PROSPECTIVE OBSERVATIONAL STUDY OF THE IMMUNOGENICITY OF VACCINES FOR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT), ALLOGENEIC HCT, AND CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY

CIBMTR SC21-07 / BMT CTN 2101

STUDY PLAN

Version 4.0

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APPENDICES (maintained separately from Study Plan)

1 BACKGROUND

As of March 14, 2021, SARS-CoV-2 had infected more than 119 million people and caused more than 2.5 million deaths world-wide.[1] Hematological cancers and, particularly, hematopoietic stem cell transplantation (HCT), increase the risk of severe COVID-19 disease and death. [2–8] The Center for International Blood and Marrow Transplant Research (CIBMTR) rapidly implemented data collection for HCT and other cellular therapy patients diagnosed with SARS-CoV-2, including recipients of chimeric antigen receptor T cells (CAR-T), increasingly used to treat high-risk hematologic cancers. To date, infections in more than 1900 patients are reported.[9] Detailed analysis of the initial 318 HCT patients with SARS-CoV-2 infection reported to CIBMTR showed outcomes were poor.[8] Specifically, for the 184 allogeneic and 134 autologous HCT recipients analyzed, the probability of survival at 30 days after infection was 68% (95% confidence interval [CI] 58 – 77%) and 67% (95% CI 55 – 78%), respectively. Risk factors for increased mortality following COVID-19 among allogeneic HCT (alloHCT) recipients included age ≥ 50 years (hazard ratio [HR] 2.53, 95% CI 1.16 – 5.52, p=0.020), male sex (HR 3.53, 95% CI 1.44 – 8.67, p=0.006), and ≤ 12 months from allogeneic HCT (HR 2.67, 95% CI 1.33 – 5.36, p=0.005). Following autologous HCT (autoHCT), only a diagnosis of lymphoma was associated with an increased risk of death (HR 2.41, 95% CI 1.08 – 5.38, p=0.033).

The development of two mRNA vaccines and an adenovirus vaccine, all authorized initially for emergency use by the Food and Drug Administration, is an exciting development in the fight against the SARS-CoV-2 pandemic. [10–12] As of September 2021, the FDA has approved the Pfizer-BioNTech (BNT162b2) mRNA vaccine for people over the age of 12, while the other 2 vaccines are approved for use under emergency use authorization (EUA). Furthermore, the FDA and CDC now recommend a third dose of mRNA vaccines for certain immunocompromised patients, which includes recipients of HCT and/or CAR-T. The mRNA vaccines also represent a new technology for vaccines that has not been studied in immune compromised patients. There is a critical need to understand the safety, efficacy, and durability of responses to all of these vaccines for patients receiving cellular therapies (i.e., HCT or CAR-T) due to the lack of testing in this population. Although standard vaccine responses following HCT are known to be diminished, guidelines recommend administration of inactivated vaccines as early as 3 – 6 months following HCT, and by extrapolation, CAR-T treatments, based on many studies demonstrating sufficient immunogenicity to plausibly reduce infection incidence and/or infection severity. [13–17] Based on these recommendations and recent National Comprehensive Cancer Network (NCCN) recommendations for COVID-19 vaccination to occur at least 3 months after cellular therapy, HCT/CAR-T patients are being vaccinated with the currently available SARS-CoV-2 vaccines[18]. However, the NCCN recommendations also stated, “Vaccine efficacy in the setting of cancer care and a weakened immune system is unknown.”

Given the absence of data pertaining to the immunogenicity of any SARS-CoV-2 vaccine in this context, heterogenous approaches to timing post-cellular therapy, and diverse eligibility criteria among centers, it is imperative to quickly identify correlates of protective vaccine responses from the first wave of vaccinated patients. Particularly important is to understand the effect of timing of vaccination on immunogenicity since such data will inform all future vaccination recommendations and identify patients who might be assessed for the need of re-vaccination over time. The findings of this study will inform appropriate stewardship of this currently limited resource and appropriate supportive care approaches. It will also inform vaccination recommendations for the future. This prospective, observational study aims to assess the safety and efficacy of the available SARS- CoV-2 vaccines in recipients of HCT or CAR-T therapy in the first year after therapy. This study is also an opportunity to assess the use of the mRNA vaccine platform, which may be used in future vaccines, and which, to date, has not been tested in patients after HCT/CAR-T. Finally, this infrastructure can be readily expanded to similarly study additional SARS-CoV-2 vaccines as they become available.

The window of opportunity to gather some critical information on vaccine efficacy, particularly the effect of timing of vaccine, is narrow. Thousands of patients will soon receive the vaccine, with timing dependent largely on when vaccine becomes available in their centers and when they can be scheduled to receive it. The ability to use the infrastructure of the CIBMTR and the BMT CTN will allow us to rapidly implement this project to take advantage of this window.

1.1 The Center for International Blood and Marrow Transplant Research

The CIBMTR is a longstanding research program (initially established at the International Bone Marrow Transplant Registry in 1972), operated by faculty and staff at the Medical College of Wisconsin and the National Marrow Donor Program/Be The Match (NMDP). It is funded by the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), the National Institute for Allergy and Infectious Disease and the US Health Services and Resources Administration to maintain a large clinical outcomes registry for HCT and cell therapy recipients. The CIBMTR's observational database of real-world data currently has information for about 575,000 HCT and cell therapy recipients. These data have contributed to more than 1500 peer- reviewed publications.

This is an observational study of patients receiving COVID-19 vaccines as part of routine care. It leverages two existing Institutional Review Board (IRB)-approved protocols managed by the CIBMTR for collection of observational data and research specimens. The first, "Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries" (Appendix A), allows collection of clinical data on HCT and cell therapy recipients in more 180 HCT centers in the United States (US). Under this protocol, the CIBMTR receives data on more than 20,000 US patients annually as well as follow-up data on previously reported patients, including extensive information on baseline patient and disease characteristics, treatment regimens and post-treatment outcomes including infections, toxicities, graft-versus-host disease (GVHD), disease control and survival. Collection of supplemental data for specific studies, if generated as part of routine clinical care, as is required for this project, is allowed under this protocol. The second protocol, "Protocol for a Research Sample Repository for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries" (Appendix B1), addresses collection of pre- and post-therapy blood samples for research. A study- specific consent form for this project, explaining its goals and the collection schedule, was approved by the NMDP IRB and will require expedited review at participating centers (Appendix B2). One hundred fifty US centers have the Sample Repository protocol open.

1.2 The Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

The BMT CTN is a multicenter clinical trials network funded by the NHLBI and the NCI. It was established in 2001 to conduct high impact Phase 2 and 3 studies in hematopoietic stem cell transplantation and cell therapy. It has opened more than 50 trials, accrued more than 12,000 patients to those trials, and published more than 120 peer-reviewed papers. The Data and Coordinating Center of the BMT CTN is operated by the CIBMTR in collaboration with The Emmes Company, LLC (Emmes). Emmes is a contract research organization headquartered in Rockville, Maryland, with a long history of coordinating government-funded clinical studies, including HCT trials and vaccine studies.

Although the proposed study is not a clinical trial but an observational study, it will make use of the BMT CTN's partnership with Emmes and its well-developed electronic data capture systems with existing modules suitable to capture, with minor modification, the necessary data needed to supplement routine CIBMTR registry data collection that will provide much of the data for this study. It will also make use of its well-established specimen tracking mechanisms (see Section 1.3). It should be noted that all supplemental data collected will be restricted to data that is generated as part of routine care.

1.3 Repository and Specimen Management

Specimen collection, processing, storage and shipping for this study will take advantage of the CIBMTR Research Repository. The CIBMTR Research Repository is a unique resource, established to collect unrelated donor-recipient pairs in 1987 and expanded to include related donor-recipient pairs in 2007 and autologous transplants in 2018; it contains > 2.9 million aliquots for > 186,000 individuals. The Repository operates under an IRB-approved protocol and consent that complies with NIH Genomic Data Sharing Policy for HCT and cellular therapy-related studies (cibmtr.org/DataManagement/ProtocolConsent/ResearchSamples/pages/index.aspx, Appendix C). The protocol permits the collection of post-HCT or post-cell therapy samples on a calendar or event-driven schedule, with schedules for specific studies allowed with a study-specific consent. The Repository maintains updated standard operating procedures (SOPs) for all aspects of operation and all procedures meet or exceed NCI Best Practices for Biospecimen Resources.

Since March 2009, The CIBMTR Research Repository has been the primary holding place for BMT CTN biospecimens intended for protocol-specific correlative studies. Samples for future research are also incorporated into most protocols and stored here. The current inventory holds >460,000 samples collected from >7,200 subjects on 23 BMT CTN protocols. It additionally holds more than 2.9 million pretreatment donor and recipient samples from patients enrolled in the CIBMTR Outcomes Registry, collected under the protocol to be used for this study (Appendix B). This includes samples from 44,454 adult recipient/unrelated donor pairs and 10,117 adult recipient/related donor pairs.

Inventory Management and Confidentiality: The Repository utilizes a LabVantage repository inventory management software system. The system is highly configurable and readily accommodates implementation of new sample collection and processing protocols. The repository inventory data is fully integrated with CIBMTR data systems for association with clinical outcomes. Samples are coded with a unique ID, linked to the HCT outcome data record, to maintain confidentiality. The repository database is limited to sample ID, submitter ID, date of receipt, date of processing, sample type and other sample-specific data. Samples are only labeled with the ID code for storage; all linking information is maintained in a separate database.

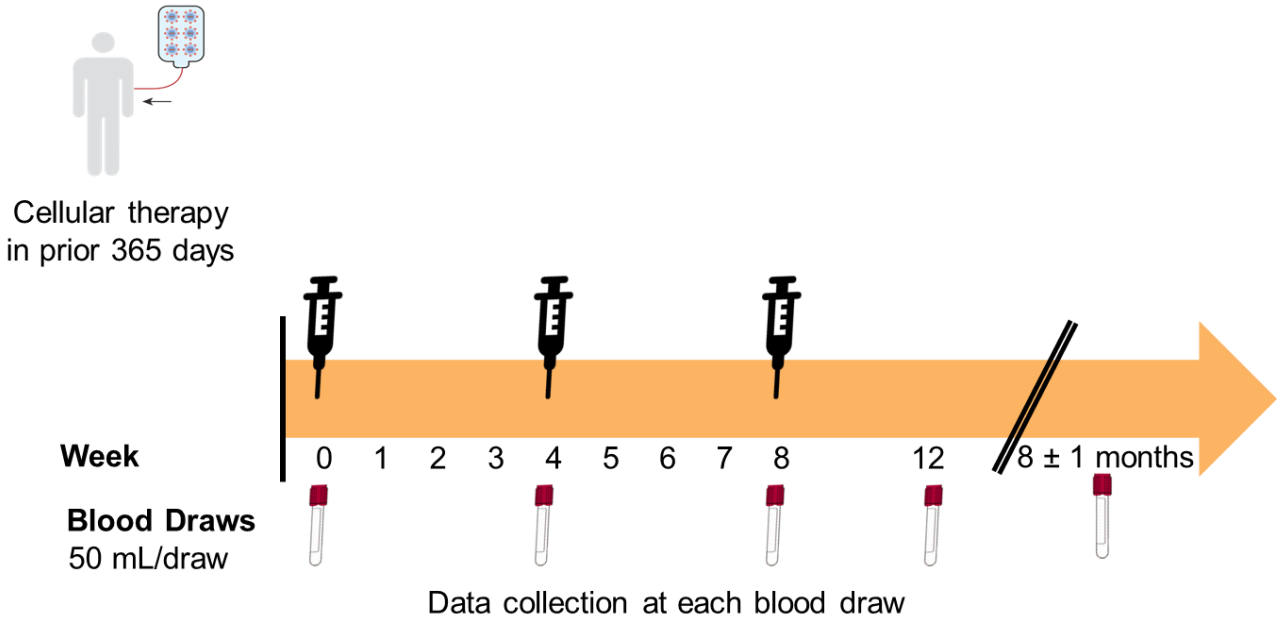
Sample tracking: GlobalTrace, which will be used to track specimens in this study, is an Emmes web-based application for specimen tracking, inventory, and shipping, used for BMT CTN studies for the past 15 years. It allows the Data and Coordinating Center to know, in real-time, which specimens were collected, where they are, and when they were received. It uses bar-coded labels to track individual samples shipped to either project laboratories or the CIBMTR Repository. Center and Repository staff use GlobalTrace to generate electronic manifests and track each individual specimen. GlobalTrace links to FedEx, UPS, and most other carrier tracking systems. Emmes has tracked >3.8 million specimens across ~750 sites using GlobalTrace, with 100% accountability. A user's guide, online training and competency assessment modules are available on the Network website. Sample acquisition forms in the Advantage forms grid provides centers additional reminders of future sample collection target dates, facilitating appointment scheduling.

2 STUDY DESIGN

2.1 Study Overview

This is an observational study of HCT/CAR-T recipients receiving SARS-CoV-2 vaccines as part of standard of care. The study will track clinical events in the real-world setting and collect specimens to assess immune responses to the vaccine, using existing data and specimen collection protocols of the CIBMTR (Appendix A and B). Clinical data and specimens are requested according to the schema below.

Figure 2.1. Study Schema (Note: If the vaccine is administered as a single dose, an eight-week specimen will still be collected for comparability to the evaluation time point after two-dose vaccines. Additionally, if patients receive a third SARS-CoV-2 vaccine dose (booster), an additional visit and sample will be collected after that dose, generally expected to be at about week 12.



The study will enroll approximately 516 patients in six cohorts defined by type of cellular therapy and timing of vaccination in terms of number of months after cellular therapy. Accrual will be monitored separately for each cohort and each cohort will be closed approximately once its accrual goal is met.

Table 2.1. Planned accrual

Time post HCT/CAR-T	AutoHCT	AlloHCT	CAR-T
< 6 months	118	151	118
6-12 months	43	43	43

2.2 Hypothesis

SARS-CoV-2 vaccines will be safe and immunogenic in 40 – 60% of patients vaccinated within the first year following autoHCT, alloHCT, or chimeric antigen receptor T-cell (CAR-T) therapy.

Immunogenicity will be higher in patients receiving vaccination 6-12 months after HCT/CAR-T than in those vaccinated earlier.

2.3 Specific Objectives

The primary objective of this study is to compare the immunogenicity of SARS-CoV-2 vaccines at 7-35 days after the second vaccine dose (or 14-35 days after a single dose vaccine) in patients starting their vaccination course less than 6 months after HCT/CAR-T versus those starting their vaccination course 6-12 months after HCT/CAR-T in three strata defined by type of HCT/CAR-T: AutoHCT recipients, AlloHCT recipients and CAR-T recipients. Immunogenicity is defined as a ≥4- fold rise in SARS-CoV-2 binding antibody titers to the spike protein receptor-binding domain (RBD) compared to the pre-vaccine #1 titers by enzyme-linked immunosorbent assay (ELISA).

The secondary objectives of this study, overall and in each cohort defined by type of therapy and timing of vaccination (Table 2.1), are to:

- Assess the durability of SARS-CoV-2 vaccine immunogenicity at 6 months after the second dose of vaccine, based on the RBD antibody titer.
- Determine the maximum RBD antibody geometric mean titers (GMT) and compare to those in participants of clinical trials evaluating these vaccines in the general population.
- Describe grade III-IV vaccine-related adverse reactions as reported by the patient at routine clinic visits.
- Determine incidence and severity of COVID-19 infections by 6 months following immunization with a SARS CoV-2 vaccine.
- Estimate incidence of new/worsened GVHD disease following immunization with a SARS CoV-2 vaccine for patients following alloHCT.
- Assess the change in antibody titers following the second dose of the vaccine and the booster dose, for patients receiving booster

For each secondary objective, the endpoint will be compared between patients vaccinated 6-12 months between HCT/CAR-T versus those vaccinated <6 months after HCT/CAR-T.

Although numbers in specific subgroups may be small, we will also perform the following exploratory analyses:

- Assess the immunogenicity of each vaccine separately.
- Assess immunogenicity in patients with and without prior COVID-19 infection.
- Assess immunogenicity in alloHCT recipients with and without GVHD.
- Assess immunogenicity in alloHCT recipients according to strategy used for GVHD prophylaxis.
- Assess immunogenicity in autoHCT recipients according to underlying disease and type of post-HCT anti-cancer maintenance used at time of vaccination.
- Assess immunogenicity in CAR-T cell recipients according to history and treatment of cytokine release syndrome.
- Identify patient characteristics associated with immunogenicity, including age, sex, race and ethnicity, performance score and prior COVID-19 infection.

2.4 Study Population

2.4.1 Inclusion Criteria

- ≤ 12 months from alloHCT, autoHCT, or CAR-T therapy
- Any age
- Previously consented to provide data for research to the CIBMTR with a valid CIBMTR Research Identification Number (CRID)
- Planned to receive a COVID-19 vaccine as part of routine clinical care
- Patients with prior COVID-19 are eligible provided the infection was > 3 months before planned vaccine administration
- Patients who received a COVID-19 vaccine prior to HCT/CAR-T are eligible if re-vaccination following HCT/CAR-T is planned as standard practice
- Signed a study-specific consent for collection of pre- and post-vaccination blood specimens for submission to the CIBMTR research repository

2.4.2 Exclusion Criteria

- No prior consent for the CIBMTR database protocol, "Protocol for a Research Database for Hematopoietic Cell Transplantation, Other Cellular Therapies and Marrow Toxic Injuries". **NOTE**: For allogeneic transplant patients only, if the patient did not previously consent but now consents to the CIBMTR database protocol, they may enroll on this study.

2.5 Study Treatments and Sample and Data Collection

Patients will be vaccinated according to institutional guidelines. The choice of SARS-CoV-2 vaccine, timing, and eligibility is at the discretion of the institution. The choice and timing of booster is at the discretion of the institution. Patients who meet this protocol's eligibility criteria and who consent to the collection of up to six blood samples will be enrolled.

2.5.1 Sample Collection

Post-vaccination samples will be collected at a routine visit closest to the indicated time period (Table 6.1). Since this patient population is within one year of treatment, frequent routine visits are expected. At each time point, 50 mL of blood will be collected for serum (5 mL) and peripheral blood mononuclear cells (45 mL). For pediatric patients, where the collection of the full 50 mL sample exceeds the maximum volume allowed per institutional guidelines, the 5 mL serum sample should be prioritized, with the remainder of allowable blood volume dedicated to the PBMC research sample collection.

Clinical data will also be reported at each sample collection time point (Section 2.5.3.). Participating clinical sites will label each blood tube with a unique sample ID label and enter the sample IDs and associated study patient and sample collection information into the GlobalTrace sample tracking system. Sample manifests will be generated and electronically sent to the CIBMTR Research Repository. CIBMTR study team members will quality control the sample-related information prior to receipt at the Repository. And, finally, the Repository will receive the samples in GlobalTrace completing the sample chain of custody and will enter the sample information into the Repository LabVantage sample management system to initiate sample processing and final sample derivative aliquot storage.

On a pre-defined schedule, the CIBMTR Research Repository will retrieve, package and ship aliquots of 1.5 mL to LabCorp for the SARS-CoV-2 Semi-Quantitative Total Antibody, Spike test. The results from these tests will be provided to the Repository for integration to the study data file and to the patient's study team for interpretation and discussion of the results with the patient. The remaining sample will be stored for future research, including neutralization assays and T-cell function studies.

2.5.2 Samples for Future Research

An important component of this project is the collection of samples suitable for future neutralization assays and assays of T-cell responses to vaccine. The design of these studies will rely on the results of the current study to inform the appropriate assessment of T-cell function in terms of number and type of patients to be studied and the best post-vaccination time points to assess.

Table 2.2. Schedule for Specimen Collection

Visit	Visit Description	Visit Window*
Time-point 1	Baseline: Pre-Vaccine #1	Within 14 days prior to vaccine administration
Time-point 2	Post Vaccine #1	Single dose vaccines: 14-35 days after dose #1 Two-dose vaccines: within 7 days prior to dose #2
Time-point 3	Post-Vaccine #2 (or similar time frame after a single dose vaccine) / Pre-vaccine dose #3 (Booster)	Single dose vaccines: 4-8 weeks after specimen obtained for Time-point 2 Two-dose vaccines: 3-8 weeks after dose #2. If vaccine dose #3 (booster) is planned, the sample should be drawn within 7 days prior to booster administration if the booster is administered ≤ 8 weeks after the dose #2.
Time-point 3b *(only required for patients receiving a booster >8 weeks after dose #2)*	Pre-vaccine dose #3 (booster) **This sample is obtained only if there are >8 weeks between dose #2 and booster dose**	Obtain sample within 7 days prior to booster administration only if there are >8 weeks (56 days) between dose #2 and booster dose
Time-point 4 *(only required for patients receiving booster)*	Post-vaccine #3 (booster) **This sample is obtained only if the patient is receiving a booster dose**	Obtain sample between 7 – 35 days following the booster
Time-point 5	Final Post-Vaccine	7 – 9 months after dose #1, ideally at 8 months ± 28 days

*Visits post-vaccine #1 should occur at closest routine clinical visit during the visit windows where possible. Ideally visits and samples are completed within the visit windows specified. However, as this is an observational study, data should still be collected for out of window assessments. The **only exception** is that Visit 1 MUST be collected within 14 days prior to vaccination #1, otherwise the patient is not eligible to enroll.

2.5.3 Data Collection

The patient's assigned study number will be their CIBMTR Research Identification Number (CRID). This will minimize data needs for this study as all pre-HCT/CAR-T therapy, age, race, gender and details of treatment including conditioning regimen and intensity, donor type, stem cell source, etc. will be available and linked to the patient through CIBMTR. The table in Appendix D lists selected data fields routinely collected and available for this study and links to existing data forms. These data are collected in FormsNet, CIBMTR's 21 CFR Part 11 compliant, web-based, electronic data capture system.

Supplemental data will be collected at each visit where specimen collection is done. Table 2.3 lists supplemental data to be reported. Some data fields are similar to those collected routinely by CIBMTR

but at different dates. These data will be collected in Emmes' Advantage eClinical platform solution, which is used for data collection by the BMT CTN. The eClinical electronic data entry system and the eClinical Global Specimen Tracking system will ensure that specimens are scanned, tracked, and managed in an integrated manner with the clinical data. Existing BMT CTN eClinical case report forms will be leveraged to efficiently collect the supplemental data necessary for this study. These data will be merged by the common CRID identifier with data from FormsNet and data from immune assays to form a final data set. Of note, the BMT CTN frequently takes advantage of the wealth of data in the CIBMTR data system and merges these data with eClinical data, as well as data from laboratories performing correlative studies, for the purpose of analysis and long-term follow-up of BMT CTN clinical trials.

Table 2.3 Supplemental Data to be Collected Pre and Post-Vaccination

Baseline	• SARS-CoV-2 Manufacturer • History of prior COVID-19 infection with date* • Current status of GVHD (allos) • Selected medications, including all potentially immune suppressive medications and posttransplant anti-cancer maintenance therapy • Other post-therapy vaccinations, with dates • Complete blood count • Performance score
All Post-Vaccination Time-points	• Intercurrent COVID-19 infection with date* • Current status of GVHD for alloHCT recipients • Selected medications, including all potentially immune suppressive medications and posttransplant anti-cancer maintenance therapy • Other intercurrent post-therapy vaccinations, with dates • Complete blood count • Performance score • Grade III-IV patient reported vaccine-related toxicities

*Triggers standard CIBMTR Respiratory Virus Infection Form, if not already completed.

3 STATISTICAL CONSIDERATIONS

3.1 Definition and Analysis of the Primary Endpoint

The primary endpoint is immunogenicity response following full vaccination measured at 14-35 days after vaccination for single-dose vaccines or 7-35 days after vaccination #2 for two-dose vaccines. Immunogenicity is defined as a ≥4-fold rise in SARS-CoV-2 binding antibody titers to the spike protein RBD compared to the pre-vaccine #1 titer. Participants with titers below the limit of detection (LOD) will be assigned a value of one-half the LOD. The proportion of participants with immunogenicity following full vaccination (14-35 days after a single dose vaccine or 7-35 days after a two-dose vaccine) will be described for each HCT/CAR-T stratum and timing of vaccination by therapy cohort using its sample proportion and 95% CIs. Only patients who provide a viable blood sample to evaluate immunogenicity at these time-points following completion of vaccine series (single or double) will be included in this estimation.

The primary analysis will be a comparison, within each HCT/CAR-T stratum, of the proportions of patients with immunogenicity between patients vaccinated 6-12 months after HCT/CAR-T and those vaccinated < 6 months after HCT/CAR-T using a two sample Z test of the difference in proportions. Two-sided testing will be performed at a significance level of 5%. 95% CIs will be provided for the differences in proportions within strata.

The study is designed to provide at least 81% power to detect a 25% difference in immunogenicity response rates between the early and late vaccination cohorts (vaccinated < 6 months after HCT/CAR-T vs. ≥ 6-12 months) in each HCT/CAR-T stratum by assigning at least 118 and 43 patients to the < 6 months and ≥ 6-12 months cohorts respectively; unequal allocation to the cohorts is planned based on the numbers of patients anticipated in these cohorts. Moreover, since the number of confounding factors (and their potential clinical effect) to be considered in secondary and exploratory analyses is high in the alloHCT stratum, its < 6-month cohort will be enriched to 151 patients. At least 492 evaluable patients in total are needed (Table 3.1). Assuming a 5% drop-out rate, this requires 516 enrolled patients as depicted in Table 2.1.

Table 3.1: Power to Detect a 25% Difference in Immunogenicity Response Between 6-12 Month and < 6 Month Cohorts with 43 and 118 Evaluable Patients

Difference in Response Rates (6-12 mos. Vs. < 6 mos.)	Power
90% vs. 65%	92.8%
80% vs. 55%	85.4%
70% vs. 45%	81.7%
60% vs. 35%	81.6%

3.2 Definition and Analysis of Endpoints for Secondary and Exploratory Objectives

- Immunogenicity at 7 months after vaccination: The proportion of participants with immunogenicity will be described for each cell therapy and time of vaccination cohort using sample proportions and 95% CIs. Within each HCT/CAR-T stratum, a comparison will be performed of the proportions of patients with immunogenicity between patients vaccinated 6-12 months and those vaccinated < 6 months after HCT/CAR-T using a two sample Z test of the difference in proportions. 95% CIs will be provided for the differences in proportions within strata.
- The immunogenicity of each vaccine (defined by manufacturer) after full vaccination will be described for each HCT/CT stratum and compared by stratum and time of vaccination. For each vaccine and HCT/CT stratum, the proportions of patients with immunogenicity will be compared between patients vaccinated 6-12 months and those vaccinated < 6 months after HCT/CAR-T using Barnard's exact tests. 95% CIs will be provided for the differences in proportions within each stratum for each vaccine.
- The distribution of the maximum RBD immunoglobulin titer will be described for each cell therapy cohort based on the GMT with 95% CI and range. Within each HCT/CAR-T stratum, the maximum titers will be compared between patients vaccinated 6-12 months after HCT/CAR-T and those vaccinated < 6 months after HCT/CAR-T using Wilcoxon rank sum tests.
- For patients receiving vaccine dose #3 (Booster), the distribution of the maximum RBD immunoglobulin titer will be described for each cell therapy cohort based on the GMT with 95% CI and range. Within each HCT/CAR-T stratum, the maximum titers will be compared between patients receiving a booster and vaccinated 6-12 months after HCT/CAR-T and those vaccinated < 6 months after HCT/CAR-T using Wilcoxon rank sum tests.
- Incidence and severity of COVID-19 infection by 6 months after vaccination #2 (7 months after single dose vaccine administration) in each stratum and cohort will be described, using data reported on the CIBMTR Respiratory Virus Infection Form (Appendix C).
- Toxicities attributable to vaccine will be described in each stratum and cohort, including Grade III-V toxicities attributed to the vaccine by the treating physician. There will be no expedited reporting of adverse events in the observational study of patients receiving usual care.

- Within the alloHCT stratum, Grade II-IV and III-IV acute GVHD, diagnosed and graded according to standard CIBMTR definitions, that is new or worsened between baseline and 6 months post full vaccination will be described for all patients and separately for those vaccinated 6-12 months after HCT/CAR-T and those vaccinated < 6 months after HCT/CAR-T.
- Within the alloHCT stratum, chronic GVHD, diagnosed according to standard CIBMTR criteria, that is new or worsened between baseline and 6 months post full vaccination will be described.
- Consideration of other patient and treatment characteristics associated with immunogenicity: The following variables will be considered for their association with immunogenicity after full vaccination (Timepoint #2 for single dose vaccines or Timepoint #3 for two-dose vaccines), using multivariate logistic regression models that adjust for HCT/CAR-T stratum and timing of vaccination:
    - Age
    - Sex
    - Underlying disease for which HCT/CAR-T was indicated
    - Co-morbidity index prior to HCT/CAR-T
    - Prior COVID-19 infection
    - Pre-HCT/CAR-T vaccination
    - Concurrent medications

    Among alloHCT recipients, the following will also be considered:

    - Presence/absence/severity of GVHD
    - Type of GVHD prophylaxis
    - Type of donor (related versus not, HLA-matched versus not)
    - Type of graft (bone marrow versus peripheral blood versus cord blood)

3.3 Accrual

Annually, ~9000 alloHCTs, ~ 13,000 autoHCTs, and ~1000 CAR-T recipients are reported to the CIBMTR by US centers. Since, currently, CTs are less frequently done than HCTs, we will preferentially recruit centers performing high numbers of CTs. This study proposal has been presented to, and received enthusiastic endorsement from, the BMT CTN Steering Committee, which includes representatives from all BMT CTN Core Centers and High-Enrolling Affiliate Centers. Among the 30 highest volume centers that participate in both the BMT CTN and the CIBMTR's Database and Repository Protocols, there were 6,823 alloHCTs, 9,482 autoHCTs and 1,597 CAR-T cell therapies done in 2019-20 and reported to CIBMTR (2020 data are still incomplete). Based on these data, it is anticipated that accrual to this observational trial will be completed within 9 months of activation.

4 SIGNIFICANCE

To date, there is no information regarding efficacy of SARS-CoV-2 vaccines following HCT/CAR-T treatments and no information on the efficacy of any mRNA vaccine in this population. The current data vacuum results in uncertainty for patients, their caregivers, and their HCT/CAR-T providers. Yet, given the pandemic and the high mortality in this patient population, providers will recommend patients be vaccinated regardless due to the possibility of response. This prospective, observational study will provide clinicians valuable data to counsel patients on their immunity against COVID-19 following vaccination. Furthermore, this will address the question of optimal timing of these vaccines to maximize efficacy. Finally, this study may inform vaccination strategies, in general, and for future mRNA vaccine platforms for patients who receive HCT/CAR-T therapies.

5 REFERENCES

1. Johns Hopkins Coronavirus Resource Center. *https://coronavirus.jhu.edu/map.html* (2021).
2. Malard, F. *et al.* COVID-19 outcomes in patients with hematologic disease. *Bone Marrow Transplantation* **55**, (2020).
3. Robilotti, E. v *et al.* Determinants of COVID-19 disease severity in patients with cancer. *Nat Med* **26**, 1218–1223 (2020).
4. Shah, G. L. *et al.* Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. *Journal of Clinical Investigation* **130**, (2020).
5. Piñana, J. L. *et al.* Risk factors and outcome of COVID-19 in patients with hematological malignancies. *Experimental Hematology & Oncology* **9**, (2020).
6. Kuderer, N. M. *et al.* Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *The Lancet* **395**, (2020).
7. Passamonti, F. *et al.* Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *The Lancet Haematology* **7**, (2020).
8. Sharma, A. *et al.* Clinical characteristics and outcomes of COVID-19 in haematopoietic stem cell transplantation recipients: an observational cohort study. *Lancet Haematology* **8**,(2021).
9. CIBMTR COVID-19 Updates. *https://www.cibmtr.org/Covid19/Pages/default.aspx* (2021).
10. Moderna COVID-19 Vaccine. *https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine* (2021).
11. Pfizer-BioNTech COVID-19 Vaccine. *https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine* (2021).
12. Plotkin, S. A. Correlates of protection induced by vaccination. *Clin Vaccine Immunol* **17**, 1055–1065 (2010).
13. Cordonnier, C. *et al.* Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7). *The Lancet Infectious Diseases* **19**, (2019).
14. Mikulska, M. *et al.* Vaccination of patients with haematological malignancies who did not have transplantations: guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *The Lancet Infectious Diseases* **19**, (2019).
15. Hill, J. A. & Seo, S. K. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. *Blood* **136**, (2020).
16. Tomblyn, M. *et al.* Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. *Biology of Blood and Marrow Transplantation* **15**, (2009).
17. Rubin, L. G. *et al.* 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clinical Infectious Diseases* **58**, (2014).
18. NCCN: Cancer and COVID-19 Vaccination. (2021).