

Frequently Asked Questions for

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

A CIBMTR/BMT CTN Study

1. What is the purpose of this study?

The purpose of the study is to assess the immune response to COVID-19 vaccines in patients receiving commercial vaccines as part of their standard care after HCT or CAR-T therapy. It will also compare responses in patients who receive the vaccine in the first six months after treatment versus those who received it 6-12 months after treatment. This will give very important and currently lacking information about the protective effects of vaccination in this vulnerable population and, possibly, identify appropriate timing of vaccination.

2. Can enrolled patients receive a 3rd dose?

Yes, patients can receive a 3rd dose. The date of administration and manufacturer are collected on study forms.

3. If a patient is scheduled for a 4th dose after enrolling in the study, how is that data collected?

For centers planning to give a 4th dose following the 3-dose series, Time-point 5 should be drawn prior to dose #4 if the timing is consistent with the visit window. However, if Time-point 5 cannot be completed prior to dose #4, the dose #4 information should be collected on the Time-point 5 visit forms. No additional samples/data are collected after Time-point 5 irrespective of additional vaccine doses after that time-point.

4. What are the inclusion criteria?

- Any age
- ≤ 12 months from alloHCT, autoHCT, or CAR-T therapy
 - i. **As of November 29, 2021, only patients who meet one of the following criteria may be enrolled on the alloHCT cohort:** pediatric patients (≤ 18 years old), racial/ethnic minority patients (i.e., patients other than those identified as non-Hispanic White), and/or patients with non-malignant disease (see Numbered Memo #2101-023).
- Previously consented to provide data for research to the CIBMTR with a valid CIBMTR Research Identification Number (CRID). Consent for the database studies must occur prior to enrollment on the 2101 study. For allogeneic transplant patients only, if the patient did not previously consent but now consents to the CIBMTR database protocol, they may enroll on the 2101 study.
- Planned to receive a COVID-19 vaccine as part of routine clinical care
- Patients with prior COVID-19 are eligible once symptoms from the acute infection have resolved
- 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

Eligibility Notes:

- No waivers or exceptions to inclusion criteria will be granted.
- Study sample #1 must be collected prior to vaccine #1, otherwise the patient is ineligible. Additionally, study sample #1 must be ≤ 12 months from HCT/CAR-T therapy and vaccine #1 could be up to 12 months from HCT/CAR-T +14 days.

5. Why is this study important?

There are very few data available on the response to vaccination in the patients we serve and no data on optimal timing of vaccination. Recent data on solid organ transplant recipients indicate much lower response rates to vaccination than in the general population (Boyarsky et al, JAMA, 2021). Filling this gap in information for HCT/CAR-T patients is important to guide clinical care. The National Comprehensive Cancer Network (NCCN) recently recommended that COVID-19 vaccination be done at least 3 months after cellular therapy, but also stated "Vaccine efficacy in the setting of cancer care and a weakened immune system is unknown." These data may also provide information on whether different vaccine products vary in eliciting immune responses in this setting or whether response is influenced by specific patient and treatment characteristics.

6. Why is it important to activate this study quickly?

As vaccines become increasingly available, all patients will be offered vaccination and the recent NCCN guidelines likely mean that many centers will try to vaccinate patients at about 3 months post-treatment. Additionally, many patients will be vaccinated before they undergo HCT or CAR-T. However, right now, due to varying rates of availability, very few, if any, patients were vaccinated prior to HCT/CAR-T and they are being vaccinated at a wide range of time-points after therapy. This will allow us to better understand the response to post HCT/CAR-T vaccination at varying time-points in the first year after therapy in patients with and without pre-HCT/CT vaccination and provide guidance for future vaccination strategies.

7. Is there a protocol for this study?

Data collection for this study is being done as part of the CIBMTR "Protocol for a Research Database for HCT, Other Cellular Therapies and Marrow Toxic Injuries". All data requested are data collected as part of routine clinical care. No separate consent is required to submit data for this protocol. Specimen collection for this study is covered by the CIBMTR "Protocol for a Research Sample Repository for HCT, Other Cellular Therapies and Marrow Toxic Injuries". Some patients may have already signed a consent for the CIBMTR Repository to allow collection of pretransplant specimens, but **ALL patients will need to sign a consent for specimen collection for this COVID vaccine study**. This NMDP IRB-approved consent template will be provided (along with age-appropriate assent documents) if your center wishes to participate in the study.

8. Will this study require IRB Submission?

Yes, but only the NMDP IRB-approved consents will need to be submitted to your IRB of Record as an amendment to the CIBMTR Protocol for a Research Database for HCT/CAR-T. **Do not submit the 2101 Study plan as a "New Protocol"**. Once you receive IRB approval, please submit approval documentation to the Repository IRB.

9. Is this a CIBMTR or a BMT CTN study?

CIBMTR and BMT CTN are collaborating on this study. The study was initially proposed by a BMT CTN State of the Science Committee, which included one of the co-chairs (Dr. Miguel Perales) and

the Scientific Director (Dr. Marcie Riches) of the CIBMTR Working Committee for Infection and Immune Reconstitution. Drs. Perales and Riches are, together with Dr. Joshua Hill, co-chairing this Study. The study is being done under IRB-approved CIBMTR protocols and most of the clinical data will come from routine CIBMTR data collection. However, the BMT CTN infrastructure is being used for specimen tracking and for supplemental data collection to enhance efficiency and speed of activation.

10. Will centers get BMT CTN credit for enrolling patients on this study?

Yes, the study is endorsed by the BMT CTN Steering Committee and enrollment credit will be earned. Effective September 1, 2021, all Core and Consortia centers will be awarded DOUBLE accrual credit for each racial/ethnic minority patient (i.e., patients who are not non-Hispanic White), pediatric patient, and non-malignant disease patient enrolled in this study.

11. What specimens are being collected?

50 mL of blood will be collected at up to 6 time-points as described in the table below. 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.

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	<u>Single dose vaccines</u> : 14-35 days after dose #1 <u>Two-dose vaccines</u> : 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	<u>Single dose vaccines</u> : 4-8 weeks after specimen obtained for Time-point 2 <u>Two-dose vaccines</u> : 3-8 weeks after dose #2. If vaccine dose #3 is planned, the sample should be drawn within 7 days prior to dose #3 administration if dose #3 is administered \leq 8 weeks after dose #2.
Time-point 3b <i>(only required for patients receiving dose #3 >8 weeks after dose #2)</i>	Pre-vaccine dose #3 This sample is obtained only if there are >8 weeks between dose #2 and dose #3	Obtain sample within 7 days prior to dose #3 administration only if there are >8 weeks (56 days) between dose #2 and dose #3
Time-point 4 <i>(only required for patients receiving dose #3)</i>	Post-vaccine #3 This sample is obtained only if the patient is receiving dose #3	Obtain sample between 7-35 days following dose #3
Time-point 5 [†]	Final Post-Vaccine	7 – 9 months after dose #1, ideally at 8 months \pm 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 Time-point 1 MUST be collected within 14 days prior to vaccination #1, otherwise the patient is not eligible to enroll.

†For centers planning to give a 4th dose following the 3-dose series, Time-point 5 should be drawn prior to dose #4 if the timing is consistent with the visit window above. However, if Time-point 5 cannot be completed prior to dose #4, the dose #4 information should be collected on the Time-point 5 visit forms. No additional samples/data are collected after Time-point 5 irrespective of additional vaccine doses after that time-point.

12. Where are specimens sent?

Specimens will be sent to the National Marrow Donor Program (NMDP) repository. Repository staff will send aliquots, in batches, to LabCorp for antibody testing. The remainder will be stored for future research, including T-cell response assessments and antibody neutralization assays. GlobalTrace, the system used to track specimens in BMT CTN trials, will be used for this study.

13. What antibody test is being used?

LabCorp will assess total antibody against the receptor-binding domain of the Spike protein of SARS-CoV-2 using a semi-quantitative Electrochemiluminescence Immunoassay (ECLIA).

14. Will results of antibody tests be made available to patients?

The serum antibody results will be posted in FormsNet under the subject's CRID. These reports will be posted starting at the end of July 2021. Samples will be batch-shipped from the Repository to LabCorp monthly for testing and results will be available in 3-6 weeks from collection. Each center will determine how results will be shared with their patients.

15. What if patients cannot return to their treatment center for specimen collection?

The study should be offered to patients who are likely to be seen over the next 6 months, and so can have specimens collected. Specimen collection has been arranged through LabCorp. This option is to be reserved for only those cases that truly require an off-site collection to be done for a patient unable to return to the Transplant Center as there are a limited number of spots available for use for this study. This offsite option is ONLY available to patients that can have the full 50 mL blood sample collected as allowed per institutional guidelines. **CBC results will not be provided back to centers.**

16. Is a patient who had a prior COVID-19 infection eligible for this study?

Yes, as long as their symptoms from the acute infection have resolved.

17. How will supplemental data be submitted?

Data will be entered via the eClinical system managed by The Emmes Company. This is the system used for all BMT CTN protocols. It is being used for this CIBMTR/BMT CTN study because of available modules that could be quickly modified to meet the supplemental data needs of this study and so allow timely activation. All data will be transferred and merged with CIBMTR data at the end of the study. The data elements to be submitted at each time point are summarized in the table below.

Supplemental Data to be Submitted Pre- and Post-Vaccination	
Baseline	<ul style="list-style-type: none">• SARS-CoV-2 vaccine manufacturer• History of prior COVID-19 infection with date (triggers submission of Respiratory Virus Infection Form 2149 in FormsNet, if not already submitted)• History of pre-HCT/CT vaccination with date and manufacturer• Current status of GVHD (alloHCT recipients)

	<ul style="list-style-type: none"> Selected medications, including all potentially immune suppressive medications, anti-COVID medications, and post-transplant anti-cancer maintenance therapy Other post-therapy vaccinations, with dates Complete blood count Performance score
All Post-Vaccination Time-points	<ul style="list-style-type: none"> Intercurrent COVID-19 infection with date (triggers submission of Respiratory Virus Infection Form 2149 in FormsNet, if not already submitted) Current status of GVHD for alloHCT recipients Selected medications, including all potentially immune suppressive medications, anti-COVID medications, and post-transplant anti-cancer maintenance therapy Other intercurrent post-therapy vaccinations, with dates Complete blood count Performance score Grade III-IV patient-reported vaccine-related toxicities

18. Is there reimbursement for submitting data and specimens?

Reimbursement for routine CIBMTR forms submitted through FormsNet (including the Respiratory Virus Infection form) will be per routine CIBMTR reimbursement procedures, under existing Master Healthcare Data and Sample Submission Agreements. Also, under these agreements, CIBMTR will automatically reimburse the following for this study, paid quarterly. Note: Centers will not receive reimbursement for samples collected at LabCorp.

- \$100 for each specimen *received*, typically up to a total of 5 specimens, unless visit 3b is completed and then up to 6 specimens could be received
- \$100 for each set of supplemental data forms *submitted* to eClinical, (typically up to a total of 5 sets unless visit 3b is completed and then up to 6 sets would be submitted) for this vaccine study, paid quarterly.

19. What samples should be collected for patients that cannot receive all 2 or 3 doses post-transplant?

The study captures the number of doses given **post-cell therapy**. If the patient only receives 1 dose post cell therapy (e.g., if a patient received two doses prior to cell therapy and will only receive the 3rd dose post-cell therapy), it is treated as a single dose vaccine on study and follows that pathway. If the patient receives 2 doses post study enrollment, follow the 2-dose vaccine pathway. If they will receive all 3 doses post cell therapy, then the patient will follow the 2 doses + 3rd dose pathway (if appropriately consented).

The CDC announced on October 26, 2021, that HCT and CAR-T-cell recipients who received doses of COVID-19 vaccine prior to receiving an HCT or CAR-T-cell therapy should be revaccinated with a primary vaccine series at least 3 months (12 weeks) after transplant or CAR-T-cell therapy. More information on this recommendation can be found at: <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#considerations-covid19-vax-immunocopromised>

20. Do the latest consent and assents need to be submitted to site IRBs?

Yes, the latest consent and assents should be submitted to site IRBs. The latest versions must be approved prior to drawing 3rd dose samples and the new 50mL blood volume. Please see #Memo 2101-013 for more information.

21. What is the difference between the Study Plan and the Site Study Guide?

The Study Plan contains information on eligibility and study conduct; the Site Study Guide contains general study information and data entry instructions for Advantage eClinical system.

22. Are patients allowed to co-enroll on other studies?

Yes, patients can be co-enrolled on other studies as this is an observational study.

23. Are patients allowed to mix and match vaccine types?

This is an observational study, so it is up to the patient's physician which vaccine they receive. Please make sure to report the correct vaccine on the data entry forms.

24. Is an enrolled patient who tests positive for COVID-19 allowed to stay on the study?

Yes, please report the COVID-19 infection on the data entry forms in Advantage eClinical and on CIBMTR Form 2149 in FormsNet. Further instruction can be found in the Site Study Guide and CIBMTR Data Reporting Guidelines.

25. I don't see Timepoint #4 in Advantage eClinical. How do I proceed?

Please review that you have indicated that the patient consented to the additional sample collection at Timepoint #3 or Timepoint #3B. Please refer to the BMT CTN 2101 Site Study Guide for more details.

26. If a dose is received after a patient completes study Time-point 5, should additional data and sample be collected?

No, once a patient completes Time-point 5, their study participation is complete, and no additional data or samples may be collected.

27. Are patients who have received Evusheld eligible for this study?

Yes, patients who have received Evusheld before or after transplant/cell therapy are eligible for this study. Evusheld receipt along with the administration date should be recorded in Advantage eClinical.

28. If a patient receives Evusheld after enrollment, can they stay in the study?

Yes, patients who receive Evusheld after enrollment can stay in the study. Evusheld receipt along with the administration date should be recorded in Advantage eClinical.