

COVID-19: Impact on HCT Outcomes Data

HHS Advisory Council Blood Stem Cell Transplantation

J. Douglas Rizzo, MD MS, SCTOD Project Director

April 27, 2020



The CIBMTR[®] (Center for International Blood and Marrow Transplant Research[®]) is a research collaboration between the National Marrow Donor Program[®] (NMDP)/Be The Match[®] and the Medical College of Wisconsin (MCW).

CIBMTR Funding Disclosure:

CIBMTR receives financial support from the government, foundations and industry entities listed below to support broad research and educational missions. These funding sources are disclosed for transparency. Scientific and administrative review processes prevent direct influence of the funding sources to the CIBMTR scientific research agenda and individual research products and findings.

The CIBMTR is supported primarily by Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); U24HL138660 from NHLBI and NCI; U24CA233032 from the NCI; OT3HL147741, R21HL140314 and U01HL128568 from the NHLBI; HSH250201700006C, SC1MC31881-01-00 and **HSH250201700007C from the Health Resources and Services Administration (HRSA)**; and N00014-18-1-2850, N00014-18-1-2888, and N00014-20-1-2705 from the Office of Naval Research; Additional federal support is provided by P01CA111412, R01CA152108, R01CA215134, R01CA218285, R01CA231141, R01HL126589, R01AI128775, R01HL129472, R01HL130388, R01HL131731, U01AI069197, U01AI126612, and BARDA. Support is also provided by Be the Match Foundation, Boston Children's Hospital, Dana Farber, Japan Hematopoietic Cell Transplantation Data Center, St. Baldrick's Foundation, the National Marrow Donor Program, the Medical College of Wisconsin and from the following commercial entities: AbbVie; Actinium Pharmaceuticals, Inc.; Adaptive Biotechnologies; Adienne SA; Allovir, Inc.; Amgen, Inc.; Anthem, Inc.; Astellas Pharma US; AstraZeneca; Atara Biotherapeutics, Inc.; bluebird bio, Inc.; Bristol Myers Squibb Co.; Celgene Corp.; Chimerix, Inc.; CSL Behring; CytoSen Therapeutics, Inc.; Daiichi Sankyo Co., Ltd.; Gamida-Cell, Ltd.; Genzyme; GlaxoSmithKline (GSK); HistoGenetics, Inc.; Incyte Corporation; Janssen Biotech, Inc.; Janssen Pharmaceuticals, Inc.; Janssen/Johnson & Johnson; Jazz Pharmaceuticals, Inc.; Kiadis Pharma; Kite Pharma; Kyowa Kirin; Legend Biotech; Magenta Therapeutics; Mallinckrodt LLC; Medac GmbH; Merck & Company, Inc.; Merck Sharp & Dohme Corp.; Mesoblast; Millennium, the Takeda Oncology Co.; Miltenyi Biotec, Inc.; Novartis Oncology; Novartis Pharmaceuticals Corporation; Omeros Corporation; Oncoimmune, Inc.; Orca Biosystems, Inc.; Pfizer, Inc.; Phamacyclics, LLC; Regeneron Pharmaceuticals, Inc.; REGiMMUNE Corp.; Sanofi Genzyme; Seattle Genetics; Sobi, Inc.; Takeda Oncology; Takeda Pharma; Terumo BCT; Viracor Eurofins and Xenikos BV. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

Topics to be addressed

- Overview of COVID-19
- Anticipated impacts on the SCTOD
 - Morbidity and mortality
 - HCT deferrals and rates
 - Performing procedure
 - Clinical research
 - Clinical Trials
 - Observational Research
 - Center capacity/operations
- CIBMTR Responses
 - Data collection
 - Plans for CPI, Audits
 - Research agenda
 - Studies relevant to new approaches to HCT
 - Studies regarding impact of COVID-19 on HCT, complications/outcomes
 - Consent for participation in research
 - Considerations for Center Specific Survival Analysis

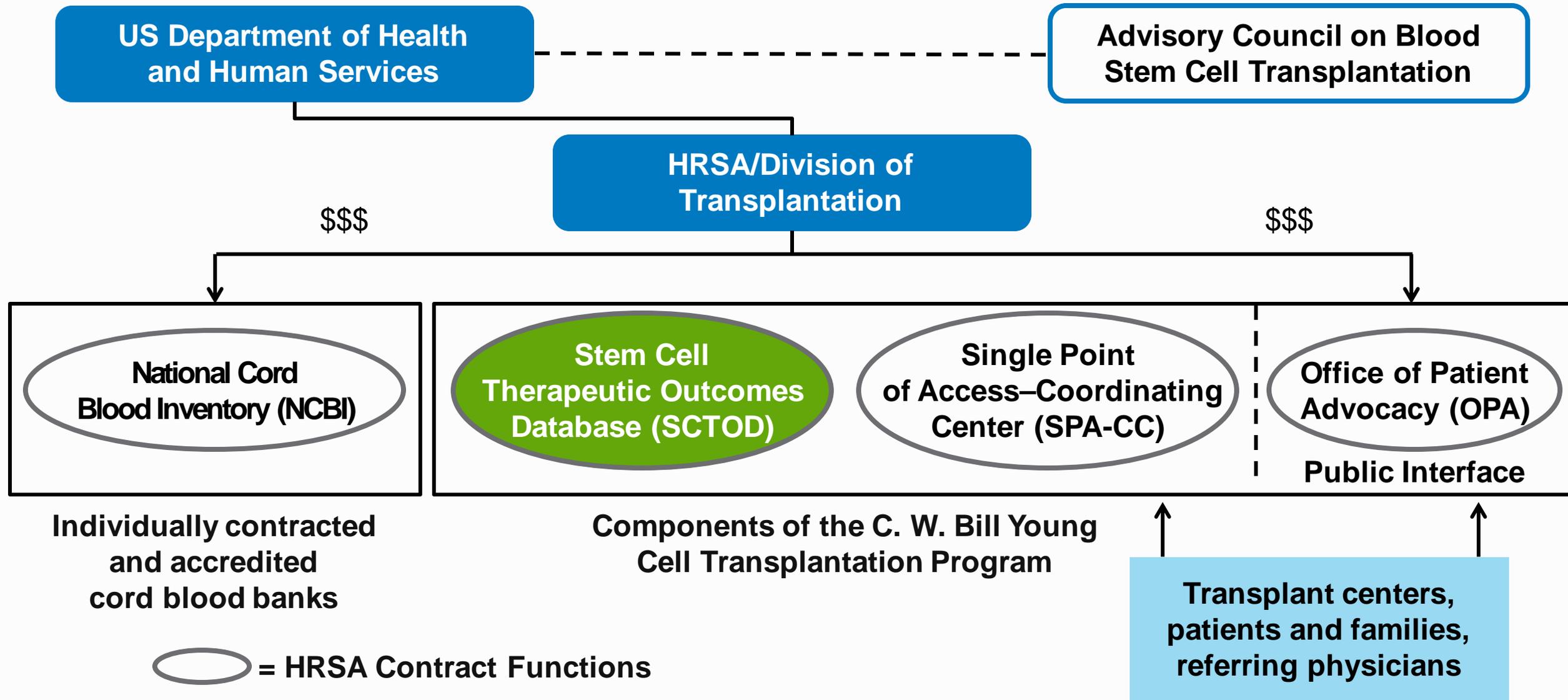
COVID 19

- Novel Coronavirus (SARS-CoV-2) with major respiratory complications
- WHO declared a Public Health Emergency of International Concern Jan 30, pandemic March 11, 2020
- As of April 16, 2020
 - US affected > 668,000 ; International affected > 2,150,000
 - US mortality > 33,000 ; International mortality >144,000
- Effective immunization, treatment TBD
- Duration of isolation, medical and economic impact - TBD

Morbidity and Mortality

- Much is unknown about the incidence of COVID-19 in patients with cancer, or hematopoietic cell transplantation (HCT) or the morbidity and mortality in these patients
- Early, small studies from Wuhan suggest:
 - Incidence doubled (0.79 vs. 0.37%)¹ in cancer patients
 - Severe complication rate also increased in cancer patients (39% v 8%)²
- Most “evidence” is very preliminary, incomplete or descriptive in nature

C.W. Bill Young Cell Transplantation Program*



Highlights of SCTOD expectations

- **Collect data (and specimens)**
 - *ALL* allogeneic HCTs with a U.S. recipient or donor
 - Related donor-recipient repository
 - Other cellular therapies
 - Quality of life data
 - Secure, efficient electronic data capture system
- **Analyze data**
 - Center-specific outcomes for U.S. related/unrelated donor transplants
 - Optimal size for the adult donor registry and cord blood unit inventory
 - Other research using the data collected under the contract
- **Disseminate data**
 - Within the Program
 - To the scientific and medical community
 - To patients, families and the public

How has COVID-19 changed how HCT is performed?

- Risks of travel restrictions for donors/donor products has led to acquisition and cryopreservation of donated stem cell product before initiation of preparative regimen
- Lung spirometry often deferred for infectious risk
- Drug shortages may impact preparative regimens
- Delayed allogeneic HCT for non-malignant or chronic disease
- Many programs are restricting transplants to inpatient only
- Patient follow-up has often been converted to virtual
- Substantial restrictions on visitation policies

What are the research impacts?

- Research office/Institutional Review Boards have:
 - Suspended human subjects research that is not interventional (and potentially of benefit to the patient)
 - Limited patient accrual to patients without standard of care options
 - Phase I or II trials, patients with refractory disease
- Clinical Trials staff moved off-site/working from home to avoid unnecessary patient exposures
- Observational research often deemed non-essential
 - Even if considered “minimal risk” and consent processes are embedded in routine consent for HCT

How has COVID-19 affected submission of HCT data?

- At most centers, data professionals are working off-site to maintain social distancing and avoid exposure to COVID-19
- In many cases, data professionals may not have routine access to the EMR and other essential systems remotely
- Data professionals subject to furlough because of economic effects on health systems
- Resulting in substantial decline in data submissions

Adapting to COVID-19 – Collecting COVID data

- The following changes were made to FormsNet to capture information on COVID-19
 - Pre- and post-transplant Transplant Essential Data (TED) forms revised to collect COVID-19 as a specific viral infection before or after HCT, or as cause of death - planned release in FormsNet May 8, 2020
 - Unprecedented timely approval by OMB April 9 – highlighting CIBMTR-HRSA-OMB collaboration
 - Comprehensive Report Form (collected on subset of HCT patients) and Cellular Therapy Essential Data form (collected on all non-HCT cell therapy patients) modified to include COVID-19 as of March 27th – both are voluntary
 - New voluntary form collecting detailed information on COVID-19 infection, treatment and outcome designed and in production – will be released in FormsNet in early May and can be submitted for all patients – TED, CRF and CTED tracks;
 - In the interim, using an innovative approach, the form can be completed via ServiceNow platform
- Frequent communication with centers using e-blast and CIBMTR website

COVID Data Collection

- Form 2149 (Respiratory Virus Post-Infusion Form) is operational in *ServiceNow*
- As of April 16,
 - # of Infections Reported: 37
 - # of Centers Reporting: 19 (4 non-US)
 - # of Deaths Reported: 7
 - Status of Infections: Resolved (4), Ongoing (13), Improved (8), Death (7), Pending (5)
- We do not put any criteria on what cases to report but do ask about how diagnosis was made so that we can report according to whatever criteria is required

Adapting to COVID-19 – Addressing Reduced Center Capacities

- Recognizing that many centers have more limited capacity for data reporting
 - Continuous Process Improvement (process for monitoring compliance with data submission timelines) has been suspended so there will be no penalties for delayed submission during the crisis
 - We are exploring ways to help centers catch up once the crisis subsides
 - Potential timeline impacts to Center Specific Survival Analysis
- On-site audits have been cancelled
 - Remote auditing being deployed at a few health systems
 - Audits will be re-scheduled as situation becomes more clear

Adapting to COVID-19 – Continuing CIBMTR Scientific Activities

- All data collection/center support systems are fully operational
- All CIBMTR staff working remotely since mid-March
 - Maintaining appropriate privacy and security procedures
- Working Committee activities are proceeding
 - Continue previously established timelines for ongoing studies but understand that PIs and Scientific Directors may be less available
 - Weekly Stats Meetings and Working Committee leadership calls proceeding
 - New studies approved following Transplant and Cellular Therapy meetings will stat - reserve hours for COVID-19-related activities

Some Noteworthy Scientific Achievements Relevant to COVID-19

- Impact of cryopreservation on transplant outcomes
 - Questions posed early March 2020
 - Analysis of 277 patients receiving HCT for hematologic malignancy with post transplant cyclophosphamide
 - Manuscript ACCEPTED for publication early April
 - Similar analysis of patients receiving calcineurin-based GVHD prophylaxis in progress
 - Analysis of patients receiving cryopreserved grafts for non-malignant disease anticipated to be complete end of April

Some Noteworthy Scientific Achievements Relevant to COVID-19

- Impact of tocilizumab (possible treatment for COVID-19 lung disease)
 - Question about safety posed last week (using data from cell therapy patients who frequently receive the drug)
 - Manuscript submitted early April

Adapting to COVID-19 – Clinical Trials

- RCI BMT and BMT CTN trials significantly affected
 - Accrual temporarily suspended for 7 trials; accrual restricted to certain graft types or certain centers at 2 others
 - On-site monitoring suspended – remote monitoring being considered
 - Measures to deliver investigational drug to enrolled patients who are remote from the transplant center necessary for one trial
 - Many scheduled visits will be done by telemedicine - some functional assessments (e.g. 6-minute walk test) being adapted to be done at home
 - Required many communications with study teams, NIH, DSMB, IRB and centers
 - Guidance issued for reporting COVID-19-related protocol deviations to IRBs
 - Data systems amended to collect information on COVID-19 and its impact (whether related to direct infection/exposure to restricted access to medical centers)
 - Impact to statistical analysis plans/finances being considered and codified

Consent Issue and Impact on Research

- Some centers have prohibited all non-interventional research in an effort to minimize patient and staff contact and potential exposure
- Would have a negative effect on CIBMTR's ability to understand the effect of the pandemic on HCT and CT patients
 - Without consent, we can still collect HCT data but only for government reporting purposes
- We believe the research restriction should not apply to CIBMTR
 - Consent can be obtained by the clinician consenting the patient to HCT or CT and data can be reported later
 - NO VISITS OR ASSESSMENTS REQUIRED THAT ARE NOT STANDARD OF CARE
- Encourage centers to consent patients even if data reporting is delayed
 - ASTCT Position Statement shared with centers' IRBs
 - Reminders to centers regarding reporting obligations and importance of research

Potential Impacts to SCTOD Reports

- Center Specific Survival Analysis – highest impact report
- Incidence of COVID-19 infection and treatment resource availability is variable
 - By location of center, residence of patient
- Impact on patients may vary by underlying condition(s)
- Transplants performed as early as March/April 2019 could be impacted –within 1 year time post transplant window
- Lack of spirometry affects calculation of HCT-comorbidity index
- Unknown impact of COVID-19 pre-HCT on HCT outcomes
- Will first affect the 2021 report (HCT years 2017-2019)

Possibilities to accommodate COVID-19 in the center specific survival?

- Eliminate transplants performed during a specific time period of risk
- Adjust expected outcome based on geographic disease incidence and severity
 - By location of HCT center, residence of recipient?
- Don't count deaths secondary to COVID-19
- Use an 'adjusted' HCT-CI without lung function across all centers for a fixed period of time
- Discussion topic of 2020 Center Outcomes Forum

