BMT CTN

Blood & Marrow Transplant Clinical Trials Network

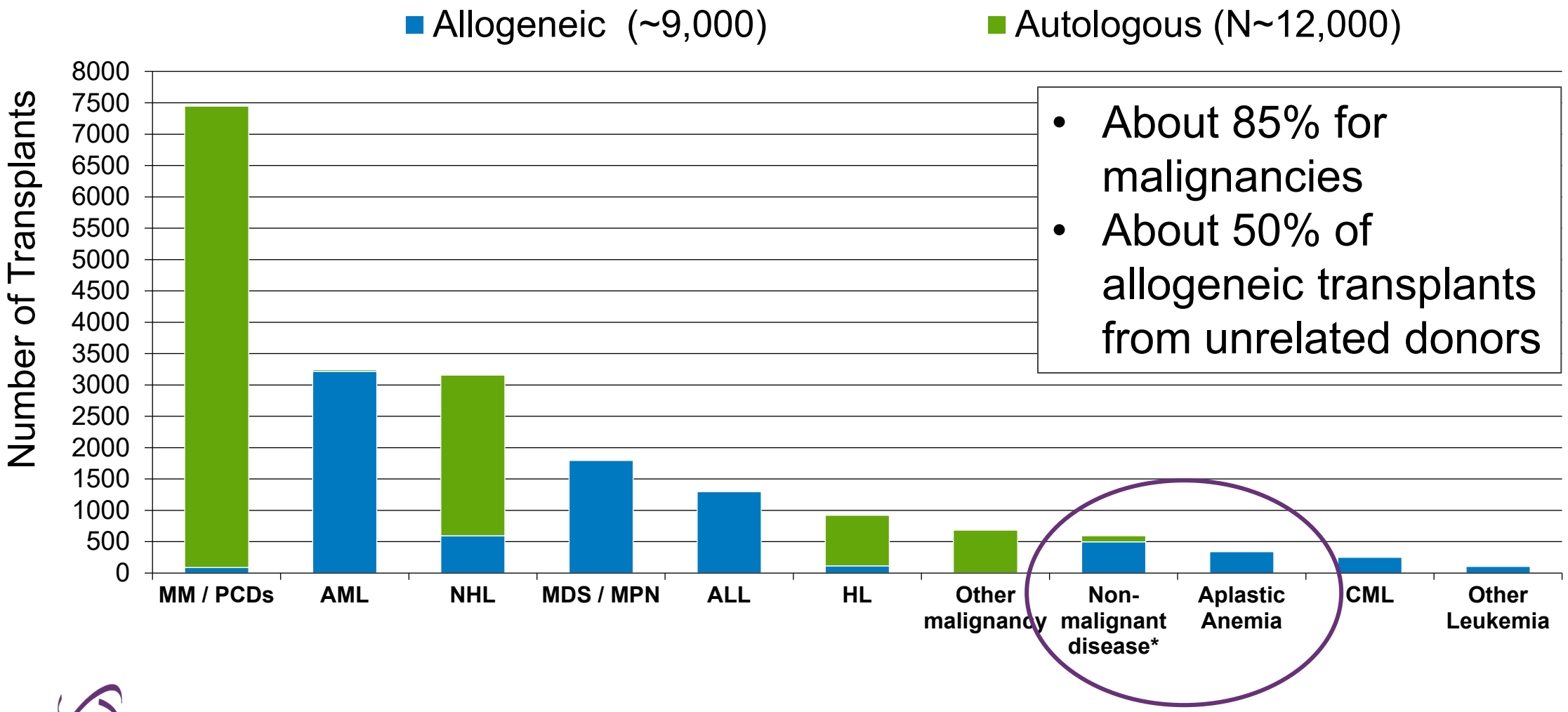
BLOOD & MARROW TRANSPLANT CLINICAL TRIALS NETWORK

20+ Years of Collaborative Research

Hematopoietic Stem Cell Transplantation (HCT) and Cellular Therapy

- HCT is an intensive therapy used primarily for hematologic malignancies as well as other rare marrow failure and immune deficiency disorders
- Cytotoxic/immune suppressive therapy followed by infusion of blood stem cells to:
  - Restore hematopoiesis destroyed by the primary disease and/or the pretransplant therapy given at myeloablative doses (allogeneic and autologous)
  - Provide an immune-mediated graft-versus-malignancy effect (allogeneic only)
- Other adoptive cellular therapies:
  - Chimeric antigen receptor immune cell therapy – immune cells modified to recognize tumor antigens
  - Tumor infiltrating lymphocytes – selection and propagation of effective tumor-specific cells
  - Gene therapies – replace defective blood stem cells to correct congenital disorders, e.g. sickle cell disease

Number of HCTs by indication in the US: the BMT CTN focuses predominantly on allogeneic transplants and, more recently, adoptive immuno- and gene therapy



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State of HCT Clinical Trials in US Prior to Year 2000 (other adoptive cell therapies were still in preclinical stage)

- Very few randomized phase III studies in allogeneic transplantation
- Most conducted by largest transplant centers, but often small and still single center
- Few opportunities for medium/small centers beyond Pharma funded studies
- No FDA approved agents for use in preventing or treating graft-versus-host disease (GVHD) following HCT
- Lack of infrastructure to take promising concepts developed at single centers forward without industry support

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Original RFA for BMT CTN by NIH

- Release date; January 4, 2001
- Objective: "The objective of this RFA is to establish a Network that will accelerate research in hematopoietic stem cell transplantation by comparing novel therapies to existing ones"
- Response: 49 Applicants (Review took place June 28, 2001; Funding Date: September 30, 2001); **16 core sites selected**
- RFA also solicited applications for a Data Coordinating Center (DCC)

Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

- Established: Sept. 2001; renewed 2006, 2011, 2017, 2024
  - 20 Core Centers/Consortia – each has an infrastructure grant
  - 75 Affiliate Centers
  - 1 Data and Coordinating Center – grant includes funds for protocol-relate expenses including reimbursement to centers
- Goal of the Program:
  - Provide the infrastructure needed to allow promising HCT and cellular therapies to be developed/evaluated in high quality multicenter studies

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Current Centers and Steering Committee Members

West
Rob Lowsky, Stanford
Ryo Nakamura, City of Hope
Fred Appelbaum, Fred Hutchinson
Rich Maziarz, Oregon Health Sciences (N=4)

Midwest
Greg Yanik, University of Michigan (N=3)
Leslie Kean, PTCTC* (N~60)
Sumi Vasu, Ohio State (N=5)
Saurab Chhabra, Medical College of Wisconsin
Daniel Weisdorf, University of Minnesota
Peter Westervelt, Washington University

East
Joe Antin, Dana Farber (N=2)
Rick Jones, Johns Hopkins University
Miguel Perales, Sloan-Kettering
Ed Stadtmauer, University of Pennsylvania
John Levine, Mt. Sinai (N=3)

South
John Wingard, University of Florida (N=2)
Joanne K. Kurtzberg, Duke University (N=2)
Helen Heslop, Baylor (N=2)
Joseph Pidala, Moffitt (N=2)
Asad Bashey, Northside (N=3)

PTCTC=Pediatric Transplant and Cell Therapy Consortium

38 Consortium Centers
Perform >60% of US allografts

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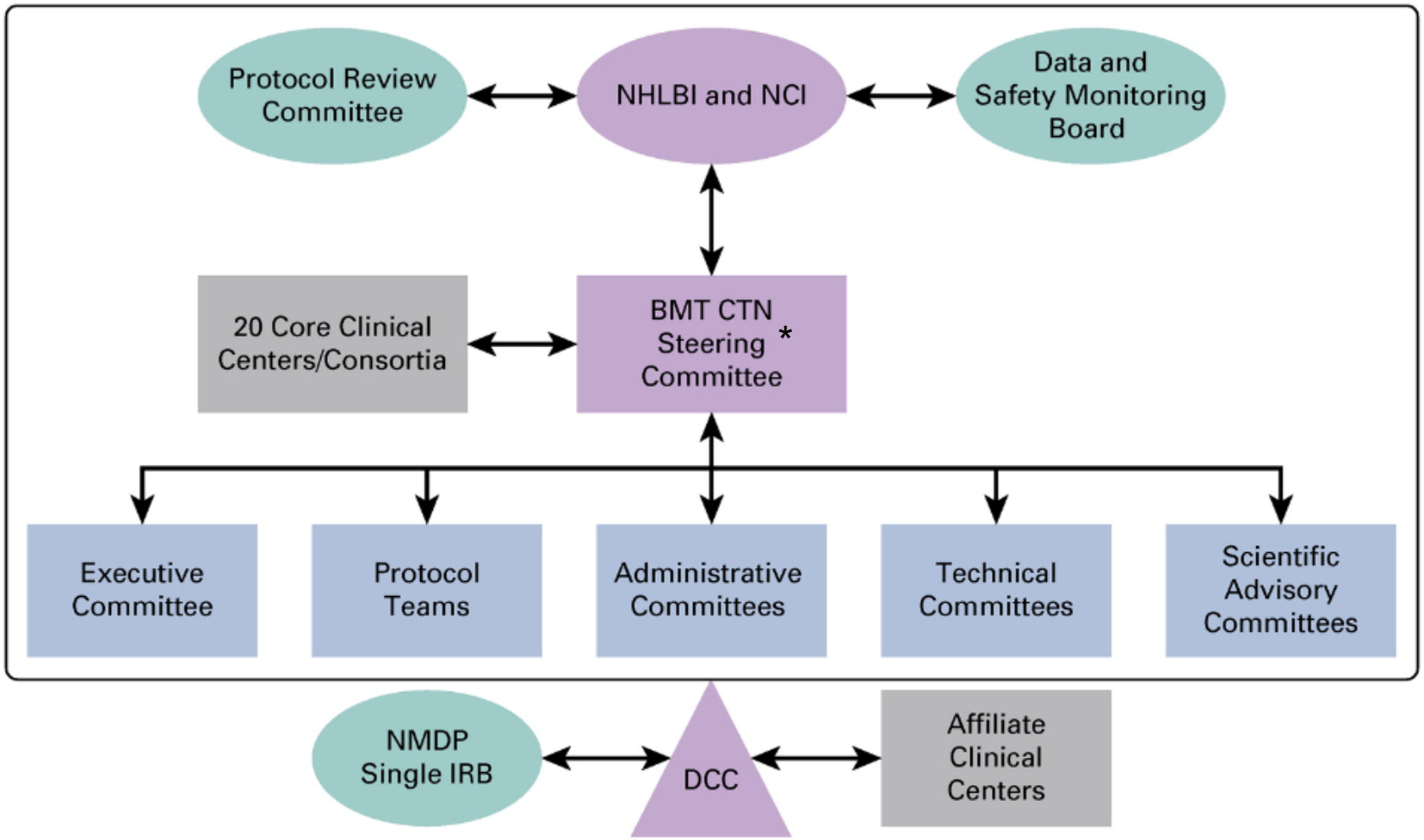
BMT CTN Organizational Structure



*Scientific agenda for each grant cycle set by Steering Committee

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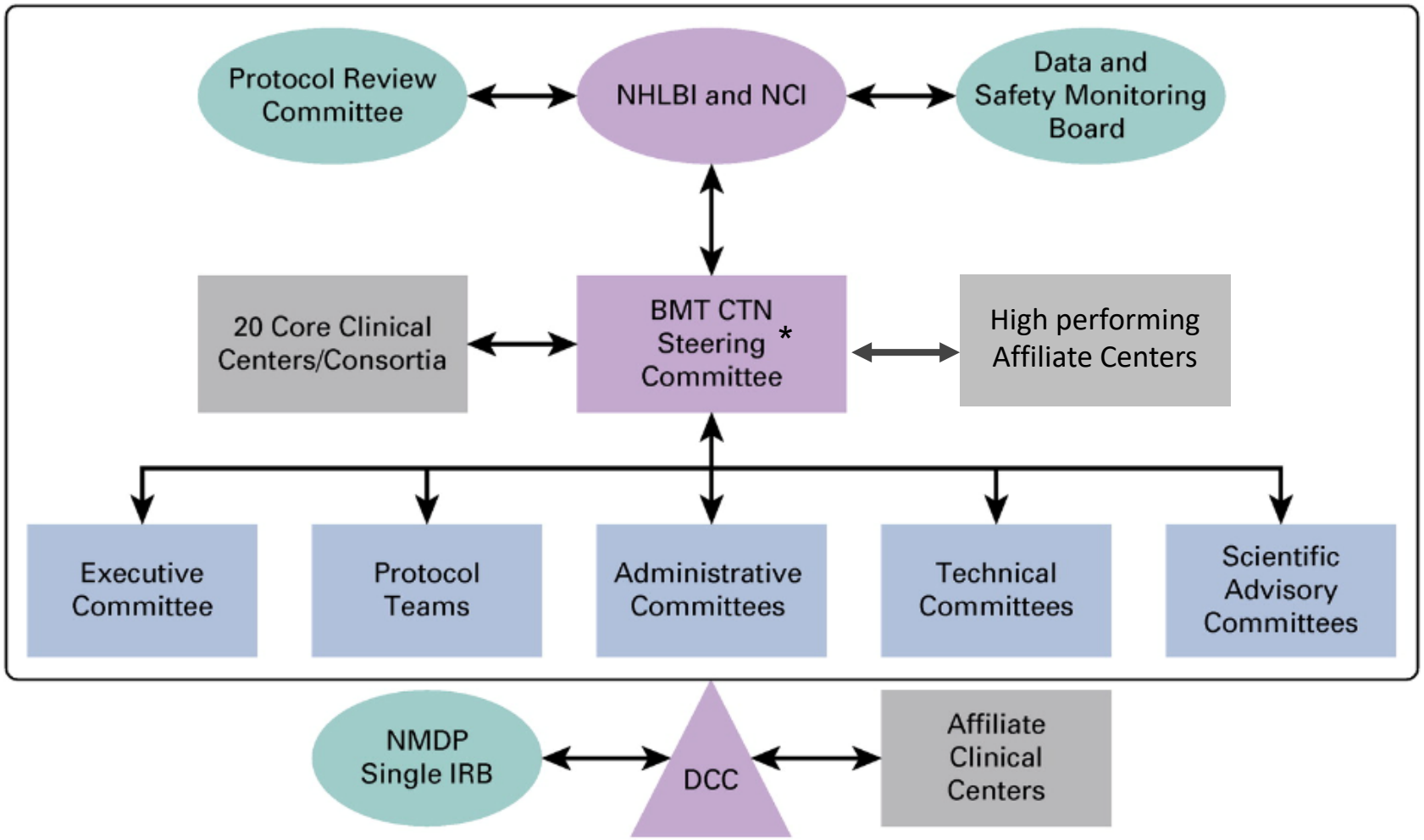
Source: Devine and Horowitz, J Clin Oncol, 2021

BMT CTN Organizational Structure



*Scientific agenda for each grant cycle set by Steering Committee

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Source: Devine and Horowitz, J Clin Oncol, 2021

BMT CTN Data and Coordinating Center

- Consortium of three organizations
  - Medical College of Wisconsin – long history of basic, clinical, population and statistical methodology research in HCT going back to the 1960s
  - National Marrow Donor Program – US registry for unrelated donors for HCT, established 1986
  - Emmes Corporation – private CRO established in 1977 that supports both industry and government projects
- Unusual arrangement but it works well
  - Benefits of CRO with experience in registration/corporate studies
  - Benefits of close involvement of academic leaders who have deep subject matter expertise but also understand clinical trials at the granular level
  - Close relationship with the opinion leaders in the field

- Research program jointly operated by the NMDP and MCW
- Began in 1972 as voluntary **patient outcomes registry;** now captures data on >99% of allografts, >90% of autografts, >60% of commercial CAR-T infusions in the US, with data for >680,000 patients
- Large biorepository of pre- and posttransplant specimens
- Portfolio includes observational, interventional, immunobiology, survey and health services research, including collection and analysis of patient reported outcomes - ~100 peer-reviewed publications annually

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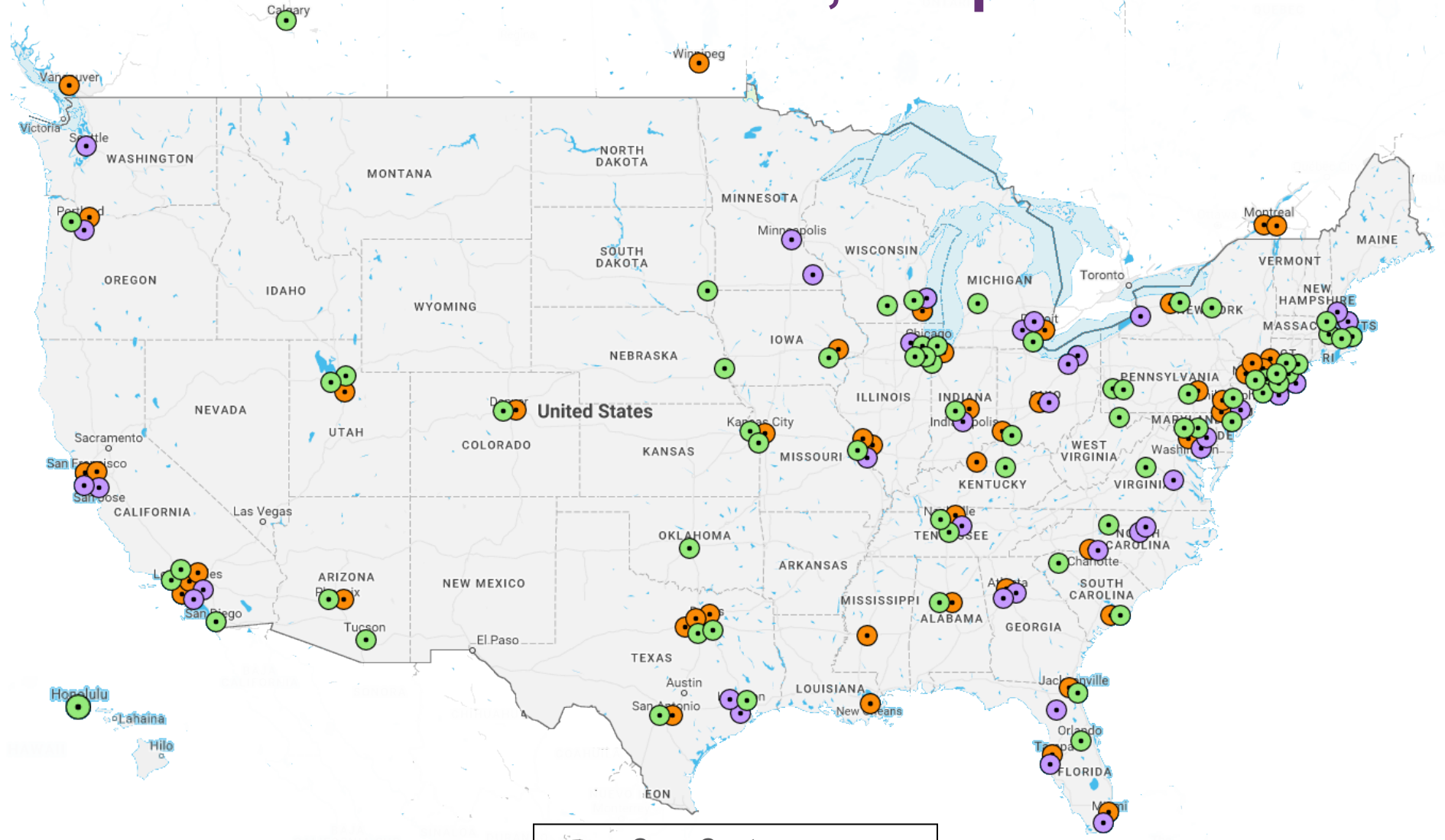
BMT CTN Centers
>125 centers have enrolled >16,800 patients since 2003



= Core Centers
= PTCTC Centers
= Affiliate Centers

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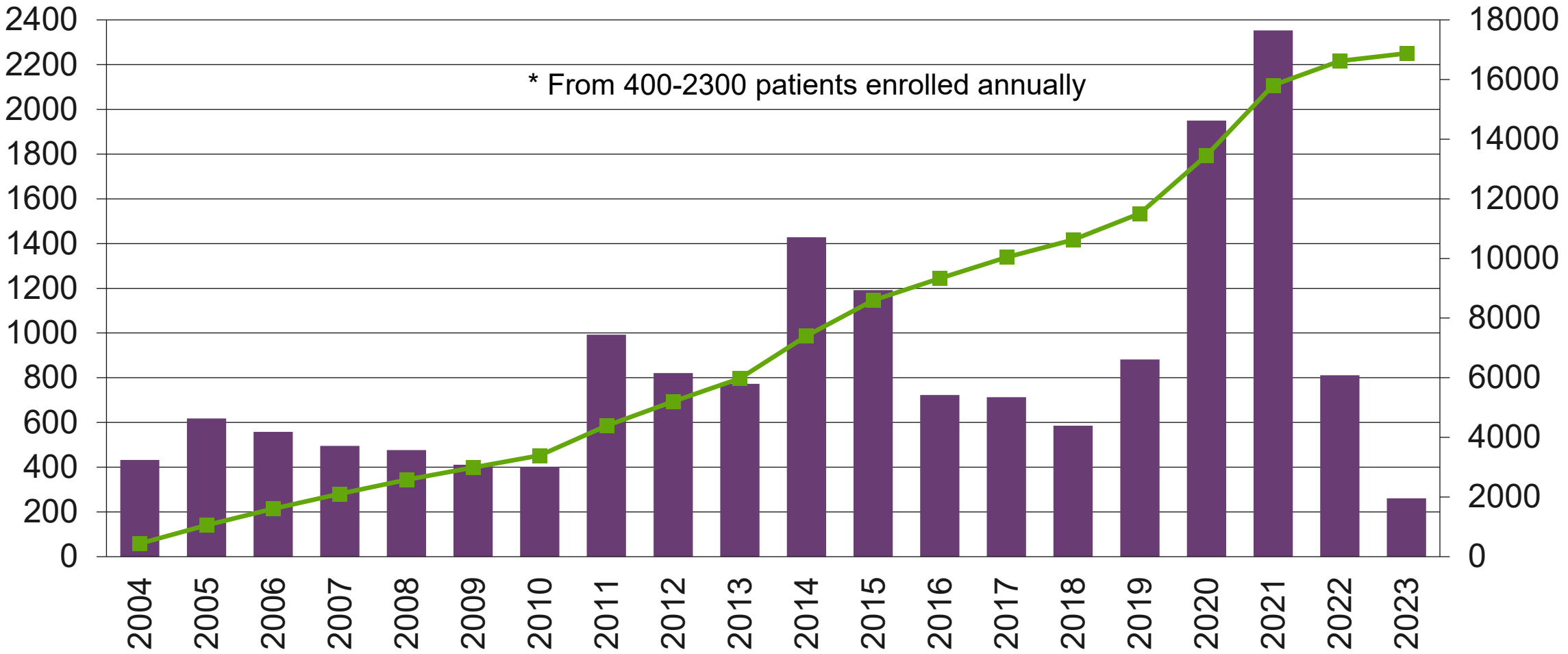
BMT CTN Yearly and Cumulative Accrual to all Protocols, 2004-2023 >16,840 patients



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Improving Therapy. Saving Lives.

BMT CTN Interventional Trials Developed since 200, resulting in >175 publications

	All Trials	Phase II*	Phase III
Donor/Graft Source	12	7	5
GVHD	12	5	7
Infection/TRM	2	0	2
Disease Control	21	10	12
Regimen Toxicity	7	6	1
QOL	3	0	3
TOTAL	58**	28	30

* 7 Randomized

** Does not include 1202 (Biomarkers), 07LT (LTFU), 1704 (CHARM), 1801 (Mi-Immune), or 2101 (COVID)

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What Have We Learned Since 2001?

Be Inclusive, Transparent

- Streamlined governance structure – most decisions (and all decisions about which trials to pursue) made via open discussions of the Steering Committee
  - Monthly videoconferences
  - In person (now hybrid) meetings three times a year
- Encourage participation
  - February 2024 SC Meeting: >100 in person and >75 virtual participants
  - Monthly 90-minute videoconferences average 150 participants
  - Intensive outreach to junior investigators, URGs
  - Strive for diversity of all kinds on Technical Committees and Protocol Teams
- Involve the larger community in periodic State of the Science Symposia
  - Focus efforts on the issues most important to them
- Collaborate
  - Academia/NCTN
  - Pharma

Simple Study Proposal Process

- Concept submitted to Executive Committee to confirm alignment with mission, lack of conflict with ongoing or planned studies
  - Proposal form at https://bmtctn.net/center-membership-study-participation
  - Committee meets monthly
- If approved, concept is presented at a Steering Committee meeting or call (monthly)
- Protocol Team* is established

Submit a New Study Concept

Proposals for clinical trials may be submitted from members of BMT CTN Core Centers, Affiliate Clinical Centers or others outside the Network.

Parties interested in submitting a proposal for consideration may complete the Proposed New Study Concept Form and return it to bmtctn@emmes.com.

*If the study will be funded in whole or part by industry, contract is negotiated by the DCC with terms governed by NIH rules; Protocol Team established after contract is executed.

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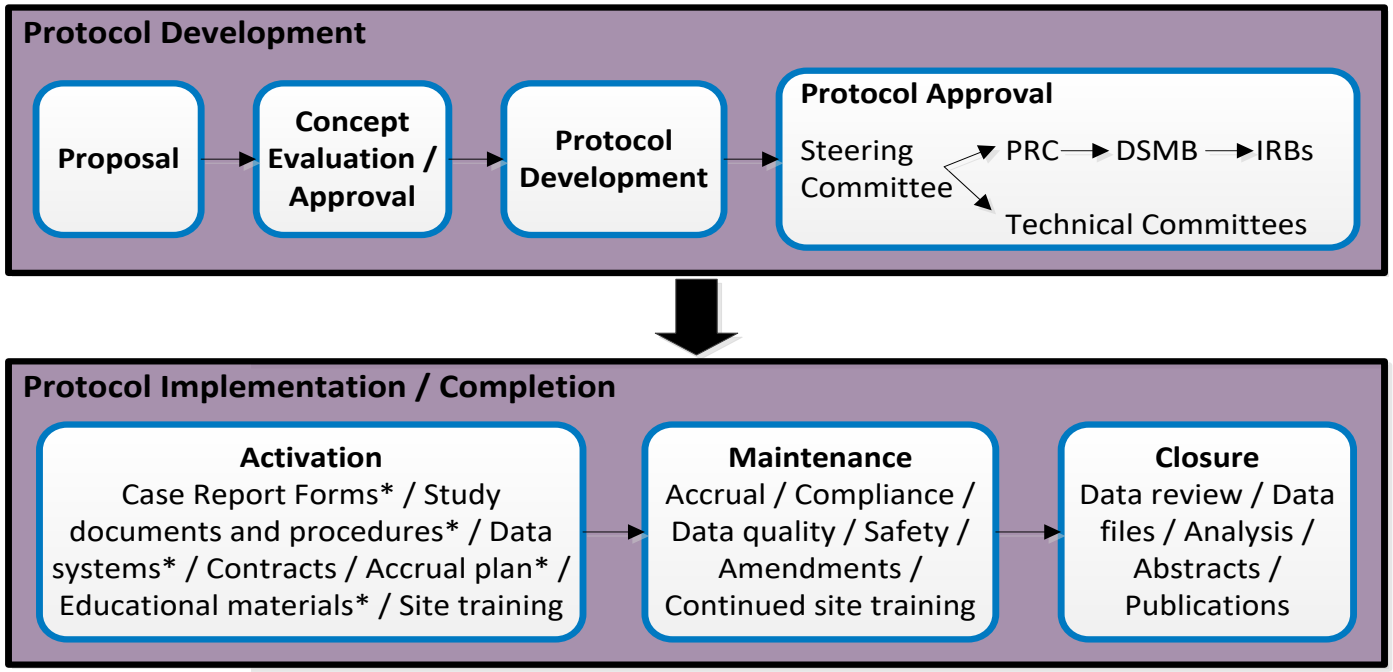
Centralized Processes

- Master contracts with >160 US centers (there are ~190 known transplant centers in the US)
- Single IRB
  - NMDP IRB – comprised of experts in transplantation and cell therapy
- Central bidding/contracting/oversight process for vendors (e.g., labs, pharmacies)
- Specimen collection, tracking and storage
  - >600,000 protocol-related biospecimens stored at the CIBMTR Research Repository
  - Data and specimens shared with investigators inside and outside the Network with a simple review and approval process (bmtctn.net)
- Electronic Patient-Reported Outcomes system
  - Managed by CIBMTR – not an extra burden on centers
  - Consistent battery of measures that allow cross-protocol comparisons

Effective Protocol Development Process

- Protocol Team
  - 2-3 Protocol Chairs
  - 6-8 representatives from Core and Affiliate Centers
  - Protocol Officer: DCC Transplant Physician
  - Protocol Coordinator
  - DCC Statistician
  - NHLBI Representative
  - NCI Representative
  - NHLBI Statistician
  - Supported by senior DCC staff, contracts, finance, data management, IT staff

- Meets **weekly** during active protocol development, monthly and as needed during enrollment and follow-up



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When Planning Protocols, Understand Your Audience

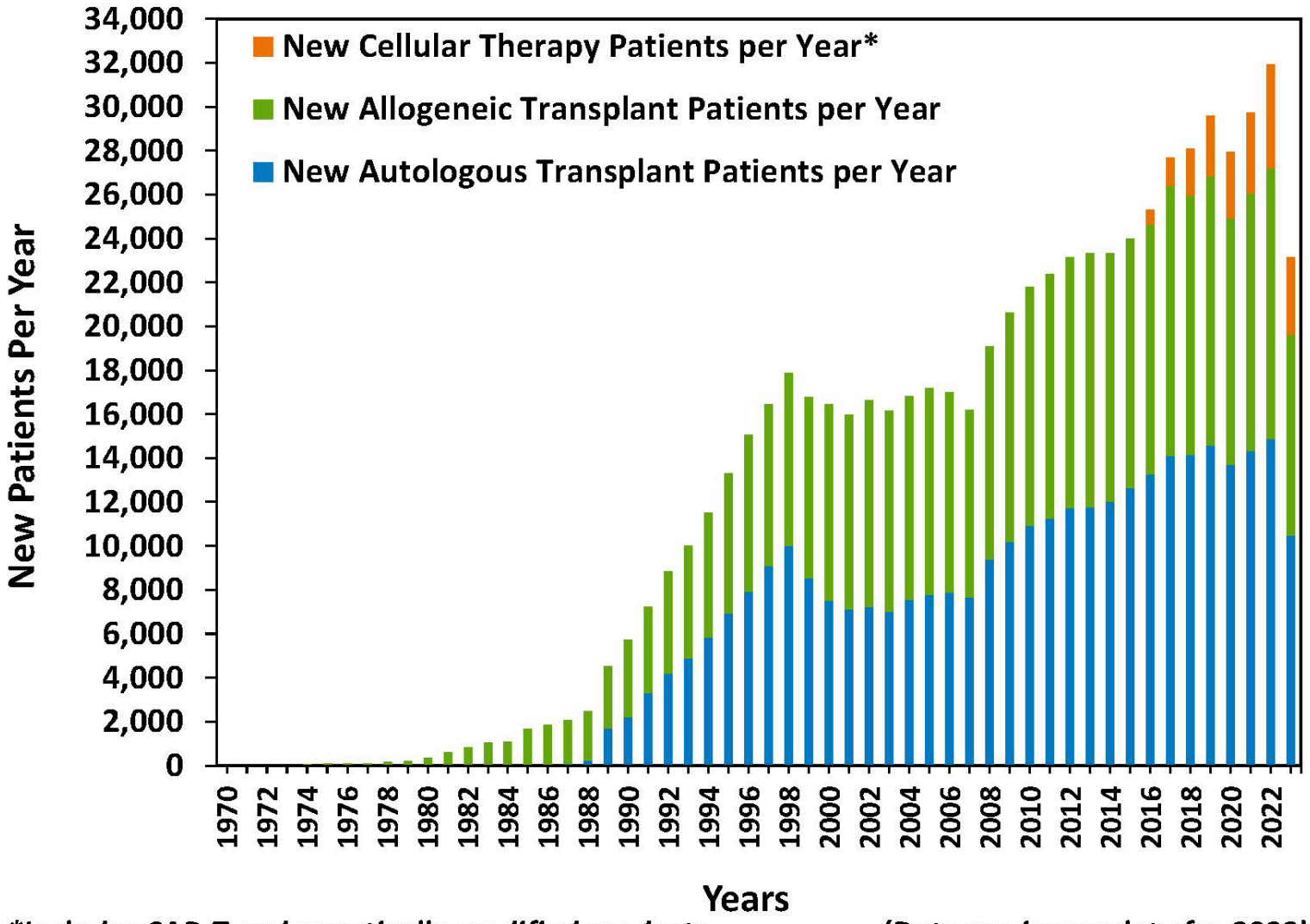
- Don’t prescribe what you don’t have to prescribe
- My favorite sentence in a study protocol:

> **Per Institutional Standards**

- Use as often as possible
  - Increases the likelihood of participation
  - Once activated, increases the likelihood of accrual
  - Decreases the likelihood of protocol violations
- Lots of things don’t matter as much as we think they do
- If you have to restrict things like preparative or immunosuppressive regimen (If they are not the subject of the study), try to give some choices

Our Biggest Asset: Being Embedded in a High-Quality, Longitudinal Registry of Real World Data

CIBMTR: A Source of Real World Data for >50 years



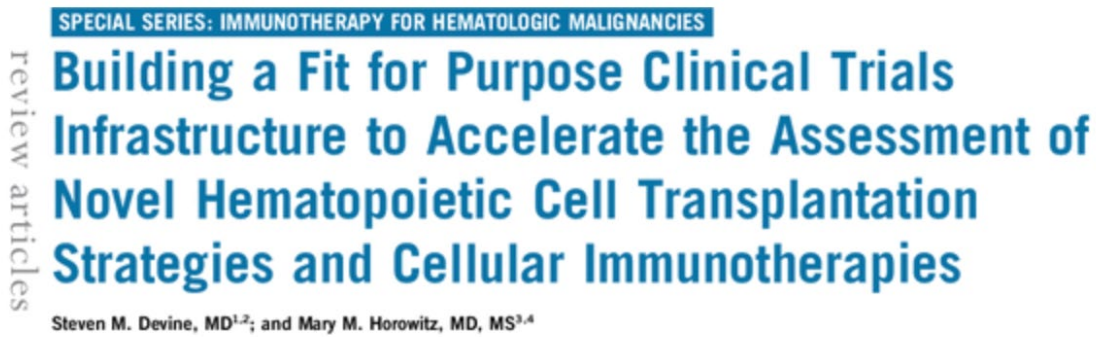
*Includes CAR-T and genetically modified products (Data are incomplete for 2023)

CIBMTR®
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Characteristics of CIBMTR's Outcomes Registry

- Population-based: defined by a specific type of therapy (HCT or cellular therapy)
  - Evolving data set reflecting community's growing understanding of important clinical variables to consider when studying outcomes
- Captures ~100% of allotransplants, ~90% of the autotransplants and ~60% of commercial CAR-T cell therapies in the US as well as data ~150 international sites
  - Allows trial designs, baseline outcome estimates, accrual projections to be made on actual experience
- Longitudinal: >15 years of follow-up for tens of thousands of patients
  - Built-in mechanism for long-term follow-up of patients treated on BMT CTN trials

BMT CTN: 23 years and counting


review articles

SPECIAL SERIES: IMMUNOTHERAPY FOR HEMATOLOGIC MALIGNANCIES

Building a Fit for Purpose Clinical Trials Infrastructure to Accelerate the Assessment of Novel Hematopoietic Cell Transplantation Strategies and Cellular Immunotherapies

Steven M. Devine, MD[1,2]; and Mary M. Horowitz, MD, MS[3,4]

Devine and Horowitz, J Clin Oncol, 2021

Lessons Learned:

Several themes have contributed to the network's success

- ***Effective Governance Structure***
- ***Robust Protocol Development Process***
- ***Centralize Processes to Achieve Efficiencies***
- ***Leverage Real World Data for optimal protocol design (CIBMTR Database)***
- **Seek academic and industry partnerships that benefit patients**
- **Understand mandate of public funding to ensure equitable access to HCT**
- **Measure Participating Center Quality**
- **Create Opportunities for the next generation of HCT/Cellular Immunotherapy Investigators**
- **Share Data and Biospecimens with the Public**
- **Partner with the HCT/CT Community to Develop Research Priorities**
- **Evolve in collaboration with the HCT/CT community to remain relevant**

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