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]

INTRODUCTION

Rapid progress in cancer therapy cannot be achieved without active patient participation in clinical trials. The past 5 years witnessed remarkable improvements in cancer response rates and survival, realized predominantly through prospective clinical research, and firmly established immunotherapy as a pillar of cancer treatment.[1,2] Allogeneic hematopoietic cell transplantation (HCT) is the epitome of cancer immunotherapy, with the landmark discovery of the graft-versus-leukemia effect made > 40 years ago.[3] HCT also created the reality of cures for life-threatening nonmalignant diseases.[4,5] Yet before the 21st century, progress in HCT was stifled by lack of a collaborative, adequately funded, and effective infrastructure for trials that could definitively test potentially breakthrough therapies. In 2000, the National Institutes of Health (NIH) recognized the gaps in translating scientific discoveries, funded predominantly through independent investigator R01 awards, into novel therapies that could change HCT practice. To address this deficiency, the NIH issued a request for applications (Request for Application No. HL-01-004) in 2001 for establishment of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Now in its 19th year, the BMT CTN has provided a successful infrastructure for clinical trials in HCT and cellular immunotherapy (CIT), enrolling > 11,000 patients on prospective studies and publishing 116 manuscripts, including 29 detailing primary study end points.[6-36] In this review, we describe development of the BMT CTN infrastructure, its current research capabilities, the means for developing its scientific priorities, lessons learned, and a roadmap for its future role in assessing novel HCT strategies and CITs targeting hematologic malignancies, solid tumors, and serious nonmalignant disorders. We foresee leveraging this experience to evolve the BMT CTN into a framework for accelerating evaluation of a burgeoning variety of cell and gene therapies, including those used to treat patients with solid tumors (Appendix, online only).[37-52]

ESTABLISHING A FIT FOR PURPOSE HCT/CIT CLINICAL TRIALS INFRASTRUCTURE: KEYS TO SUCCESS

We outline several themes key to the success of the BMT CTN and that we believe also apply more generally to any successful publicly funded clinical trials enterprise.

Create an Effective Governance Structure

The initial structure funded 16 clinical Core Centers geographically distributed throughout the United States. The Data and Coordinating Center (DCC) was funded separately from the Core Centers and is a consortium of three organizations, each with extensive experience in HCT clinical research—the Center for International Blood and Marrow Transplant Research (CIBMTR), the Emmes Company, and the National Marrow Donor Program (NMDP)/Be The Match. The CIBMTR is a collaborative research program of the Medical College of Wisconsin (MCW; Milwaukee, WI) and NMDP/Be The Match (Minneapolis, MN) with offices on both campuses. The Emmes Company is a contract research organization (CRO) in Rockville, Maryland, with experience conducting HCT trials for the National Heart, Lung, and Blood Institute (NHLBI). The DCC grant was awarded to MCW with subcontracts to NMDP/Be The Match and Emmes. Today, the BMT CTN is in its fourth grant cycle. It is co-funded by the NHLBI and the National Cancer Institute (NCI). Although subsequent grant cycles brought some changes, including increasing the number of Core Centers to 20, the basic organizational structure and delineation of responsibilities remain intact (Figs 1A and 1B).

The BMT CTN Steering Committee (SC) sets the scientific agenda and oversees selection, design, execution, and analysis of all BMT CTN studies. The SC includes the principal investigator (PI) of each Core Center and the DCC, the NHLBI project officer, the NCI project officer, a representative of each of the NCI-funded cancer cooperative groups, and representatives of affiliate centers (centers not awarded separate grants) that meet standards for exemplary accrual and

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 9, 2020 and published at ascopubs.org/journal/jco on January 12, 2021: DOI https://doi.org/10.1200/JCO.20.01623

CONTEXT

Key Objective

This review describes the development and evolution of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), a National Institutes of Health–funded clinical trials infrastructure dedicated to accelerating the assessment of innovative hematopoietic cell transplantation (HCT) strategies and cellular Immunotherapies (CITs).

Knowledge Generated

Over its 19-year history, the BMT CTN has adapted in response to its successes and failures. It has engaged an increasingly broad and diverse group of stakeholders within the HCT and CIT fields.

Relevance

We outline several themes key to the success of the BMT CTN that can be applied to other successful publicly or philanthropically funded clinical trials enterprises dedicated to studying immunotherapies.

participation. Viewing the network as a national resource, we sought from the outset to create a culture of inclusivity and encouraged all qualified centers to participate. Although only SC members can vote, SC meetings are open to other individuals from Core Centers and affiliate centers. The SC elects a chair, who serves a 2-year term as vice-chair, 1-year term as chair-elect, a 2-year term as chair, and a 1-year term as immediate past-chair. An Executive Committee (EC) composed of the chair, chair-elect, immediate past-chair, DCC PI, NMDP and Emmes co-PIs, and NHLBI and NCI representatives meets monthly to ensure seamless communication between operations, SC leadership, and NIH. The chair, chair-elect, and immediate past-chair also meet weekly with DCC PIs and staff.

Establish a Robust Protocol Development Process

Figure 2 outlines the BMT CTN protocol development process. This process was substantially streamlined over the life cycle of the network, leading to greater efficiency and reduced timelines. We developed several metrics to monitor protocol development from protocol team formation to activation and implementation, described previously.[30] The process begins with SC approval of the concept; the SC meets monthly so concepts can be reviewed in a timely manner. The value of the study and its alignment to the mission of the network and NHLBI/NCI is strongly considered. If the protocol requires funds from the parent BMT CTN grant, costs and funds availability are also considered. Of note, some studies are fully funded by the BMT CTN grant, some are funded by other NIH grants, some are fully funded by corporate sponsors, and some by both NIH and corporate sponsors. If approved, two or three protocol chairs are appointed, typically the individual(s) proposing the idea and others with a significant relevant interest. The Core Center PIs are then invited to nominate protocol team members based on the interests and expertise of individuals within their center or consortium (several core members are composed of a group of centers). The DCC assigns a protocol officer (PO) and a PhD statistician. The PO is a physician member of the DCC from the CIBMTR (MCW or NMDP) who coordinates activities between the team and DCC leadership. Nominated protocol team members are selected by the EC based on merit, level of enthusiasm, years of experience, and likelihood of accrual based on the center's or individual's prior experience. The NHLBI/NCI project officers and an NHLBI statistician also participate in each team. After a near final draft of the protocol is completed, the study is presented to the SC for a vote to approve, disapprove, or return with recommended changes. If approved, the next step involves NHLBI review processes (Fig 2). If the study passes NHLBI review, the protocol is released to sites to initiate the activation process or first submitted to the US Food and Drug Administration (FDA) if an Investigational New Drug (IND) application is required (approximately 30% of current BMT CTN studies). Once the protocol is released to sites, activation is expected to occur within 180 days. Each protocol is given accrual goals with a typical slower ramp-up period, followed by a steady state that is continuously monitored by the DCC, and if necessary, action plans are instituted quickly. Studies falling behind schedule are subject to closure, but typically, the protocol team develops a series of steps and protocol amendments, if needed, to correct. Only three of the 39 studies led by the BMT CTN (excluding collaborative studies where an NCI group was the lead) closed because of poor accrual. Among the remaining 36 studies, 31 completed accrual or are accruing at or ahead of schedule.

Leverage a Critical Asset: The CIBMTR Database

The BMT CTN built on a long-standing infrastructure for HCT clinical research. In 1972, just 4 years after the first successful HCTs, the International Bone Marrow Transplant Registry at MCW began as a voluntary effort to collect and analyze data from centers pioneering the therapy. In 1986, the NMDP was established to build a US unrelated donor registry; it also established a program to collect data

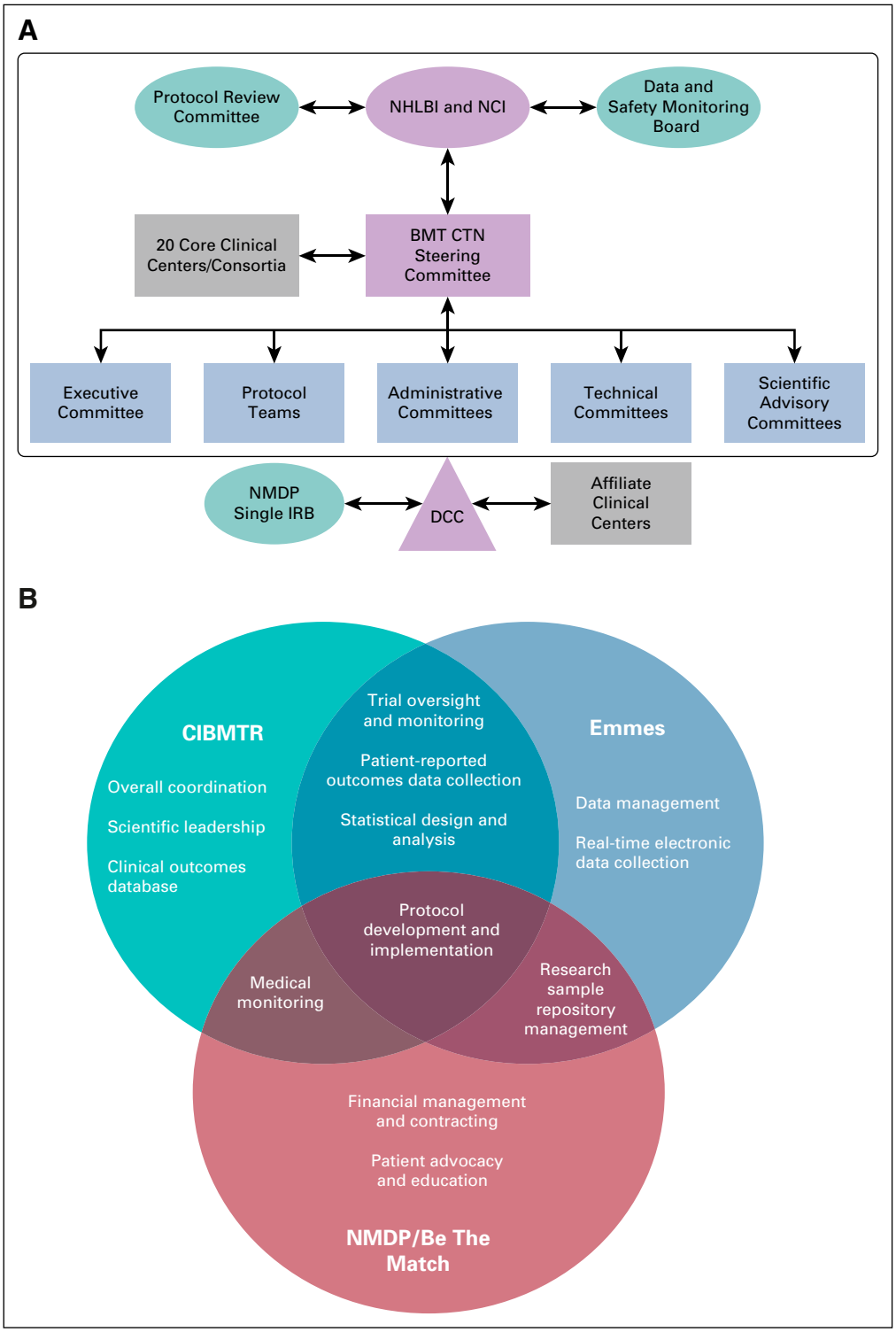

FIG 1. (A) The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) is composed of a network of organizations that work together to achieve common goals. It includes the following elements: Data and Coordinating Center (DCC), 20 Core Centers/Consortia, a network of affiliate centers, Steering Committee, protocol teams, technical committees, administrative committees, ad hoc committees, and National Heart, Lung, and Blood Institute (NHLBI) review committees. These are described in greater detail in the BMT CTN Annual Progress Report.[36] (B) This depicts the delineation of responsibilities between the three organizations that compose the DCC. Several are overlapping. CIBMTR, Center for International Blood and Marrow Transplant Research; IRB, institutional review board; NCI, National Cancer Institute; NMDP, National Marrow Donor Program.

on the transplantations it facilitated and created a repository of pretransplantation donor-recipient samples. In 2004, these two research programs integrated through an affiliation agreement between MCW and the NMDP, forming the CIBMTR. The CIBMTR is now a multifaceted research program with participation of approximately 200 US transplantation centers and > 130 international centers; data on > 500,000 HCTs and > 2,000 CIT recipients; and programs in outcomes research, immunobiology, health services, statistical methodology, bioinformatics, and clinical trials.

The CIBMTR database is a critical asset, providing access to comprehensive, current data on the population for whom network trials are intended. The CIBMTR maintains, with

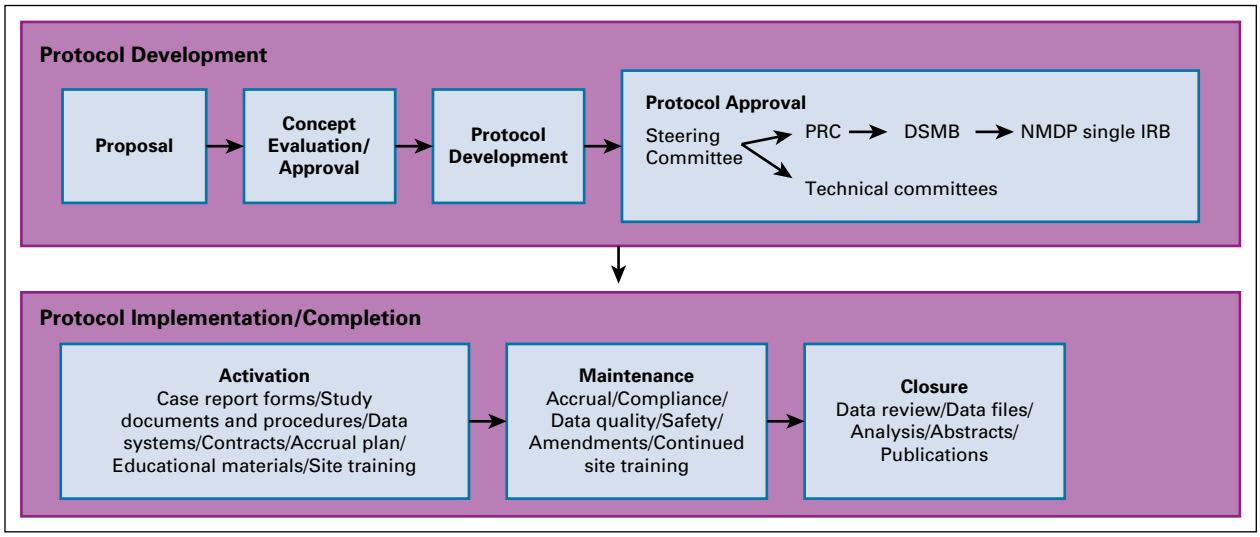

FIG 2. Once formed, the protocol team typically holds weekly calls managed by a Data and Coordinating Center (DCC) protocol coordinator. Calls follow an 8- to 12-week development process wherein each chapter of the protocol is assigned to specific team members and with deadlines for completion. Once approved by the Steering Committee (SC), each protocol undergoes independent scientific review by the protocol review committee (PRC) and review by the Data and Safety Monitoring Board (DSMB). Metrics include time from protocol team formation to DSMB approval, which can be ≤ 6 months for industry-sponsored studies. Once protocols are released to sites, it should take < 180 days to site activation and 56 days from protocol activation to first patient enrolled. IRB, institutional review board; NMDP, National Marrow Donor Program.

separate NIH and Health Resources and Services Administration support and aided by a 2005 federal requirement for reporting HCT outcomes data, an observational database of almost all US HCTs.[53] Thus, the BMT CTN can assess numbers of potentially eligible patients using real-world data rather than relying on investigator estimates. In fact, systematic comparison of investigator estimates with database estimates documents clearly the tendency of clinicians to overestimate potential enrollment by a factor of 3-4. This can lead to misleading feasibility assessments, unrealistic accrual targets, and, at times, premature closure of trials.[54,55] The CIBMTR database mitigates these risks.

The database also allows comparisons of single-arm studies of therapies being considered for phase II or III trials, with patient-level data available to adjust for confounding factors, rather than relying on anecdotal or published experience.[13] Two recent phase III trials (ClinicalTrials.gov identifiers: NCT03959241 and NCT02345850) use composite end points informed by the CIBMTR analysis. The design of these trials would have been very different without the ability to explore their effects using CIBMTR data.

CIBMTR, through the Cellular Immunotherapy Data Resource (CIDR),[56] now also collects data on a large fraction of patients receiving non-HCT CIT, such as chimeric antigen receptor (CAR) T cells. This resource was established as part of the larger Cancer Moonshot initiative to establish an immuno-oncology translational network.[57] The focus of the CIDR is on collecting CIT data so that they can be analyzed and shared with the academic community, as CIBMTR has done for HCT data since its inception, including the mandatory 15-year follow-up of patients receiving genetically modified cells. It will provide a resource for generating knowledge and fostering further study both within and outside of the BMT CTN infrastructure and will be used to assist in design of trials for these therapies.

CIBMTR data complement data collected through the BMT CTN's clinical trials system, thereby easing the data reporting burden for centers. As we seek to understand the impact of COVID-19 on clinical trial end points, rapid implementation of a system to collect COVID-related information on all HCT recipients through CIBMTR is now in place[58] and will provide crucial information to make those judgments.

Finally, because the CIBMTR follows HCT and CIT recipients over the long term, a separate long-term follow-up system is not necessary for patients on BMT CTN trials, and analysis of long-term survivors is planned for most trials.[30] The value of having CIBMTR data to design, conduct, and monitor studies cannot be underestimated and is perhaps the most critical factor contributing to the network's success.

Centralize Processes to Achieve Efficiencies

Many processes were centralized by the BMT CTN to achieve efficiency (Table 1). For instance, the DCC long recognized that a single institutional review board (sIRB) could streamline trial activation. Once the US Department of Health and Human Services released its proposed revisions to the Common Rule, recommending that sIRB review be mandated for federally supported multicenter studies, the DCC took action to prepare for this, using the

TABLE 1. BMT CTN Organization and Governance Responsibilities

Entity	Role
Core Clinical Centers	Conducting BMT CTN studies Protocol team membership Identification/retention of patients Assuring data quality and accuracy Participating on Steering Committee Manuscript preparation
DCC	Day-to-day management of BMT CTN activities Overall coordination and administration Maintaining/updating SOPs Regulatory support/tracking and compiling data Assuring data quality and accuracy Clinical site monitoring Contracting/subcontracting Meeting coordination Maintaining biorepository
NHLBI and NCI	Administrative support Participation on Executive Committee Monitoring compliance with NIH policies Management of grants Partnering with awardees Financial stewardship
Steering Committee	Provide overall scientific governance Set overall scientific agenda Formulate and implement policy decisions Appoint protocol teams Monitor protocol timelines Attend monthly calls and face-to-face meetings
Executive Committee	Overall scientific management of BMT CTN Approval of protocol team composition Set agenda for Steering Committee meetings and calls Availability for day-to-day management decisions
DSMB	Monitor patient safety on studies Review accrual and overall study performance Submit recommendations regarding study conduct and continuation to NHLBI
NMDP sIRB	Provide ethical review of BMT CTN studies Ensure patient safety during study conduct Provide ongoing review of patient safety during study conduct Streamline approval process
Administrative/technical committees	Review publications for compliance with BMT CTN and NIH policies Provide review of ancillary study requests Review requests for access to biorepository samples Provide review of developing studies from CRA perspective Provide review of studies from pharmaceutical perspective

Abbreviations: BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CRA, clinical research associate; DCC, Data and Coordinating Center; DSMB, Data and Safety Monitoring Board; NCI, National Cancer Institute; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; NMDP, National Marrow Donor Program; sIRB, single institutional review board; SOP, standard operating procedure.

NMDP institutional review board (IRB).[59] Its members are HCT and CIT experts and thus are uniquely suited to serve as the sIRB for the BMT CTN. The DCC worked with the NMDP IRB to put appropriate processes in place, including developing an IRB Authorization Agreement, a local context questionnaire, and a form for reporting potential serious, continuing noncompliance, or unanticipated problems for network centers.

The NMDP also negotiates and manages all contracts for all aspects of BMT CTN activities. Master agreements are in place with all Core Centers, > 60 affiliate centers, and several national clinical trials network groups. Once a protocol budget is approved, the DCC executes riders to these agreements, saving time and expense.

The DCC is responsible for procuring services for protocols, such as correlative laboratory studies, sample storage, and drug distribution. The DCC issues a request for proposals; negotiates pricing, terms, and conditions; and places contracts or purchase orders. A CIBMTR immunobiology research scientist and the protocol chair provide assistance with

identifying potential suppliers, developing the statement of work, selecting experts to review responses, and establishing review criteria. Most centrally procured supplies are competitively bid with some exceptions if correlative studies that strengthen the scientific objectives of trials require collaboration with highly specialized academic laboratories. These laboratories provide a unique combination of investigator leadership, specialized or proprietary testing methodologies, or other one-of-a kind contributions justifying a select source partnership to meet scientific objectives. However, the DCC still exerts due diligence, requesting detailed accounting of direct and indirect costs, staff qualifications, analytical methods and equipment, and quality assurance procedures and negotiating on price before a final award is made.

Understand the Mandate of Public Funding to Ensure Equitable Access to HCT and CIT

The BMT CTN is dedicated to addressing disparities in access to HCT and CIT. The immunogenetics of HCT creates one of the starker examples of access inequality in all of medicine, because HLA barriers to successful transplantation vary by ethnic group.[60] The likelihood of identifying a well-matched volunteer donor for patients without an HLA-identical relative is > 70% for Whites but as low as 20% for African Americans. Socioeconomic disparities in access to expensive CITs such as CAR-T cells also likely exist, but data are sparse.[61] BMT CTN's commitment to addressing disparities is reflected by the portfolio of studies conducted. Both umbilical cord blood and

TABLE 2. BMT CTN Center Performance Rating Criteria

Metric	Rating	Criteria
Scientific and administrative activity (maximum score, 10 points)	Outstanding (10 points)	Holds Steering Committee chair, past-chair, or chair-elect position or protocol team chair plus > 70% of team calls participation
	Acceptable (5.1-9 points)	% call participation × 10
	Needs improvement (0-5 points)	Attends < 33% of protocol team calls
Accrual (maximum score, 60 points)	Outstanding (60 points)	Accrues > 24 patients and meets ≥ 100% of projected accrual or enrolls ≥ 48 patients
	Acceptable (40-59 points)	Score = (actual/projected) × 60, then adjust for maximum Centers enrolling ≥ 20 patients can get a maximum score of 60; centers enrolling < 20 patients can only get a maximum of 45 points even if meeting or exceeding projections
	Needs improvement (< 40 points)	Score < 40 points Centers enrolling < 18 patients can only get a maximum of 10 points even if meeting or exceeding projections
Activation and enrollment (maximum score, 10 points); metrics include the following: ≥ 4 protocols activated within preceding 4 years; ≤ 56 days to consent preview; ≤ 180 days to activation; ≤ 56 days from activation to first patient enrolled	Outstanding (10 points)	Meets 4 of 4 metrics
	Acceptable (5 points)	Meets 2-3 of 4 metrics
	Needs improvement (0 points)	Meets < 2 of 4 metrics
Data quality (maximum score, 10 points): metrics include the following: data audit error rate ≤ 2%; ≤ 2% protocol deviations; ≤ 5 forms > 30 days past due per patient; CIBMTR form compliance ≥ 90%	Outstanding (10 points)	Meets 4 of 4 metrics
	Acceptable (5 points)	Meets 2-3 of 4 metrics
	Needs improvement (0 points)	Meets < 2 of 4 metrics
Laboratory compliance (maximum score, 10 points): average compliance percentage for all participating protocols	Outstanding (10 points)	Outstanding (OS)
	Acceptable (5.1-9.0 points)	Above average (AA) ≥ 7.5; acceptable (AC) = 5.1-7.4
	Needs Improvement (0-5 points)	Unacceptable (UA) = 0-2.4; marginally acceptable (MA) ≥ 2.5
Overall assessment (maximum score, 100 points)	Outstanding	≥ 90 points
	Acceptable	60-90 points
	Needs improvement	< 60 points (center required to submit action plan)

Abbreviations: BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CIBMTR, Center for International Blood and Marrow Transplant Research.

haploidentical transplantations provide opportunity to bridge this access gap, and recognizing this, the network designed two successful parallel phase II studies in 2006 to explore both approaches.[14] These led to the development of a randomized phase III study comparing both graft sources (ClinicalTrials.gov identifier: NCT01597778). Of note, 28% of participants were ethnic minorities, an unprecedented rate for an HCT study. Among all patients receiving allotransplantations on BMT CTN trials in 2016-2019, 12% were African American compared with 8% among all US allotransplantations reported to CIBMTR.

Measure Participating Center Quality

The DCC has developed a series of metrics that are simple and meaningful for quantifying center performance on an annual basis and generates reports that are reviewed by each center, the DCC, and NIH leadership (Table 2). Centers are rated each year as "outstanding," "meets requirements," or "needs improvement." The focus is on center and, therefore, network improvement. Like any evaluative process that compares one to the norm, there are some contentious issues, but overall, centers treat these evaluations seriously and generally correct deficiencies over time.

Seek Academic and Industry Partnerships That Benefit Patients

During the first 10 years of the BMT CTN (2001-2011), opportunities for collaborations with industry were limited. However, some studies fully funded by the NIH would not have been possible without in-kind contributions from pharma.[30] It was not until 2015, after establishing a strong clinical research infrastructure with a proven track record, that opportunities for co-development with industry were actively sought. The BMT CTN EC realized that such partnerships would allow the network to address more unmet patient needs and, simultaneously, that interest in HCT and CIT among the private sector was increasing. The BMT CTN is now actively conducting four FDA registration trials under IND, with several others under development or consideration. The proportion of network funding obtained through corporate sponsorship has increased substantially since 2016 (Fig 3).

The unique composition of the DCC, with two mission-driven nonprofit organizations focused on HCT and CIT (CIBMTR and NMDP) and a for-profit CRO (Emmes Company) with HCT experience, presents exciting opportunities for industry engagement. The CIBMTR maintains strong ties to national and international academic leaders in HCT and CIT based on its longstanding reputation for research leadership and is well suited to act as a convener of experts in HCT and CIT. The BMT CTN DCC is able to facilitate the merger of academic leadership and oversight into small and large industry-sponsored trials. Other academic organizations have forged similar relationships.[62-64] Typically, an industry sponsor developing a product hires a CRO to help execute clinical development for regulatory approval through a series of necessary trial phases. Academic experts are separately brought in to provide consultation, scientific oversight, and safety monitoring, as well as interpretation of trial results. However, the trial process (study design, data analyses, interpretation, and reporting of results) rests mainly with the industry sponsor and CRO. The BMT CTN presents a unique opportunity for combining the benefits of an academic research organization (ARO) with the range of services provided by a traditional CRO. This ARO-CRO model provides greater opportunity for academic leadership and oversight throughout the product and clinical trial development process, enhancing scientific integrity and offering the sponsor firsthand knowledge of relevant study end points, eligibility requirements, and statistical expertise. Such capabilities may not be readily available to the sponsor or stand-alone CRO, particularly in a complex environment such as HCT or CIT. The ARO (CIBMTR/NMDP/SC/protocol team) provides academic expertise and oversight, together with NIH leadership, and leverages the infrastructure of a well-established global CRO (Emmes), providing a full range of services frequently lacking in organizations relying heavily on NIH or other foundation support for their infrastructure.

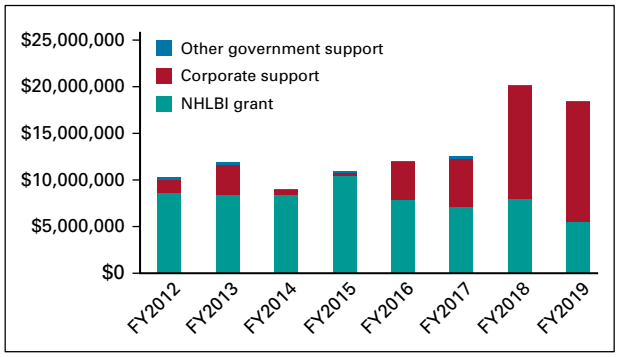

FIG 3. Blood and Marrow Transplant Clinical Trials Network (BMT CTN) revenue by year. The graph depicts the growth in industry support for BMT CTN studies from 2012 to 2019. FY, fiscal year; NHLBI, National Heart, Lung, and Blood Institute.

Another unique aspect is access to the CIBMTR and CIDR HCT and CIT databases and the value of having information on almost all US transplantations and a growing number of other CITs, as described earlier. This greatly facilitates accurate estimates of accrual, can pinpoint patient volume at potential participating sites, and provides critical estimates of rates or incidence of relevant clinical outcomes. This allows a statistical design based on accurate, contemporary real-world data rather than published results in patients who may have been treated up to 10 years earlier. Furthermore, the existing master agreements with most US centers can greatly facilitate the activation process for industry trials. Recognition of these resources has accelerated the growth of collaborations with an increasing array of industry partners over the past 5 years.

Create Opportunities for the Next Generation of HCT and CIT Investigators

The BMT CTN is committed to actively generating opportunities for the career development of junior investigators and does this in a variety of ways. First, all face-to-face meetings or conference calls of the SC are open access; anyone interested is invited to join. Second, involvement in network support committees (Table 1) is open to all through a nomination process (including self-nomination). Third, the nominating process for protocol team membership encourages PIs to nominate junior investigators, and a strong effort is made to have junior investigators compose at least 50% of the protocol team and, often, fill one of the study chair positions. This process has been effective because now 75% of all protocol members are below the level of full professor.

Sharing Data and Biospecimens With the Public

Because of space constraints, we cannot describe these processes in detail, but BMT CTN data and biospecimen sharing policies and procedures can be found on the BMT CTN Web site[65] and the NIH Web site.[66]

HOW DOES THE NETWORK DEVELOP ITS RESEARCH PRIORITIES?

Reviewing the State of the Science

The BMT CTN SC sets the scientific agenda for the network and serves as a forum for presentation of all clinical trial concepts. Although new concepts can be presented at any time in the life cycle of a funding period, the process of setting the agenda begins at the renewal of the grant cycle (typically every 5-7 years). One key element of the long-term success of the BMT CTN is the incorporation of a State of the Science Symposium (SOSS) every 6-7 years.[67,68] The SOSS brings together subject matter experts in 10-12 key areas of relevance to HCT and CT. Each category has a committee, for which a chair and a DCC liaison is assigned by the EC. The chair and liaison then solicit nominations from the SC PIs for eight to 12 additional committee members. If certain expertise is required outside of the list of nominees, the chair can nominate outside individuals. Each committee is charged with surveying the current and near future landscape of the science and then generating two to four trial concepts they believe hold the greatest scientific rationale and potential for progress. After holding three to four meetings, the committee chairs write a report outlining the committee's deliberations and recommendations. This report is reviewed by at least two subject matter experts external to the network, often from countries outside of the United States, to formally provide feedback and critique. All stakeholders come together for a 2-day in-person meeting to hear the committee presentations. A planning committee comprising SOSS committee chairs, NIH representatives, and external reviewers prioritizes the trial concepts. Three SOSSs have been held (in 2001, 2007, and 2014). Although the proceedings of the initial symposium in 2001 (which preceded establishment of the network) were not published, the BMT CTN completed nine of its recommended studies. The 2014 SOSS was the largest to date, with 13 committees including 112 committee members, 20 external reviewers, and > 300 attendees at the open forum.[67] Ultimately, 12 concepts were prioritized, resulting in the development of six clinical trials. The next SOSS is planned for February 2021 (Table 3).

How Will the Network Need to Evolve for the Future?

The 2021 SOSS will provide an opportunity to generate a vision for the future scientific agenda of the BMT CTN. In the meantime, we will need to continuously evaluate and update our processes. The COVID-19 pandemic forced us to reflect on some of our potential vulnerabilities and to consider how we can leverage available technologies to crisis-proof our process. We have had to use remote site monitoring at sites that permit access, although permission is highly variable. We are considering whether to include requests for remote monitoring on all of our future agreements with sites, although executing these will be challenging. Remote visits are possible through telehealth technology and are likely here to stay.[69,70] We need to incorporate this technology into future trials. We must consider how we can further develop means of capturing data from sources such as the electronic medical record in an automated fashion, easing the burden imposed of manual data entry and its inherent limitations. The NMDP and MCW are actively funding a CIBMTR initiative called Data Transformation that seeks to reduce the reporting burden on centers and develop prototypes for electronic

TABLE 3. BMT CTN State of the Science Committees

Committee	Chair	DCC Liaison
Clinical Trial Design	Eric Leifer	Brent Logan
Comorbidity and RRT	Richard Maziarz	Ed Stadtmauer
GVHD	John Levine	Richard Jones
Hemoglobinopathies	Mark Walters	Helen Heslop
Infection/Immune Reconstitution	Marcie Riches	Marcie Riches
Late Effects/QOL/Economics	Betty Hamilton	Bronwen Shaw
Lymphoid Malignancies	Frederick Locke	Mehdi Hamadani
Myeloid Malignancies	Yi-Bin Chen	Steven Devine
Nonmalignant Disorders	Amy DeZern	Mary Eapen
Optimal Donor/Graft Source	Karen Ballen	Mary Horowitz
Pediatric Malignancies	Leslie Kean	Rachel Phelan
Plasma Cell Disorders	Parameswaran Hari	Marcelo Pasquini

Abbreviations: BMT CTN, Blood and Marrow Transplant Clinical Trials Network; DCC, Data and Coordinating Center; GVHD, graft-versus-host disease; QOL, quality of life; RRT, regimen-related toxicity.

data transfer.[71] We are also actively involved in electronic capture of patient-reported outcomes (PROs), and although outside the scope of this review, we have several initiatives to increase the collection of PROs and incorporate them into standard follow-up procedures.[72,73] The system is now used in four active BMT CTN studies. Leveraging remote tracking software and patient-wearable devices and accessing smartphones to collect and generate data from study participants will have to be considered and will present unique challenges and opportunities. As we generate more data and access new data sources, we will need stronger relationships with bioinformatics colleagues to take advantage of available artificial intelligence and machine learning platforms to analyze the data we generate.[74] Finally, we are pursuing means to collect biospecimens from patients remote from the treating site and performing some tests and evaluations in and delivering drugs to patients' homes or other remote sites, reducing the inconvenience and risk of travel back to the HCT/CIT center while maintaining protocol compliance.[75] Building on the tradition of using real-world data to plan, execute, and complement clinical trials in HCT, the CIDR will provide this opportunity to assist in planning, executing, and understanding CIT trials as well as a practical and consistent infrastructure for long-term follow-up of patients receiving gene-modified CIT products.

Now in its 19th year of existence, the BMT CTN has met the challenge of providing an effective infrastructure for the development and conduct of complex multicenter HCT and CIT studies, engaging a growing variety of stakeholders along the way but never forgetting we exist to improve the lives of the patients we serve. We have become more efficient and focused and believe the network is now poised to expand its horizons to study a rapidly increasing portfolio of cell and gene therapies that target diseases encompassed within the mission of the NHLBI and NCI and would be difficult to study outside of a well-established infrastructure.[5,23,29,37,38,42,43,45,52,76-85] Continued public funding will enable us to expand our collaborations with the academic community and private sector and allow us to leverage the infrastructure we have created to further advance progress in the treatment of patients with serious malignant and nonmalignant conditions.

AFFILIATIONS

[1]National Marrow Donor Program/Be The Match, Minneapolis, MN
[2]Center for International Blood and Marrow Transplant Research, Minneapolis, MN
[3]Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, WI
[4]Division of Hematology-Oncology, Department of Medicine, Medical College of Wisconsin, WI

CORRESPONDING AUTHOR

Steven M. Devine, MD, National Marrow Donor Program/Be The Match, 500 N 5th St, Minneapolis, MN 55401; Twitter: @BeTheMatch; e-mail: sdevine2@nmdp.org.

SUPPORT

Supported by Grant No. U24HL138660 from the National Heart, Lung, and Blood Institute and the National Cancer Institute; Grants No. U24CA076518 and U24CA233032 from the National Cancer Institute; and Contracts No. HHSH250201700006C and HHSH250201700007C with the Health Resources and Services Administration.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.01623.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Markham MJ, Wachter K, Agarwal N, et al: Clinical cancer advances 2020: Annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 38:1081, 2020
2. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2020. CA Cancer J Clin 70:7-30, 2020
3. Weiden PL, Flournoy N, Thomas ED, et al: Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. N Engl J Med 300: 1068-1073, 1979
4. Stenger EO, Shenoy S, Krishnamurti L: How I treat sickle cell disease with hematopoietic cell transplantation. Blood 134:2249-2260, 2019
5. Georges GE, Storb R: Hematopoietic stem cell transplantation for acquired aplastic anemia. Curr Opin Hematol 23:495-500, 2016
6. Allen CE, Marsh R, Dawson P, et al: Reduced-intensity conditioning for hematopoietic cell transplant for HLH and primary immune deficiencies. Blood 132: 1438-1451, 2018
7. Alousi AM, Weisdorf DJ, Logan BR, et al: Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: A randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. Blood 114:511-517, 2009
8. Alvarnas JC, Le Rademacher J, Wang Y, et al: Autologous hematopoietic cell transplantation for HIV-related lymphoma: Results of the BMT CTN 0803/AMC 071 trial. Blood 128:1050-1058, 2016
9. Ambinder RF, Wu J, Logan B, et al: Allogeneic hematopoietic cell transplant for HIV patients with hematologic malignancies: The BMT CTN-0903/AMC-080 trial. Biol Blood Marrow Transplant 25:2160-2166, 2019
10. Anasetti C, Logan BR, Lee SJ, et al: Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med 367:1487-1496, 2012

11. Anderlini P, Wu J, Gersten I, et al: Cyclophosphamide conditioning in patients with severe aplastic anaemia given unrelated marrow transplantation: A phase 1-2 dose de-escalation study. Lancet Haematol 2:e367-e375, 2015
12. Bolaños-Meade J, Logan BR, Alousi AM, et al: Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN 0802. Blood 124:3221-3227, 2014
13. Bolaños-Meade J, Reshef R, Fraser R, et al: Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: A randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). Lancet Haematol 6:e132-e143, 2019
14. Brunstein CG, Fuchs EJ, Carter SL, et al: Alternative donor transplantation after reduced intensity conditioning: Results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. Blood 118:282-288, 2011
15. Carpenter PA, Logan BR, Lee SJ, et al: A phase II/III randomized, multicenter trial of prednisone/sirolimus versus prednisone/sirolimus/calcineurin inhibitor for the treatment of chronic graft-*versus*-host disease: BMT CTN 0801. Haematologica 103:1915-1924, 2018
16. Cutler C, Logan B, Nakamura R, et al: Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. Blood 124:1372-1377, 2014
17. Devine SM, Carter S, Soiffer RJ, et al: Low risk of chronic graft-versus-host disease and relapse associated with T cell-depleted peripheral blood stem cell transplantation for acute myelogenous leukemia in first remission: Results of the Blood and Marrow Transplant Clinical Trials Network protocol 0303. Biol Blood Marrow Transplant 17:1343-1351, 2011
18. Devine SM, Owzar K, Blum W, et al: Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: Results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502. J Clin Oncol 33:4167-4175, 2015
19. Jacobsen PB, Le-Rademacher J, Jim H, et al: Exercise and stress management training prior to hematopoietic cell transplantation: Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. Biol Blood Marrow Transplant 20:1530-1536, 2014
20. Krishnan A, Pasquini MC, Logan B, et al: Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): A phase 3 biological assignment trial. Lancet Oncol 12:1195-1203, 2011
21. Laport GG, Wu J, Logan B, et al: Reduced-intensity conditioning with fludarabine, cyclophosphamide, and high-dose rituximab for allogeneic hematopoietic cell transplantation for follicular lymphoma: A phase two multicenter trial from the Blood and Marrow Transplant Clinical Trials Network. Biol Blood Marrow Transplant 22:1440-1448, 2016
22. McCarthy PL, Owzar K, Hofmeister CC, et al: Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 366:1770-1781, 2012
23. Pidala J, Hamadani M, Dawson P, et al: Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: The BMT CTN 1501 trial. Blood 135:97-107, 2020
24. Ravandi F, Othus M, O'Brien SM, et al: US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. Blood Adv 1:250-259, 2016
25. Scott BL, Pasquini MC, Logan BR, et al: Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol 35:1154-1161, 2017
26. Shenoy S, Eapen M, Panepinto JA, et al: A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. Blood 128:2561-2567, 2016
27. Smith EP, Li H, Friedberg JW, et al: Tandem autologous hematopoietic cell transplantation for patients with primary progressive or recurrent Hodgkin lymphoma: A SWOG and Blood and Marrow Transplant Clinical Trials Network phase II trial (SWOG S0410/BMT CTN 0703). Biol Blood Marrow Transplant 24:700-707, 2018
28. Spellecy R, Tarima S, Denzen E, et al: Easy-to-read informed consent form for hematopoietic cell transplantation clinical trials: Results from the Blood and Marrow Transplant Clinical Trials Network 1205 study. Biol Blood Marrow Transplant 24:2145-2151, 2018
29. Stadtmauer EA, Pasquini MC, Blackwell B, et al: Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: Results of the BMT CTN 0702 trial. J Clin Oncol 37:589-597, 2019
30. Steering Committee of the Blood and Marrow Transplant Clinical Trials Network: The Blood and Marrow Transplant Clinical Trials Network: An effective infrastructure for addressing important issues in hematopoietic cell transplantation. Biol Blood Marrow Transplant 22:1747-1757, 2016
31. Tomblyn MR, Ewell M, Bredeson C, et al: Autologous versus reduced-intensity allogeneic hematopoietic cell transplantation for patients with chemosensitive follicular non-Hodgkin lymphoma beyond first complete response or first partial response. Biol Blood Marrow Transplant 17:1051-1057, 2011
32. Vose JM, Carter S, Burns LJ, et al: Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: Results from the BMT CTN 0401 trial. J Clin Oncol 31:1662-1668, 2013
33. Wagner JE Jr, Eapen M, Carter S, et al: One-unit versus two-unit cord-blood transplantation for hematologic cancers. N Engl J Med 371:1685-1694, 2014
34. Wingard JR, Carter SL, Walsh TJ, et al: Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood 116:5111-5118, 2010
35. Yanik GA, Horowitz MM, Weisdorf DJ, et al: Randomized, double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor: Enbrel (etanercept) for the treatment of idiopathic pneumonia syndrome after allogeneic stem cell transplantation: Blood and Marrow Transplant Clinical Trials Network protocol. Biol Blood Marrow Transplant 20:858-864, 2014
36. Blood and Marrow Transplant Clinical Trials Network: BMT CTN 2020 progress report. https://web.emmes.com/study/bmt2/public/Progress%20report/2020%20BMT%20CTN%20Progress%20Report%20Public%20Version.pdf
37. Weber EW, Maus MV, Mackall CL: The emerging landscape of immune cell therapies. Cell 181:46-62, 2020
38. Locke FL, Go WY, Neelapu SS: Development and use of the anti-CD19 chimeric antigen receptor T-cell therapy axicabtagene ciloleucel in large B-cell lymphoma: A review. JAMA Oncol 6:281-290, 2020
39. Yamamoto TN, Kishton RJ, Restifo NP: Developing neoantigen-targeted T cell-based treatments for solid tumors. Nat Med 25:1488-1499, 2019
40. Schultz L, Mackall C: Driving CAR T cell translation forward. Sci Transl Med 11:eaaw2127, 2019
41. Riley RS, June CH, Langer R, et al: Delivery technologies for cancer immunotherapy. Nat Rev Drug Discov 18:175-196, 2019
42. Majzner RG, Mackall CL: Clinical lessons learned from the first leg of the CAR T cell journey. Nat Med 25:1341-1355, 2019
43. Brown CE, Mackall CL: CAR T cell therapy: Inroads to response and resistance. Nat Rev Immunol 19:73-74, 2019
44. Bailey SR, Maus MV: Gene editing for immune cell therapies. Nat Biotechnol 37:1425-1434, 2019
45. Salter AI, Pont MJ, Riddell SR: Chimeric antigen receptor-modified T cells: CD19 and the road beyond. Blood 131:2621-2629, 2018

46. Neelapu SS, Tummala S, Kebriaei P, et al: Chimeric antigen receptor T-cell therapy: Assessment and management of toxicities. Nat Rev Clin Oncol 15:47-62, 2018
47. June CH, Sadelain M: Chimeric antigen receptor therapy. N Engl J Med 379:64-73, 2018
48. Blumenthal GM, Pazdur R: Approvals in 2017: Gene therapies and site-agnostic indications. Nat Rev Clin Oncol 15:127-128, 2018
49. Ciurea SO, Schafer JR, Bassett R, et al: Phase 1 clinical trial using mbIL21 ex vivo-expanded donor-derived NK cells after haploidentical transplantation. Blood 130:1857-1868, 2017
50. Neelapu SS, Locke FL, Bartlett NL, et al: Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 377:2531-2544, 2017
51. Pal SK, Miller MJ, Agarwal N, et al: Clinical Cancer Advances 2019: Annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 37:834-849, 2019
52. Schuster SJ, Bishop MR, Tam CS, et al: Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 380:45-56, 2019
53. D'Souza A, Fretham C, Lee SJ, et al: Current use of and trends in hematopoietic cell transplantation in the United States. Biol Blood Marrow Transplant 26: e177-e182, 2020
54. Seruga B, Ocana A, Amir E, et al: Failures in phase III: Causes and consequences. Clin Cancer Res 21:4552-4560, 2015
55. Lee SJC, Murphy CC, Geiger AM, et al: Conceptual model for accrual to cancer clinical trials. J Clin Oncol 37:1993-1996, 2019
56. Center for International Blood and Marrow Transplant Research: Cellular Immunotherapy Data Resource (CIDR) shares knowledge. https://www.cibmtr.org/About/WhatWeDo/CIDR
57. Aelion CM, Airhihenbuwa CO, Alemagno S, et al: The US Cancer Moonshot initiative. Lancet Oncol 17:e178-e180, 2016
58. Center for International Blood and Marrow Transplant Research: COVID-19 updates. https://www.cibmtr.org/Covid19/Pages/default.aspx
59. National Marrow Donor Program: Institutional Review Board Human Research Protection Program. https://network.bethematchclinical.org/research/institutional-review-board/
60. Gragert L, Eapen M, Williams E, et al: HLA match likelihoods for hematopoietic stem-cell grafts in the US registry. N Engl J Med 371:339-348, 2014
61. Fu S, Rybicki L, Abounader D, et al: Association of socioeconomic status with long-term outcomes in 1-year survivors of allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 50:1326-1330, 2015
62. Goldenberg NA, Spyropoulos AC, Halperin JL, et al: Improving academic leadership and oversight in large industry-sponsored clinical trials: The ARO-CRO model. Blood 117:2089-2092, 2011
63. Rasmussen K, Bero L, Redberg R, et al: Collaboration between academics and industry in clinical trials: Cross sectional study of publications and survey of lead academic authors. BMJ 363:k3654, 2018
64. Snyder DC, Brouwer RN, Ennis CL, et al: Retooling institutional support infrastructure for clinical research. Contemp Clin Trials 48:139-145, 2016
65. Blood and Marrow Transplant Clinical Trials Network: BMT CTN research samples collections. https://web.emmes.com/study/bmt2/Researchsample.html
66. National Institutes of Health: NIH data sharing policy. https://grants.nih.gov/grants/policy/data_sharing/
67. Appelbaum FR, Anasetti C, Antin JH, et al: Blood and Marrow Transplant Clinical Trials Network State of the Science Symposium 2014. Biol Blood Marrow Transplant 21:202-224, 2015
68. Ferrara JL, Anasetti C, Stadtmauer E, et al: Blood and Marrow Transplant Clinical Trials Network State of the Science Symposium 2007. Biol Blood Marrow Transplant 13:1268-1285, 2007
69. Dorsey ER, Topol EJ: Telemedicine 2020 and the next decade. Lancet 395:859, 2020
70. Hollander JE, Carr BG: Virtually perfect? Telemedicine for Covid-19. N Engl J Med 382:1679-1681, 2020
71. Center for International Blood and Marrow Transplant Research: CIBMTR Data Transformation. https://www.cibmtr.org/DataManagement/DataTransformation/Pages/default.aspx
72. Shaw BE, Brazauskas R, Millard HR, et al: Centralized patient-reported outcome data collection in transplantation is feasible and clinically meaningful. Cancer 123:4687-4700, 2017
73. Shaw BE, Syrjala KL, Onstad LE, et al: PROMIS measures can be used to assess symptoms and function in long-term hematopoietic cell transplantation survivors. Cancer 124:841-849, 2018
74. Topol EJ: High-performance medicine: The convergence of human and artificial intelligence. Nat Med 25:44-56, 2019
75. Waterhouse DM, Harvey RD, Hurley P, et al: Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: Findings from an American Society of Clinical Oncology survey. JCO Oncol Pract 16:417-421, 2020
76. Feucht J, Sun J, Eyquem J, et al: Calibration of CAR activation potential directs alternative T cell fates and therapeutic potency. Nat Med 25:82-88, 2019
77. Geyer MB, Rivière I, Sénéchal B, et al: Safety and tolerability of conditioning chemotherapy followed by CD19-targeted CAR T cells for relapsed/refractory CLL. JCI Insight 5:e122627, 2019
78. Shadman M, Gauthier J, Hay KA, et al: Safety of allogeneic hematopoietic cell transplant in adults after CD19-targeted CAR T-cell therapy. Blood Adv 3: 3062-3069, 2019
79. Stadtmauer EA, Faitg TH, Lowther DE, et al: Long-term safety and activity of NY-ESO-1 SPEAR T cells after autologous stem cell transplant for myeloma. Blood Adv 3:2022-2034, 2019
80. Tully S, Feng Z, Grindrod K, et al: Impact of increasing wait times on overall mortality of chimeric antigen receptor T-cell therapy in large B-cell lymphoma: A discrete event simulation model. JCO Clin Cancer Inform 3:1-9, 2019
81. Brudno JN, Lam N, Vanasse D, et al: Safety and feasibility of anti-CD19 CAR T cells with fully human binding domains in patients with B-cell lymphoma. Nat Med 26:270-280, 2020
82. Depil S, Duchateau P, Grupp SA, et al: 'Off-the-shelf' allogeneic CAR T cells: Development and challenges. Nat Rev Drug Discov 19:185-199, 2020
83. Liu E, Marin D, Banerjee P, et al: Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. N Engl J Med 382:545-553, 2020
84. Wang M, Munoz J, Goy A, et al: KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med 382:1331-1342, 2020
85. Wang N, Hu X, Cao W, et al: Efficacy and safety of CAR19/22 T-cell cocktail therapy in patients with refractory/relapsed B-cell malignancies. Blood 135: 17-27, 2020

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Steven M. Devine
Honoraria: Kiadis
Consulting or Advisory Role: Bristol Myers Squibb
Research Funding: Orca Bio (Inst), Kiadis (Inst)
Travel, Accommodations, Expenses: Orca Bio

Mary M. Horowitz
Consulting or Advisory Role: Magenta (Inst), Janssen Research & Development (Inst), Medac (Inst)
Research Funding: Biovitrum (Inst), Jazz Pharmaceuticals (Inst), Magenta (Inst), Novartis (Inst), Kite/Gilead (Inst), Actinium Pharmaceuticals Inst), Amgen (Inst), Amneal (Inst), Anthem (Inst), Bluebird Bio (Inst), Bristol Myers Squibb (Inst), Chimerix (Inst), CSL Behring (Inst), Cyto-Sen Therapeutics (Inst), Daiichi Sankyo (Inst), Gamida Cell (Inst), GlaxoSmithKline (Inst), Mesoblast (Inst), Miltenyi Biotec (Inst), Neovii Biotech (Inst), Oncoimmune (Inst), Pfizer (Inst), Pharmacyclics (Inst), Regeneron (Inst), Sanofi (Inst), Seattle Genetics (Inst), Shire (Inst)

No other potential conflicts of interest were reported.

APPENDIX

Can the Blood and Marrow Transplant Clinical Trials Network Model Be Leveraged to Facilitate Cellular Immunotherapy Studies in Solid Tumors?

There are many facets of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) model of relevance to the conduct of cellular immunotherapy (CIT) studies in solid tumors, particularly studies progressing beyond phase I. The Center for International Blood and Marrow Transplant Research (CIBMTR) now manages the Cellular Immunotherapy Data Resource (CIDR),[56] which collects data on a large fraction of patients receiving non–hematopoietic cell transplantation (HCT) CIT, such as chimeric antigen receptor T cells. This resource was established as part of the larger Cancer Moonshot initiative to establish an immuno-oncology translational network (IOTN).[57] The focus of the CIDR is on collecting CIT data so that they can be analyzed and shared with the academic community, as CIBMTR has done for HCT data since its inception, including the mandatory 15-year follow-up of patients receiving genetically modified cells. It will provide a resource for generating knowledge and fostering further study both within and outside of the BMT CTN infrastructure and will be used to assist in design of trials for these therapies. It can be used by the IOTN, separately or in collaboration with the BMT CTN, in a fashion similar to the CIBMTR HCT database to understand the current solid tumor CIT landscape, set baseline rates of response and toxicities, and identify the centers most actively recruiting patients with particular solid tumor malignancies. Similar to the BMT CTN Data and Coordinating Center (DCC), a centralized system for coordination of patient screening, sampling and analysis of tissues, transport of tissues to centralized laboratories, delivery to biorepositories, and overall coordination with clinical centers would be feasible and would streamline processes and lower costs. Building on the tradition of using real-world data to plan, execute, and complement clinical trials in HCT, the CIDR will be able to provide this opportunity to assist in planning, executing, and understanding unique challenges presented by CIT trials in solid tumors in addition to providing an infrastructure for long-term follow-up of patients receiving gene-modified CIT products.

Does the BMT CTN Model Accelerate Patient Recruitment Into High-Priority HCT and CIT Studies?

We believe the answer to this question is yes for a number of reasons. First, the entire protocol development process is one of transparency and engagement of the relevant stakeholders. The protocol team is composed of individuals nominated as a result of their expertise and enthusiasm. Along the development process, the protocol team is actively involved in every aspect of the protocol. Periodically, the protocol team provides updates to the BMT CTN Steering Committee (SC) and seeks relevant input. The involvement of such a broad group of stakeholders increases the sense of ownership of the studies and, through this level of engagement, leads to better acceptance of the studies at the time of network activation. In the past few years, we believe this is why many of the studies have come out of the gates running and have accrued quickly from the onset, rather than experiencing a protracted accrual process as is often the case with complex, multicenter studies. The CIBMTR database, the real source of truth for HCT activity throughout the United States, is used to reality check the accrual estimates generated by each individual site and leads to a more realistic study accrual plan, including the number of sites required to complete the study within a reasonable time frame.

The centralized DCC network structure with existing contractual agreements in place makes launching multiple trials faster and less costly than contracting with separate contract research organizations (CROs) for individual studies. The network infrastructure allows us to line up a large number of centers ready to participate, thereby making it possible to efficiently conduct trials in rare diseases such as severe aplastic anemia or uncommon malignancies such as FLT3 internal tandem duplication mutation–positive acute myeloid leukemia.

What Are Some of the Lessons We Have Learned and Are There Pitfalls That Can Be Avoided?

Much has been learned along the way. Multiple processes described in our manual of procedures (MOP) have been updated over the course of 19 years as we have been educated about how our DCC, the National Institutes of Health (NIH), and our core and affiliate sites operate. The frequent SC meetings provide a forum for continuous feedback from the network, and the monthly Executive Committee calls enable us to have frequent input from our National Heart, Lung, and Blood Institute and National Cancer Institute (NCI) partners.

One good example is the network specimen biorepository. Initially, this was a source of weakness of the network, because many protocol-specified specimens were not obtained at all or on time. We realized our processes were opaque and also required greater resourcing. Now, we have much clearer processes and budget for resources appropriately, while at the same time identifying the most valuable and efficient partners. The biorepository has been transformed from a weakness to a great strength that is being actively leveraged by a growing array of clinical and translational investigators within and outside our network.

We have also learned about the types of questions to be asked in large phase III studies. Understanding from the outset what is currently and what is likely to remain a relevant question or unmet need for the HCT community is critical. The State of the Science Symposium process has been helpful in this regard because we receive wide input from the community at large about the questions of greatest relevance. We now continuously ask how the results of the trials, once completed, will affect current practice. We have learned that trials must be completed on time or else the question may be less relevant. If the accrual goals are unrealistic based on a review of the CIBMTR database or if the difference between standard of care and a new therapy is not large enough to be widely adopted, we typically decide not to perform the study.

The COVID-19 Pandemic Has Imposed Many Financial Constraints on Philanthropic Organizations, So Clinical Trials May Lack Sufficient Funds. Can a Network Model Help in This Regard?

As discussed throughout this article, we have tried to leverage existing infrastructure as much as possible to gain efficiencies and save money. The initial investment the NIH has made in the centralized academic research organization–CRO model we have developed is now able to lower costs mainly by accelerating accrual to studies and in developing accurate accrual plans. We can more easily identify the sites most likely to recruit in a certain disease and use existing contractual mechanisms to speed the activation of studies at individual centers. The NMDP single institutional review board streamlines the process of ethical review, and we have the CIBMTR infrastructure in place to perform long-term follow-up for HCT recipients and the NCI-funded CIDR to perform long-term follow-up in non-HCT CIT recipients. This should facilitate the future conduct of multicenter CIT studies in patients with solid tumors in collaboration with the NCI and industry partners. We will continue to focus on gaining efficiency while lowering costs and accelerating accrual. The pandemic has taught us to develop more nimble processes, including remote methods for site activation and safety and quality monitoring, without compromising patient safety or trial integrity. Lessons learned will hopefully lead to continued cost savings as we endeavor to generate knowledge even under the most challenging conditions.