in the manuscript preparation phase during weekly Coordinating Center Statistical Meetings.
- Collaborated between clinical outcomes and IT staff members to enhance the Research Database.

Advisory Committee:

- Instructed Working Committee Chairs to only accept proposals for high priority studies that were immediately actionable.
- Monitored Working Committee progress on specific metrics to support and encourage Chairs and assist them, when needed.

B.2.2.3 UTILIZE DATA FROM OBSERVATIONAL STUDIES TO SUPPORT DECISIONS REGARDING DESIGN OF PROSPECTIVE CLINICAL TRIALS AND/OR AMENDMENTS OF SUCH TRIALS

The CIBMTR Research Database is an important resource to the BMT CTN and Resource for Clinical Investigations in Blood and Marrow Transplant (RCI BMT), which conduct multicenter clinical trials. These data are used to design, monitor, and analyze clinical trials. CIBMTR data provides an important resource for the determination of feasibility and study planning. Additionally, long-term follow-up data of patients enrolled in BTM CTN and RCI BMT trials are obtained through routine CIBMTR data collection

processes, resulting in considerable cost-savings. The CIBMTR Coordinating Center provides expertise and other resources that support both large and small trials in several ways:

- **Trial planning**. Investigators planning clinical trials in HCT use the Research Database to determine which patient populations may be available for trials. With the aid of CIBMTR Coordinating Center staff, they can estimate how changing eligibility criteria will affect patient accrual. The Research Database provides a more precise, less biased estimate of the baseline outcomes of interest than literature reviews, expert opinions, or personal experience at a transplant center. The database can identify the most common supportive care and other practices in potentially eligible patients so that clinical protocols can be written that are acceptable to most transplant centers. The CIBMTR routinely makes this information available to BMT CTN and RCI BMT protocol teams and provides it to other investigators upon request.
- **Data collection instruments**. The CIBMTR has an open policy for sharing data collection forms and database structures. The forms are freely available on the CIBMTR website and are the basis for data collection in many clinical trials. These forms reflect the knowledge and expertise not only of Coordinating Center personnel but also the many transplant experts on Working Committees who evaluate and revise the data collection forms.
- **Statistical consultation**. Coordinating Center personnel have provided statistical review of several HCT clinical trial protocols and are considered expert resources. CIBMTR faculty members serve as protocol statisticians for the BMT CTN and RCI BMT.
- **Trial interpretation**. The Research Database is a valuable tool for evaluating results of clinical trials, especially single-arm studies. Using the database, the Coordinating Center can provide matched controls for patients treated in single and multi-institution studies of transplant strategies, thus allowing more accurate estimation of treatment effects after controlling for patient characteristics. The BMT CTN uses this approach to evaluate Phase II data before embarking on large Phase III trials.

B.2.2.3.a BMT CTN

The BMT CTN is the US national trials group charged with developing and conducting multicenter phase II and III clinical trials focused on HCT. The CIBMTR is the lead institution for the BMT CTN Data and Coordinating Center, which it runs in collaboration with NMDP and the EMMES Corporation, a contract research organization based in Rockville, MD. The BMT CTN's accomplishments over the past year include:

- Opened one new trial to accrual, bringing the total number of launched trials to 34;
- Accrued 1,316 patients to trials, increasing the total number of accrued patients to 7,303;
- Managed 11 open protocols with overall accrual for open studies at about 175% of projections;
- Published 12 peer-reviewed manuscripts, including 5 primary results manuscripts;
- Presented 10 abstracts of study results at national and international meetings.

B.2.2.3.b RCI BMT

The Coordinating Center developed the RCI BMT in 2005. This resource conducts prospective research within the CIBMTR, providing researchers in the field of HCT with infrastructure and expertise in HCT clinical trial conduct and analysis. The RCI BMT's goal is to help investigators generate data allowing novel and innovative ideas to move into the larger Phase II or Phase III setting into such groups as the BMT CTN or the national cancer cooperative groups. This year the RCI BMT's accomplishments include:

- Managed 5 open protocols, which accrued 2,477 patients;

- Completed analysis and submitted abstracts, which were accepted, for 12 protocols;
- Completed accrual on 3 protocols;
- Managed 2 Food and Drug Administration investigational new drug protocols for Be The Match Operations: PBSC Procurement and Cord Blood Access, which accrued 2,174 and 548, respectively;
- Continued the development of three other protocols;
- Supported five studies involving unrelated donor data or sample collection for investigators.

B.2.2.3.b.1 Survey Research Group

The Survey Research Group, a team within the RCI BMT was created to assist HCT researchers in developing and conducting research involving questionnaires, direct subject interviews, and patient reported outcomes. The group is responsible for collecting high quality, scientifically valid data from donors, patients, and their families. The Survey Research Group utilizes standardized and semi-structured telephone interviews as well as self-administered questionnaires. While many of their research studies are part of the RCI BMT portfolio, the SRG has also partnered with the BMT CTN, Bioinformatics Research, and Health Services Research Program to assist these groups with their research portfolio.

The Survey Research Group consists of a supervisor, research assistant, and five research interviewers. This team conducts surveys regarding medical health, quality of life, and healthcare utilization, and it provides support in the collection of study materials, such as consent forms and buccal swab kits by following up with subjects via telephone when needed. The Survey Research Group plays a key role in the overall success and productivity of the RCI BMT team by providing a unique resource and HCT researchers. The group's accomplishments over the past year include:

- Supported eight active studies;
- Participated in the development of one upcoming study.

B.2.2.4 ASSIST IN LONG TERM FOLLOW-UP OF PATIENTS PARTICIPATING IN CLINICAL TRIALS

The CIBMTR assists in long term follow-up of all patients involved in the BMT CTN and RCI BMT clinical trials except those led by cooperative groups. After the primary and/or secondary study endpoints have been reached, the CIBMTR takes primary responsibility for follow-up. In 2014, the CIBMTR was involved in follow-up for 4,670 patients from 29 clinical trials (**Table B.2.D**).

The CIBMTR is also involved in a large prospective outcomes study evaluating patients who do versus those who do not receive keratinocyte growth factor (KGF) to prevent mucositis. This US Food and Drug Administration-required study is sponsored by Sobi, which manufactures KGF. Study accrual was completed in May 2014 with 2,261 matched pairs. While the primary purpose of this study is to follow a large number of patients to support the long term safety of this therapy, because of the study size and duration, we expect this cohort to be a valuable resource for other CIBMTR studies of late effects after HCT.

Table B.2.D. CIBMTR Long Term Follow-Up of Patients Enrolled in BMT CTN Clinical Trials					
BMT CTN Protocol	**Accrual Status**	**Date Opened to Accrual**	**Date Closed to Accrual**	**Number of Patients Enrolled**	**Number of Patients Followed in 2014**
0101 Randomized double-blind trial of fluconazole vs voriconazole for the prevention of invasive fungal infections in alloHCT recipients	Closed	12/1/2003	9/21/2006	600	280
0102 Trial of tandem autoHCT with or without post-second autoHCT maintenance therapy vs single autoHCT followed by matched sibling NMA alloHCT for patients with multiple myeloma	Closed	11/15/2003	3/30/2007	709	374
0201 Phase III randomized, multicenter trial comparing G-CSF mobilized PBSC with marrow transplantation from HLA compatible unrelated donors	Closed	1/20/2004	10/16/2009	551	183
0202 AutoHCT vs NMA alloHCT for patients with chemosensitive follicular non-Hodgkin lymphoma beyond first complete response or first partial response	Closed	7/28/2004	3/2/2006	30	20
0301 Fludarabine-based conditioning for allogeneic marrow transplantation from HLA-compatible unrelated donors in severe aplastic anemia	Closed	1/24/2006	12/2/2013	97	76
0302 Initial systemic treatment of acute GVHD: a Phase II randomized trial evaluating etanercept, mycophenolate mofetil, denileukin diftitox (Ontak), and pentostatin	Closed	8/25/2005	3/24/2008	180	54
0303 Single-arm, multicenter Phase II trial of transplants of HLA-matched, CD34+ enriched, T cell depleted PBSCs isolated by the CliniMACS system in the treatment of patients with AML in first or second morphologic complete remission	Closed	6/30/2005	12/24/2006	47	25

Table B.2.D. CIBMTR Long Term Follow-Up of Patients Enrolled in BMT CTN Clinical Trials					
BMT CTN Protocol	**Accrual Status**	**Date Opened to Accrual**	**Date Closed to Accrual**	**Number of Patients Enrolled**	**Number of Patients Followed in 2014**
0401 Phase III Rituxan / BEAM vs Bexxar / BEAM with autoHCT for persistent or relapsed chemotherapy-sensitive diffuse large B cell non-Hodgkin lymphoma	Closed	12/7/2005	7/17/2009	224	84
0402 Phase III randomized, multicenter trial comparing sirolimus / tacrolimus with tacrolimus / methotrexate as GVHD prophylaxis after HLA-matched, related PBSC transplantation	Closed	11/20/2006	10/28/2011	314	158
0403 Randomized double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor Enbrel (etanercept) for the treatment of acute noninfectious pulmonary dysfunction (idiopathic pneumonia syndrome) following alloHCT	Closed	8/27/2007	9/14/2011	37	6
0501 Multicenter, open label, randomized trial comparing single vs double umbilical cord blood HCT in pediatric patients with leukemia and MDS	Closed	10/16/2006	2/29/2012	224	136
0502 Phase II study of alloHCT for older patients with AML in first morphologic complete remission using a NMA preparative regimen	Closed	1/29/2007	12/29/2011	41	10
0601 Unrelated donor HCT for children with severe sickle cell disease using a RIC regimen	Closed	6/27/2008	4/24/2014	38	33
0603 Multicenter, Phase II trial of NMA conditioning and HCT of partially HLA-mismatched bone marrow for patients with hematologic malignancies	Closed	10/17/2008	5/17/2010	55	24
0604 Multicenter, Phase II trial of NMA conditioning and HCT of umbilical cord blood from unrelated donors in patients with hematologic malignancies	Closed	12/23/2008	3/31/2010	54	19

Table B.2.D. CIBMTR Long Term Follow-Up of Patients Enrolled in BMT CTN Clinical Trials					
BMT CTN Protocol	**Accrual Status**	**Date Opened to Accrual**	**Date Closed to Accrual**	**Number of Patients Enrolled**	**Number of Patients Followed in 2014**
0701 AlloHCT using RIC for relapsed follicular cell non-Hodgkin lymphoma using related or unrelated donors	Closed	4/27/2009	10/22/2012	65	56
0702 Trial of single autologous transplant with or without consolidation therapy vs tandem autoHCT with lenalidomide maintenance	Closed	6/1/2010	11/15/2013	758	660
0801 Phase II/III randomized, multicenter trial comparing sirolimus plus prednisone and sirolimus / calcineurin inhibitor plus prednisone for the treatment of chronic GVHD	Closed	4/15/2010	3/26/2013 (Ph II) 12/9/2013 (Ph III)	161	122
0802 Multicenter randomized, double blind, Phase III trial evaluating corticosteroids with mycophenolate mofetil vs corticosteroids with placebo as initial systemic treatment of acute GVHD	Closed	2/1/2010	11/14/2011	236	117
0803 High-dose chemotherapy with autologous stem cell rescue for aggressive B cell lymphoma and Hodgkin lymphoma in HIV-infected patients	Closed	7/12/2010	5/15/2013	43	36
0901 Randomized, multicenter Phase III study of alloHCT comparing regimen intensity in patients with MDS or AML	Closed	6/2/2011	4/18/2014	272	226
0902 Phase III randomized, multicenter trial testing whether exercise or stress management improves functional status and symptoms of autoHCT and alloHCT recipients	Closed	1/3/2011	6/1/2012	711	494
0903 AlloHCT for hematological cancers and MDS in HIV-infected individuals	Open	5/11/2012	N/A	14	12

Table B.2.D. CIBMTR Long Term Follow-Up of Patients Enrolled in BMT CTN Clinical Trials					
BMT CTN Protocol	**Accrual Status**	**Date Opened to Accrual**	**Date Closed to Accrual**	**Number of Patients Enrolled**	**Number of Patients Followed in 2014**
1101 Multi-center Phase III randomized trial of RIC and HCT of double unrelated umbilical cord blood vs HLA-haploidentical related bone marrow for patients with hematologic malignancies	Open	6/19/2012	N/A	134	123
1102 Multi-center biologic assignment trial comparing RIC alloHCT to hypomethylating therapy or best supportive care in patients aged 50-75 with intermediate-2 and high risk MDS	Open	12/16/2013	N/A	46	10
1202 Prospective multi-center cohort for the evaluation of biomarkers predicting risk of complications and mortality following alloHCT	Open	6/11/2013	N/A	1,271	1,256
1203 Multi-center Phase II trial randomizing novel approaches for GVHD prevention compared to contemporary controls	Open	9/17/2014	N/A	10	10
1204 RIC for children and adults with hemophagocytic syndromes or selected primary immune deficiencies	Open	11/14/2013	N/A	27	27
1205 Easy-to-read informed consent (ETRIC) for HCT clinical trials	Open	11/26/2013	N/A	39	39

B.2.2.5 LINK OUTCOMES DATA TO IMMUNOLOGIC DATA AVAILABLE FROM THE NMDP SAMPLE REPOSITORY

The CIBMTR leverages the NMDP's investment in the development of an unrelated donor-recipient specimen Research Sample Repository with the NIH's investment in the CIBMTR Research Database. These data are used to perform studies that link genetic and immunobiologic data with clinical phenotype data.

The Related Donor Research Sample Repository is a unique opportunity to enhance immunobiologic research. Related donor and recipient samples are better matched than unrelated recipients for human leukocyte antigen (HLA), a measure of immunological compatibility, thus reducing the confounding effects of HLA disparity in clinical research. The Related Donor Research Repository facilitates an organized approach to studying transplant biology across the full spectrum of allogeneic HCT.

As of December 2014, the number of centers submitting related recipient-donor sample pairs for the Related Donor Research Sample Repository increased to 63 centers (up from 52 in 2013). The related pair samples are an important addition to the existing sample repository. There was an approximately 40% increase in the related donor transplant sample inventory in the last year.

As of December 2014, the Research Repository included:

- 1,815,832 aliquots;
- 18,901 cell lines;
- 54,556 samples from unrelated donors and 3,870 from related donors;
- 52,626 samples from unrelated recipients and 4,113 from related recipients;
- 9,643 samples from unrelated cord blood units;
- 31,464 samples from complete unrelated adult donor-recipient pairs, 3,483 from complete related donor-recipient pairs, and 3,322 from unrelated cord-recipient pairs.

The Immunobiology Research group continues to manage the Research Repository inventory and immunogenetic testing programs that add critical HLA and killer-cell immunoglobulin-like receptors data for use in CIBMTR clinical outcomes studies. In 2014, the group enhanced the testing programs by incorporating additional typing. The Immunobiology Research group completed high resolution HLA typing on 1,145 related and 2,500 unrelated HCT donor / cord and recipient pairs bringing the total to more than 17,500 unrelated donor / cord and recipient pairs that have been retrospectively high resolution typed for HLA-A, -B, -C, -DRB1 and -DQB1; more than 70% include -DPB1. These HLA data have facilitated seminal publications on the impact of high resolution HLA matching in unrelated donor (Lee et. al. Blood 2007) and umbilical cord blood (Eapen et al. Blood 2013) transplantation.

In 2014, the Immunobiology Research group implemented a new inventory management system, LabVantage, for clinical trial specimens collected for the BMT CTN and RCI BMT. The sample inventory details were also integrated into the CIBMTR Data Warehouse to support inventory query report automation. Additionally, the group distributed 8,313 research samples in support of Working Committee studies.

B.2.2.6 PROVIDE NOVEL OBSERVATIONAL STUDIES IN HEMATOLOGIC MALIGNANT AND NON-MALIGNANT BLOOD DISORDERS, INCLUDING USE OF GENETICALLY ENGINEERED CELLULAR PRODUCTS

Currently, there are 209 Scientific Working Committee studies in progress. Numbers of new, ongoing, and completed studies by year are displayed in **Table B.2.E**. We continue to encourage new investigators to participate in and lead studies. In 2014, as in the past two years, more than half of the proposals submitted for consideration at the 2015 BMT Tandem Meetings were developed by principal investigators who had not previously submitted a proposal to use our data.