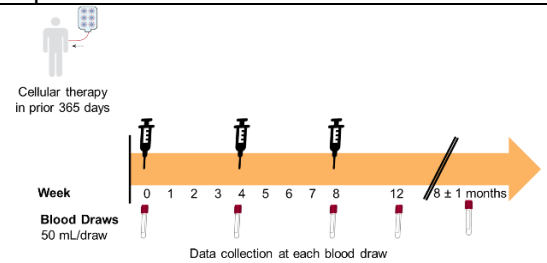
List of Changes

CIBMTR SC21-07/BMT CTN 2101 COVID v4.0

Dated: 29SEP2021

The following changes, and the rationale for the changes, were made from Version 3.0 to Version 4.0 of the **Study Plan**. Additionally, there were a few administrative changes, including corrections to typos and formatting.

#	Section number, title, and page number of original	Original text:	Changed to:	Rationale
1.	Title page	VERSION 3.0	VERSION 4.0	Administrative
2.	1. Background Page 1	The development of two mRNA vaccines and, recently, an adenovirus vaccine, all authorized for emergency use by the Food and Drug Administration, is an exciting development in the fight against the SARS-CoV-2 pandemic.	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. 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.	Updated language to reflect changing SARS-CoV-2 vaccine landscape
3.	2.1 Study Overview Page 4	**Figure 2.1. Study Schema** (Note: If the vaccine is administered as a single dose, an eight-week and 12-week specimen will still be collected for comparability to the	**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	Updated study time points due to availability of booster shots.

<table>
<tr><th>#</th><th>Section number, title, and page number of original</th><th>Original text:</th><th>Changed to:</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>evaluation time point after two-dose vaccines</td><td>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.</td><td></td></tr>
<tr><td>4.</td><td>2.1 Study Overview
Page 4</td><td></td><td> 
</td><td>Graphic updated to reflect updated study time points due to availability of booster shots.</td></tr>
<tr><td>5.</td><td>2.1 Study Overview
Page 5</td><td>The study will enroll approximately 732 patients in six cohorts defined by type of cellular therapy and timing of vaccination in terms of number of months after cellular therapy.</td><td>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.</td><td>Total accrual target was reduced to ensure sufficient budget is available to run the additional booster samples.</td></tr>
<tr><td>6.</td><td>Table 2.1 Planned accrual
Page 5</td><td>Table 2.1. Planned accrual
<table><tr><th>Time post HCT/CAR-T</th><th>AutoHCT</th><th>AlloHCT</th><th>CAR-T</th></tr><tr><td>< 6 months</td><td>108</td><td>150</td><td>108</td></tr><tr><td>6-12 months</td><td>108</td><td>150</td><td>108</td></tr></table></td><td>Table 2.1. Planned accrual
<table><tr><th>Time post HCT/CAR-T</th><th>AutoHCT</th><th>AlloHCT</th><th>CAR-T</th></tr><tr><td>< 6 months</td><td>118</td><td>151</td><td>118</td></tr><tr><td>6-12 months</td><td>43</td><td>43</td><td>43</td></tr></table></td><td>Total accrual target was reduced to ensure sufficient budget is available to run the additional booster samples.</td></tr>
<tr><td>7.</td><td>2.3 Specific Objectives
Page 5</td><td>[N/A text added]</td><td>• Assess the change in antibody titers following the second dose of the vaccine and the booster dose, for patients receiving booster</td><td>Additional secondary objective added due to addition of vaccine booster.</td></tr>
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8.	2.4.2 Exclusion Criteria Page 7	• No consent for the CIBMTR Registry	• 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.	Clarification of the CIBMTR study name and that allo patients can simultaneously consent to both studies.
9.	2.5 Study Treatments and Sample and Data Collection Page 7	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. Patients who meet this protocol's eligibility criteria and who consent to the collection of four blood samples will be enrolled.	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.	Addition of language clarifying that booster timing is at the institution's discretion and patients may have up to 6 blood samples drawn with the new booster time point.
10.	2.5.1 Sample Collection Page 7	At each time point, 30 mL of blood will be collected for serum (5 mL) and peripheral blood mononuclear cells (25 mL). For pediatric patients, where the collection of the full 30 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.	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.	Blood volume increased for consistency with recently revised CIBMTR Sample Repository Protocol version 13.
11.	2.5.1 Sample Collection Page 8	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 after obtaining the final six-month assay results.	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.	Results will be provided approximately 6 weeks after sample collection.

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<tr><td>12.</td><td>Table 2.2. Schedule for Specimen Collection
Page 9</td><td>
<table>
<tr><th colspan="3">Table 2.2. Schedule for Specimen Collection</th></tr>
<tr><td>Time-point 1</td><td>Baseline: Pre-Vaccine #1</td><td>Up to 14 days prior to vaccine administration</td></tr>
<tr><td>Time-point 2</td><td>Post Vaccine #1</td><td>Single dose vaccines: 14-35 days after vaccination
Two-dose vaccines: within 7 days prior to administration of the second dose</td></tr>
<tr><td>Time-point 3</td><td>Early Post-Vaccine #2 or similar time frame after a Single Dose Vaccine</td><td>Single dose vaccines: Earliest routine clinical visit between 4 and 8 weeks after specimen obtained for Time-point 2
Two-dose vaccines: Between 7 and 35 days post-vaccine #2</td></tr>
<tr><td>Time-point 4</td><td>6-7 Months Post-Vaccination</td><td>Single dose vaccines: Closest routine clinical visit to 7 months post-vaccination, ideally ±28 days
Two-dose vaccines: Closest routine clinical visit to 6 months post-vaccination, ideally ±28 days</td></tr>
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</td><td>
<table>
<tr><th colspan="3">Table 2.2. Schedule for Specimen Collection</th></tr>
<tr><th>Visit</th><th>Visit Description</th><th>Visit Window*</th></tr>
<tr><td>Time-point 1</td><td>Baseline: Pre-Vaccine #1</td><td>Within 14 days prior to vaccine administration</td></tr>
<tr><td>Time-point 2</td><td>Post Vaccine #1</td><td>Single dose vaccines: 14-35 days after dose #1
Two-dose vaccines: within 7 days prior to dose #2</td></tr>
<tr><td>Time-point 3</td><td>Post-Vaccine #2 (or similar time frame after a single dose vaccine) / Pre-vaccine dose #3 (Booster)</td><td>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</td></tr>
<tr><td>Time-point 3b (only required for patients receiving a booster >8 weeks after dose #2)</td><td>Pre-vaccine dose #3 (booster) This sample is obtained only if there are >8 weeks between dose #2 and booster dose</td><td>Obtain sample within 7 days prior to booster administration only if there are >8 weeks (56 days) between dose #2 and booster dose</td></tr>
<tr><td>Time-point 4 (only required for patients receiving booster)</td><td>Post-vaccine #3 (booster) This sample is obtained only if the patient is receiving a booster dose</td><td>Obtain sample between 7 – 35 days following the booster</td></tr>
<tr><td>Time-point 5</td><td>Final Post-Vaccine</td><td>7 – 9 months after dose #1, ideally at 8 months ± 28 days</td></tr>
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*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.
</td><td>The sample collection schedule table was updated to reflect new booster time point and a footnote was added to clarify visit windows.</td></tr>
<tr><td>13.</td><td>3.1 Definition and Analysis of the Primary Endpoint
Page 11</td><td>The study is designed to provide 80% power to detect a 20% difference between the early and late vaccination cohorts in each HCT/CAR-T stratum, requiring at least 97 evaluable patients in each cohort (Table 3.1). Assuming a 10% drop-out rate, this requires 108 enrolled patients per cohort. 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, we will enrich that stratum to 150 patients per cohort. Consequently, the targeted enrollment is 732 patients as depicted in</td><td>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</td><td>Total accrual target was reduced to ensure sufficient budget is available to run the additional booster samples.</td></tr>
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<tr><td></td><td></td><td>Table 2.1.
<table><tr><th colspan="2">Table 3.1: Power to Detect a 20% Difference in Immunogenicity Response with 97 Evaluable Patients per Cohort According to Specific Rates of Response</th></tr><tr><th>Difference in Response Rates (6-12 mos. Vs. < 6 mos.)</th><th>Power</th></tr><tr><td>90% vs. 70%</td><td>94%</td></tr><tr><td>80% vs. 60%</td><td>86%</td></tr><tr><td>70% vs. 50%</td><td>81%</td></tr><tr><td>60% vs. 40%</td><td>80%</td></tr></table></td><td>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><tr><th colspan="2">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</th></tr><tr><th>Difference in Response Rates (6-12 mos. Vs. < 6 mos.)</th><th>Power</th></tr><tr><td>90% vs. 65%</td><td>92.8%</td></tr><tr><td>80% vs. 55%</td><td>85.4%</td></tr><tr><td>70% vs. 45%</td><td>81.7%</td></tr><tr><td>60% vs. 35%</td><td>81.6%</td></tr></table></td><td></td></tr>
<tr><td>14.</td><td>3.2 Definition and Analysis of Endpoints for Secondary and Exploratory Objectives Page 13</td><td>• Immunogenicity at 6 months after vaccination #2 (7 months for single dose vaccines): 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.</td><td>• Immunogenicity at 7 months after vaccination #2: 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.</td><td>Updated to reflect the revised timepoints.</td></tr>
<tr><td>15.</td><td>3.2 Definition and Analysis of Endpoints for Secondary and Exploratory Objectives Page 13</td><td>[N/A text added]</td><td>• 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.</td><td>Additional secondary objective added due to addition of vaccine booster.</td></tr>
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