C. W. Bill Young Cell Transplantation Program

STEM CELL THERAPEUTIC OUTCOMES DATABASE

Stem Cell Therapeutic and Research Act of 2005 (P.L. 109-129)

* Authorizing law, preceded by efforts to:
  * Enact authorizing legislation for collection and distribution of cord blood units (CBU)
  * Re-authorize the National Bone Marrow Donor Registry (managed by NMDP)
  * 2004 Conference Report required an Institute of Medicine (IOM) study; report issued April 14, 2005
  * Appropriations totaled nearly $24 million ($1 million specified for IOM study)

Stem Cell Therapeutic and Research Act of 2005 (P.L. 109-129)

* Signed December 20, 2005
* Aims are to increase:
  * Number of unrelated donor transplants
  * Public inventory of high quality CBU from diverse populations
  * Number of CBU available for research
* Opportunity to help more patients obtain transplants, other therapy
Established by legislation passed in 2005
Successor to National Bone Marrow Donor Registry (contract held by NMDP since 1987)
5 components:
- Bone Marrow Coordinating Center
- Cord Blood Coordinating Center
- Single Point of Access/Office of Patient Advocacy
- Cord Blood Banks
- Stem Cell Therapeutic Outcomes Database

Guided by three principles:
- Single Point of Access for patients and physicians to all sources of blood stem cells
- Collection of high-quality diverse CBU, expeditiously
- Complete data on clinical outcomes of transplants

Stem Cell Therapeutic and Research Act of 2005:
C. W. Bill Young Program Structure

Department of Health and Human Services
Advisory Council
HRSA/Division of Transplantation
Accrediting Organizations
Cord Blood Banks
Bone Marrow Coordinating Center
Cord Blood Coordinating Center
Outcomes Database
Infrastructure
Public Interface
Transplant Centers
Referring Physicians
HRSA Contract Organizations
Other New Organizations or Relationships
Patients
Coordinating Centers
- Provide access to adult donors and cord blood units
  - Recruitment/HLA typing
  - Inventory management
  - Patient-specific searches
  - Facilitate graft collection, transport
- Some operational research

SPA/OPA
- Allow patients to identify potentially suitable adult donors and cord blood units through a single search
- Support patients and families through the search and transplantation process

Cord Blood Banks
- Collect, store and distribute cord blood for transplantation
- Relationships with hospitals/obstetricians
SCTOD

- Collect data on outcomes of all allogeneic hematopoietic stem cell transplants in the US
- Collect data on outcomes of all transplants facilitated by the CW Bill Young Program – even if transplant done outside the US
- Include alternative uses of hematopoietic stem cells
- Core set of data – sufficient to allow center-specific survival and other analyses
  - Subset of Report Form data
- Establish related donor-recipient specimen repository
Under the Contract, the CIBMTR, operating as the SCTOD, will-
- Collect data on **ALL** allogeneic hematopoietic cell transplants with a recipient or donor in the U.S.
- Collect data on other cellular therapies, too
- Establish related donor-recipient repository
- Establish electronic data capture systems
- Disseminate data within the Program
- Make data publicly available
- Perform and publish center-specific outcomes for U.S. transplant centers
- Perform analyses of optimal size for the adult donor registry and cord blood unit inventory
- Conduct and support other research using the data collected under the contract
HOW DOES THIS RELATE TO WHAT WE ARE ALREADY DOING?

CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH
- Established July 2004
- A research affiliation between the IBMTR and the NMDP to support clinical research in BMT & related fields
- Clinical Research includes
  - Observational Studies (including immunobiologic correlates)
  - Clinical Trials
  - Health Services Research
  - Statistical Methodology

IBMTR
- Established in 1972 to monitor and study outcomes of bone marrow transplants
- Maintains a database of clinical information on recipients of autologous and allogeneic hematopoietic stem cell transplants in ~450 centers in 47 countries
- Collates basis data set on all patients in member centers (registration) and comprehensive data (research) on a subset
- Provides scientific and statistical support for analyzing those data
NMDP

- 1986 – U.S. government appropriated funds to establish the National Bone Marrow Donor Registry (Donor Panel)
- 1988 – U.S. Organ Transplant Amendments Act – mandated collecting outcome data (Recipient Registry); also collects donor outcomes
- ~150 transplant centers and 90 donor centers
- Collects comprehensive data on all transplants it facilitates in member centers
- Repository with matched recipient/donor blood samples

CIBMTR – 2 Campuses

- Milwaukee – Medical College of Wisconsin
  - 5 MDs; 5 PhDs and 6 MS statisticians; 37 additional research and administrative staff
- Minneapolis – NMDP Coordinating Center
  - 3 MDs; 4 MS statisticians; 9 additional research and administrative staff
- Close relationship with NMDP Operations staff who provide support in multiple areas – increasing interaction with new contract

Location of Centers Participating in the CIBMTR 2007
CIBMTR DATA COLLECTION

- Basic ("essential") data
  - All patients
  - Transplant Essential Data (TED)/ EBMT MED-A
- Comprehensive data
  - Subset of patients
  - CIBMTR: Report Form collected prospectively on patients identified at time of TED submission
  - NMDP:(Slightly different) Report Form collected on all patients receiving transplants facilitated by NMDP

CIBMTR
Number of Cases Registered, 1984-2005

Three Main Areas of Scientific Activity

- Observational Research
  - Clinical outcomes
  - Immunobiology
- Statistical Methodology
- Clinical Trials Support
  - BMT CTN
  - RCI BMT
THREE MAIN AREAS OF SCIENTIFIC ACTIVITY FUNDED BY FEDERAL GRANTS/CONTRACTS

Observational Research
- Clinical outcomes
- Immunobiology

Statistical Methodology
- SCTOD Contract (HRSA)
- CIBMTR Resource Coop Agreement (NIH)

Clinical Trials Support
- RCI BMT
- EMT CTN
- Clinical Trials Coop Agreement (NIH)

Current Data Flow

CURRENT DATA COLLECTION

TED
CURRENT DATA COLLECTION

TED

H-Form

CURRENT DATA COLLECTION

TED

TED/MED-A

CURRENT DATA COLLECTION – numbers of cases collected

H-Form

TED/MED-A
CHALLENGE

Accommodate the many demands for data in a way that meets the needs of SCTOD and all other users, ensures quality, is maximally efficient and minimizes demands on transplant centers.

TED/MED-A not sufficient to meet needs of the SCTOD

- Center-specific analyses mandated
  - Assess quality of transplant centers
  - Essential to have sufficient data to adjust for patient mix
    - Measures of clinical status and co-morbidities
  - Product information essential for C.W. Bill Young Program to assess quality of operations (graft procurement, processing, storage, transport)

CIBMTR REPORT FORM NOT APPROPRIATE FOR MANDATORY SCTOD REPORTING

- Detailed patient, disease, transplant outcomes
  - Up to 70 pages
  - 6-10 hours to complete
- SCTOD forms require approval from US Office of Management and Budget
  - Data collection burden must be justified
**CHALLENGE**

Accommodate the many demands for data in a way that meets the needs of all users, ensures quality, is maximally efficient and minimizes demands on transplant centers

- Meet the needs of the SCTOD
- Have detailed data on a sufficient number of patients data for research
- Not drive people crazy (crazier)
Data Needs for Cord Blood Banks

We must figure out the management of -
- Significant adverse events – Real time
- Other adverse events - Periodic
- “Real-time” data that’re not significant AEs
- Periodic data reports
  - monthly, bimonthly, quarterly

INTERNATIONAL PERSPECTIVE

- BMT as a therapy is unique in requiring a high level of international cooperation especially for unrelated donor transplants
- US government is not unique in its interest in collecting data on HCT
  - Several countries already have mandatory reporting
  - Variability in data collected and data used
INTERNATIONAL CONSENSUS ON COMMON DATA SET

- Facilitate collaboration
- Inform policy makers as to the appropriate level of data collection
- Minimize burden to transplant centers since data entered in one system could be transferred to another – enter once, use often

Future Data Flow?

Meeting the Challenge – Collecting Data on all Allografts

- Data Working Group – internal group with representatives from SCTOD, Coordinating Centers, SPA/OPA, CB Banks addressing Program needs, logistics
  - Meets at ~6 wk intervals
  - Subcommittees addressing specific aspects of the Program
- Data Advisory Group – broad participation of data users/suppliers
Data Advisory Group

- ASBMT
- BMT CTN
- EBMT
- APBMT
- PACT
- NIH
- HRSA
- FDA
- FACT
- Transplant Centers
- Physicians
- Data managers
- CB Banks
- Donor Centers
- Patients/families

Meeting the Challenge – Electronic Data Collection (EDC) Systems

- Goal: support systems that are already operating well; replace inefficient paper systems to enhance speed and accuracy
  - Continue to accept StemSoft data
  - Continue to accept EBMT electronic TED data
- Short-term solution: FormsNet2.0, a web-based EDC, designed to capture TED and Report Forms – July 2007
- Long-term solution: AGNIS

AGNIS: A Growable Network Information System
**Future Data Flow?**

- EBMT
- Expanded MED-A
- MED-B

**Expanded TED**

- Non-US: US Auto
- US Related: Unrelated

**CIBMTR**

- H- Forms

**Single CIBMTR Database**

**From the Transplant Center Perspective**

- Clinical trial data
- Clinical care data
- SCTOD Data
- Registry Research Data

**MULTIPLE DATA USES – Collect once, use often**

**Initiatives in Data Management:**

- **AGNIS:** A Growable Network Information System
  - Funded by NIH Roadmap
- **BMT CTN – Children’s Oncology Group Data Exchange**
  - Simplifies access for Pediatric BMT Group
  - Funded by NIH Roadmap and NHLBI
- **These projects leverage the resources of NCI's caBIG (Cancer Bioinformatics Grid)**
Meeting the Challenge –
Ensuring Sufficient Data for Research

❖ Revise and harmonize IBMTR and NMDP forms – single form to be available in July
  • No duplicate reporting
  • Single audit/quality improvement program
❖ Re-examine selection algorithms for comprehensive data forms
  • May not need to submit full form for every unrelated donor transplant

Meeting the Challenge –
Making Data available

❖ Websites – CIBMTR, NMDP, new C.W. Bill Young Program website
  • Increased emphasis on providing outcomes data
❖ Information services – access to more detailed data
❖ Working Committees – access to research data and statistical expertise

Meeting the Challenge:
Related Donor-Recipient Specimen Repository

❖ Will build on experience with NMDP Unrelated Research Repository
❖ Implementation plan for collection of related pairs
  • Sample type
  • Center Participation
  • Data collection
  • Sample access and distribution
  • Timeline
NMDP Research Repository

- Established in 1988
  - Pretransplant blood specimens from all unrelated stem cell transplants facilitated by NMDP (~215 recipients, ~230 donors per month)
  - Relocated from San Francisco, California to Minneapolis in Fall of 2006
- Protocol based on survey of investigators to establish sample collection and storage priorities in 2004
  - Repository receives 20ml of whole blood from Donors and Recipients; any source of DNA from infused CBUs

NMDP Repository Inventory Summary

- Specimen Type Summary
  - Donor and Recipient pairs N = 12,973
  - Unique Donors N = 21,324
  - Unique Recipients N = 18,540
  - Unique CBU N = 198
- Sample Type Summary
  - PBMCs N = 162,893 vials
  - Granulocytes N = 63,775 vials
  - Whole Blood N = 141,668 vials
  - Whole Blood in DMSO N = 47,206 vials
  - Filter Cards N = 67,653 cards
  - Serum N = 38,260 vials
  - B-LCLs N = 138,954 vials

NMDP Repository Usage

- Support unrelated hematopoietic stem cell transplant research
  - Retrospective transplant outcome analysis
  - Comprehensive collection of clinical outcome data
  - Pair clinical data with stored sample testing
  - Example: NMDP Donor/Recipient Pair project
    - Allele level HLA testing at 11 loci
    - 9,000 transplant pairs tested, since 1996
    - Over 15 additional studies approved or in process
- Shipped over 9,500 samples in 2005
Related Donor-Recipient Repository
Specimen Collection Priorities

- Minimal burden to patient and donor
  - Reasonable volumes for pediatric and adult patients
- Specimen material suitable for current and future DNA based assay systems
- Storage procedures consistent with core competencies of NMDP Research Repository

SCTOD Repository Steering Committee Recommendation

- 10 ml from each donor and recipient
  - Single blood tube
- Processing and storage
  - 1 filter paper card, 5 – 75ul spots
  - 5 – 1ml aliquots at -80°C
  - 4 – 1ml aliquots in LN
    - 3 – 1ml aliquots at NMDP
    - 1 – 1ml aliquot stored off site in Master Repository
- Flexible processing and storage protocols to accommodate short draws

Center Participation

- Centers will be recruited to generate a representative sample of related allogeneic transplant activity in the U.S.
  - Equivalent numbers as is currently collected for unrelated donor repository
- Collection limited to U.S. centers that currently participate in the NMDP Unrelated Research Sample Repository
- Center selection analysis in progress
  - QOL and Long Term Follow-up
Performance and Reimbursement

- Performance monitoring
  - Modeled on NMDP CPI program
  - All NMDP centers must achieve 75% submission
- Reimbursed $35/sample and $10/valid excuse
  - Excuses: Refuse to participate or medical deferral

Case Selection

- Collect all consecutive related allogeneic transplant cases from select centers
  - Standard collection protocol
- Paired pre-transplant samples only

Data Collection

- Collect SCTOD Transplant Essential Data (TED) form and Product Insert (from harmonized Form)
- Ensure data on SCTOD TED is sufficient for studies utilizing research samples
Sample Access and Distribution

- Samples released for studies through the CIBMTR Working Committee process
- Inventory summaries and query tool to be available on program.gov Web site

Timeline

- February 2007: Submit final project plan to HRSA for approval.
- March 2007 (pending HRSA approval): Submit protocol and consent changes to NMDP/MCW IRBs
- April 2007: Release protocol and consents for approval at local IRBs
- Summer 2007: Implement specimen collection at approved sites

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CIBMTR PRODUCTIVITY

- >400 Centers registered >14,000 transplants in 2005
- 17 Working Committees
  - 196 Approved Studies (19 involving specimens from repository)
- American Society of Hematology
  - 2005: 9 studies presented
  - 2006: 12 studies presented
- Publications:
  - 2006: 20 studies published
  - 2007 to date: 10 in press; 17 under review
- >1600 patients enrolled on clinical trials

Some Key Findings

- HLA-mismatched cord blood transplants acceptable alternative for adults unable to find a matched unrelated adult donor
- Cord blood may be preferable graft type for unrelated donor transplants in children
- Consolidation therapy beneficial prior to autotransplantation for AML
- Survival similar with PB and BM transplants but more CGVHD with PB
- Access to BMT and BMT outcomes influenced by race
- QOL of long-term survivors – and their spouses – affected by BMT

These studies are possible because of the commitment of individuals in many centers to work together and share data.
DATA DOESN'T JUST HAPPEN

• Providing the data needed to do good clinical research is hard work

CIBMTR Centers
2006