COVID19-TB-02

Immunogenicity of a third dose of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine in kidney transplant recipients who failed to respond after two previous doses

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SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: COVID19-TB-02	**Version Number/Date: v3.0/January 14, 2022**
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IND Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
Return Signed Form to: The original signature page must be kept for your records. Return an electronic PDF copy of the signed signature page (*as described below) to the DAIT Regulatory Management Center via the applicable DAIT RMC email to DAITRegulatory_SiteRegistration (SM) at DAITReg@ppd.com.	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Conference for Harmonisation (ICH) document entitled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements.
As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

*[*The site Principal Investigator should sign and date at the indicated location below. A written signature/date is acceptable (e.g., scanned and sent via email as a PDF version). An electronic signature is also acceptable (e.g., sent via email as a PDF version).]*

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Immunogenicity of a third dose of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine in kidney transplant recipients who failed to respond to two previous doses.
Short Title	COVID Protection After Transplant Pilot (CPAT-P) Study
Clinical Phase	Phase II
Number of Sites	Single Center (Johns Hopkins University)
IND Sponsor/Number	NIAID/ IND# 27215
Study Objectives	To elicit an antibody response to vaccination against SARS-CoV-2 in kidney transplant recipients who have failed to respond to two doses of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine.
Study Design	An open label, non-randomized pilot study in kidney transplant recipients who received two doses of either mRNA COVID-19 vaccine and have a negative (<0.8 U/mL) or low (titer ≤50 U/mL) SARS-CoV-2 antibody response using the Roche Elecsys® anti-RBD assay. Eligible participants will receive a third dose of the same mRNA vaccine as the prior two doses.
Primary Endpoint	The primary endpoint is the proportion of participants who achieve an antibody response >50 U/mL measured at 30 days after the third dose of vaccine using the Roche Elecsys® anti-RBD assay. All subjects with detectable antibody will in addition have neutralizing antibody titers and further quantification and characterization of antibody using the best available assay.
Safety, Secondary, and Exploratory Endpoint(s)	**Secondary Safety Endpoints:** • Local and systemic vaccine reactogenicity and/or allergy • Serious adverse events occurring during the 30 days following the third dose of vaccine • Treated acute cell-mediated and/or antibody-mediated allograft rejection (clinical or biopsy-proven) within 60 days following the third dose of vaccine • Development of de novo donor-specific anti-HLA antibody within 90 days of the vaccine • Graft loss within 60 days of the vaccine • Death within 60 days of the vaccine **Exploratory Mechanistic Immunogenicity Endpoints:** • Range of antibody responses and other measures of immunologic protection • Anti-S1 and anti-RBD serology • Additional serological panels and correlates of neutralizing antibody • Neutralizing antibody assays

	• SARS-CoV-2 virology, diagnostics, and sequencing, including novel variants of concern • Antigen-specific B cell response • Antigen-specific T cell response • Evidence of immune activation and metabolic profile by transcriptomics and cytokine signaling • Durability of de novo donor-specific anti-HLA antibody
Accrual Objective	The study will enroll up to 200 participants who have a negative (<0.8 U/mL) or low (≤50 U/mL) titer antibody by the Roche Elecsys® assay, with a minimum of 50 and up to 100 participants in each stratum (non-responder vs low responder).
Study Duration	Accrual: 4 weeks Vaccination and Follow-up: 8-12 months Total Duration: a minimum of 8 months and up to 13 months
Treatment Description	A third dose of the same mRNA platform COVID-19 vaccine as previously received (100mcg Moderna or 30mcg Pfizer-BioNTech)
Inclusion Criteria	Individuals must meet all the following criteria to be eligible: 1. Able to understand and provide informed consent. 2. Individual ≥ 18 years of age. 3. Recipient of kidney transplant ≥12 months prior to enrollment, without treated allograft rejection in the 6 months preceding enrollment. 4. Received 2 doses of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine as specified in the respective FDA EUAs, >30 days and <8 months prior to study entry. 5. Negative (titer <0.8U/mL) or low (antibodies detected at titer ≤ 50 U/mL) response to the vaccine at ≥ 30 days from dose 2 of the Moderna COVID-19 vaccine or the Pfizer BioNTech vaccine, using the Roche Elecsys® anti-RBD assay.
Exclusion Criteria	Individuals who meet any of the following criteria will not be eligible: 1. Recipient of any number of doses of any COVID vaccine product other than the Moderna COVID-19 vaccine or the Pfizer-BioNTech COVID-19 vaccine. 2. Known history of severe allergic reaction to any component of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine. 3. Thrombotic events, myocarditis, or pericarditis temporally associated with prior dose of COVID-19 vaccine. 4. Any change in transplant immunosuppression regimen (drug or dose) in response to suspected or proven rejection within the last 6 months. 5. Significant graft dysfunction (see Study Definitions for further details). 6. Receipt of any cellular depleting agent (e.g. ATG, Rituximab, Alemtuzumab, Cyclophosphamide) within 12 months preceding enrollment. 7. Receiving systemic immunomodulatory medication(s) for any condition other than transplant. 8. Any untreated active infection.

	9. Infection with HIV. 10. Maintenance immunosuppressive regimen that includes belatacept or abatacept. 11. Recent (within one year) or ongoing treatment for malignancy. 12. Any past or current medical problems, treatments, or findings which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the candidate's ability to comply with study requirements or may impact the quality or interpretation of the data obtained from the study.
Pausing Rules	If the following occur, enrollment may be temporarily halted and an expedited DSMB review take place: **Reactogenicity**: Two Grade 4 or higher reactogenic adverse events (AEs) that are definitely or possibly related to the vaccine **Allergy**: Five participants in the first 100 participants vaccinated, or 5% of all participants thereafter experiencing a Grade 3 systemic allergic reaction that is definitely or possibly related to the vaccine

Study Contacts: Participating Centers

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Table of Contents

Glossary of Abbreviations

ATG	Anti-thymocyte globulin
CFR	Code of Federal Regulations
COP	Correlate of Protection
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
EUA	Emergency Use Authorization
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
SOT	Solid Organ Transplant
SUSAR	Serious Unexpected Suspected Adverse Reaction

Study Definitions Page

Acute Cellular-Mediated Rejection	A clinical and histologic event that meets the Banff 2015 criteria for acute cellular rejection.
Antibody-Mediated Rejection	A clinical and histologic event that meets the Banff 2015 criteria for antibody mediated rejection.
Biopsy-Proven Rejection	Histologic evidence of rejection on biopsy meeting Banff 2015 criteria.
Donor Specific Antibodies (DSA)	Antibodies directed donor human leukocyte antigens (HLA). Identification of DSA will carried out at a central laboratory; see lab manual.
Graft Failure (Kidney)	Any of the following events: renal dialysis of more than 3 months duration; listing for re-transplantation; death with functioning graft.
Lost to Follow-up	Missing sequential visits including the final visit.
Medical Monitor	The physician who is responsible for Sponsor oversight of safety aspects of the trial. The medical monitor will determine the attribution of Serious Adverse Events after considering all investigator input.
Negative Antibody Response	A measurement of <0.8 U/mL using the Roche Elecsys® ® SARS-CoV-2 anti-RBD Igg assay.
NIAID Project Manager	NIAID assigned project manager who is responsible for all day to day protocol related issues, including version control, consent review, etc.
Principal Investigator	The physician responsible for supervising the conduct of the clinical investigation and to protecting the rights, safety, and welfare of participants consistent with 21 CFR Part 312.
Participant Premature Termination	Participants who are lost to follow up, withdraw consent, or die during the study. Data and specimens will no longer be expected from participants who are terminated from the study.
Program Officer	NIAID official who oversees the programmatic and budgetary aspects of the grant.
Low Antibody Response (entry criterion)	A measurement of $\leq$50 U/mL using the Roche Elecsys® SARS-CoV-2 anti-RBD Igg assay.
Protocol Mandated Procedures	A procedure or intervention that is a study requirement at the specified time point in the protocol.
Regulatory Affairs Officer	NIAID-assigned officer responsible for regulatory aspects of the study.
Significant Graft Dysfunction	Estimated Glomerular Filtration Rate less than 30mL/min/1.73m^2.
Site Principal Investigator	Lead investigator listed on the FDA Form 1572 at a particular clinical site who is responsible for the conduct of the study at that site.
Study Therapy	The investigational product is a third dose of either the Moderna COVID-19 Vaccine or Pfizer-BioNTech COVID-19 vaccine.

Treated Rejection	Any clinical event, with or without supporting evidence from a biopsy, which the treating physician diagnosis as “rejection” AND for which the patient is treated with steroids, lytic therapy, or an increase in dose or number of immunosuppressive medications.

1. Background and Rationale

1.1 Background and Scientific Rationale

COVID-19 disproportionately affects vulnerable populations, including those with impaired immune defenses. Organ transplant recipients are particularly at risk as a result of both the need for life-long immunosuppressive therapy to prevent rejection and a high prevalence of other risk factors for severe COVID-19 including cardiovascular disease, hypertension, and diabetes. The consequences of COVID-19 are severe in organ transplant recipients; in one study of a large (n=482) cohort of patients who had a confirmed diagnosis of COVID-19 by polymerase chain reaction, 78% were hospitalized, and of those, 39% required ICU care and 31% required mechanical ventilation. Mortality at 28 days from diagnosis was 17.8% overall and 20.5% among those who were hospitalized. Risk factors for mortality included age >65 years, congestive heart failure, chronic lung disease and obesity.[1-5]

SARS-CoV-2 vaccines are highly immunogenic and effective in the general population. Transplant recipients were excluded from landmark trials, but it has become evident during the post-EUA experience that the response to vaccination is substantially lower among organ transplant recipients as compared to the general population: in a cohort of 436 transplant recipients who had received two doses of either the Moderna COVID-19 vaccine or the Pfizer-BioNTech COVID-19 Vaccine, a positive anti-spike response was detectable in only 17% after the first dose and 30-60% after two doses in multiple studies. Associations with suboptimal vaccine response include treatment with antimetabolite therapies such as mycophenolate or azathioprine, which are known to impair lymphocyte function and response to new antigens (such as influenza vaccination).[10-14]

It is critical to understand risk stratification for vaccine failure given mounting reports of serious breakthrough infections in fully vaccinated SOT recipients.[35] Persistent knowledge gaps include characterization of humoral vaccine responses (e.g., level and durability of neutralizing antibody, including versus novel variants), B cell memory responses, and antigen-specific T cell responses in transplant recipients.[15,16] Strategies to improve vaccine response to viral antigens in immunocompromised persons are largely based on experiences with influenza and hepatitis B vaccines; these include administration of additional vaccinations, higher antigen dosing, and mixing of vaccine platforms such as those containing immunostimulatory adjuvants.[17,18] Development of a strategy for eliciting an antibody response to COVID vaccines in transplant recipients is complex as the pharmacologic immunosuppression that prevents response to the vaccine also prevents rejection of a life-sustaining allograft. Potential interventions include administration of a third dose of vaccine; alternate vaccine strategies including higher doses of vaccine or the use of adjuvanted vaccines; and, most high risk, transient modification of a patient's immunosuppressive regimen before and after vaccine administration. A decision algorithm for an individual patient must consider the likelihood of success of a low risk intervention (i.e. a third dose of vaccine), the type of transplant (e.g. kidney, heart or lung), the likelihood and consequences of allograft rejection if the patient's immunosuppressive regimen is modified (e.g. the low likelihood of permanent injury after an episode of liver rejection versus the high likelihood of permanent injury after an episode of lung rejection), and the individual's risk for severe disease or death from COVID-19 if they remain without antibody protection.

As a first step in addressing this problem, this study will investigate the effect of a third dose of mRNA vaccination in immunologically stable kidney transplant recipients who demonstrate a negative (<0.8 U/mL) or low (≤50 U/mL) immune response to the two-dose series. Anti-S1/RBD levels are well correlated with neutralizing antibody versus SARS-CoV-2 and vaccine sero-protection.[37,38] The precise cutoff that connotes protection in is not fully established. Thresholds ranging from 15 units/mL[3]-144 units/mL[40] have been correlated with live virus neutralization in prior studies of convalescents. An analysis of vaccine efficacy across trials indicates a level 2-4-fold higher for vaccine-evoked neutralization (compared to convalescents) best correlates with vaccine efficacy.[41] Thus, for screening purposes, a level of 50 units/mL on this commercial assay would be a pragmatic cutoff representing a conservative lower bound under which protection is unlikely.

Response to the third dose for the primary endpoint will be evaluated using the MSD multiplex assay and will be correlated with clinical and immunologic immunophenotyping including extensive evaluation of cellular immunity. Our goal is to identify pre-vaccination clinical and/or laboratory characteristics that help distinguish those who can benefit from a third dose of mRNA vaccine versus those who require a more complex approach. Our findings will inform a subsequent adaptive trial of higher-risk interventions, such as mixed platform vaccine dosing or immunosuppressive modulation, to induce vaccine response.

Rationale for Selection of Investigational Product or Intervention

This single-arm trial will administer a third dose of mRNA vaccination to SOT recipients who demonstrate low or negative anti-spike antibody response after completion of two doses of either the Moderna COVID-19 Vaccine or the Pfizer-BioNTech Vaccine, as described in their respective Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs). These vaccines have proven safe and highly immunogenic in the general population, with publication of large Phase III trials data supporting FDA EUA.[19,20] This third-dose vaccine intervention was chosen due to demonstrated safety of the two-dose series in SOT recipients (see 1.4) and experience with the efficacy of additional dosing strategies doses of other vaccines (e.g., hepatitis and influenza vaccines)[17,18] in immunocompromised people. Based on the results of this pilot trial, future studies will incorporate other potentially riskier strategies for those who fail to respond to a third dose of mRNA vaccine, such as mixed platform or adjuvanted doses. Use of vaccine products that have achieved Emergency Use Authorization status and have progressed through Phase III trials, such as the Johnson & Johnson Ad.COV2.26 vaccine, would be appropriate interventions in this setting. The adjuvanted virus-like nanoparticle (VLP) vaccine NVX-CoV2373 might also be considered given that other adjuvanted subunit vaccines, such as the recombinant varicella zoster (Shingrix), hepatitis B (HEPLISAV-B), and HPV (Gardasil) vaccines, have been administered safely and with good effect in transplant recipients.[17,18,21-23]

1.2 Preclinical Experience

Studies performed in murine models in the 1970s and 1980s showed that the repeated immunization of up to 4 doses continues to have a positive impact on the titer, isotype, and affinity of the induced antibody responses.[24,25] Similarly preclinical murine data indicate that immunization schedules that include third doses markedly increase the frequency and functional properties of antigen specific T cell immune responses.[26]

There are no specific preclinical studies addressing whether and how these effects of immunization schedule on vaccine-induced immunity are affected by the immunosuppressant medications used in transplantation.

1.3 Clinical Studies

The Moderna and Pfizer-BioNTech vaccines are known to have excellent immunogenicity in the general adult population, even against some of the recently identified SARS-CoV-2 variants.[27,28] The vaccines are well-tolerated, with mostly mild-to-moderate local and systemic reactogenicity that is more pronounced after the second dose.[29,30] However, organ transplant recipients have recently been shown to have much less reliable and robust responses to the vaccines.[10,12] In a large (N=658) prospective cohort study of U.S. transplant recipients, only 15% of patients had a positive anti-spike/RBD response after a first dose of either the Moderna or the Pfizer vaccine, with improvement to only 54% by four weeks after the second dose of vaccine. Patients who had a positive response after the first dose of vaccine had higher titers of antibody after dose two as compared with those who had a negative response after dose one but did have a measurable response after dose two. In those with a positive antibody response after dose two, antibody levels were substantially lower than in immunocompetent vaccine recipients. Associations with lack of vaccine response included older age, use of antimetabolite therapies, history of kidney transplantation (versus other organ transplant), more recent transplantation, and receipt of the Pfizer-BioNTech vaccine (versus the Moderna mRNA-1273 vaccine). In a French study of 101 kidney transplant recipients maintained on belatacept-based immunosuppression, only 6% of patients had measurable anti-spike antibodies after 2 doses of the Pfizer-BioNTech vaccine. In that study, SARS-CoV-2-specific T-cell responses by EliSpot were present in only 30% of those tested (N=23) after two doses of vaccine.[32]

2. Study Hypotheses/Objectives

2.1 Hypotheses

A subset (≥25%) of kidney transplant recipients who had a negative or low response to two doses of the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine will achieve an increase in SARS-CoV-2 antibody titers following a third dose of the same mRNA vaccine.

Patient characteristics associated with response to a third dose of vaccine (e.g. prior vaccine response, immunosuppressive regimen, and immunologic characteristics) will be identified.

2.2 Primary Objective(s)

The primary objective of this study is to elicit an increase in SARS-CoV-2 antibody titers to greater than 50 U/mL in kidney transplant recipients who did not achieve this level of antibody after two doses of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine. Antibody response will be evaluated 30 days following the investigational dose of vaccine using the Roche Elecsys® anti-RBD assay. All participants with measurable SARS-CoV-2 antibody titers will also have neutralizing antibody titers and further quantification and characterization of antibody using the best available assay.

2.3 Secondary Safety Objective(s)

- To determine the incidence of adverse events (AEs) and serious adverse events (SAEs), including reactogenicity, following the third dose of COVID-19 vaccine.
- To determine the incidence of alloimmune events (e.g., kidney rejection and development of de novo DSA) following the third dose of vaccine.

2.4 Secondary Immunogenicity Objectives

- Correlations of antibody response with immunosuppressive regimen and clinical and immunologic phenotype.
- To determine whether response to a third dose of either mRNA vaccine differs between those participants who had a negative response to the first two doses and those that had a low response after the first two doses.
- To assess whether response to third dose of COVID-19 vaccine is associated with clinical phenotype (e.g., age, organ type, time post-transplant, immunosuppressive regimen).
- To evaluate durability of response over 1-year in those who have an antibody response to the third dose of vaccine.

2.5 Exploratory Mechanistic Objectives

- To identify immunologic correlates of vaccine response.
- To evaluate immune activation in response to the vaccine.

3. Study Design

3.1 Description of Study Design

This is an open label, non-randomized pilot study in kidney transplant recipients who received two doses of either the Moderna COVID-19 vaccine or the Pfizer-BioNTech COVID-19 vaccine and have a negative (<0.8 U/mL) or low (titer ≤50 U/mL) SARS-CoV-2 antibody response. The study will enroll up to 200 participants with a minimum of 50 and up to 100 participants in each stratum (non-responder vs low responder). Eligible participants will receive a third dose of the same mRNA COVID-19 vaccine as they received previously.

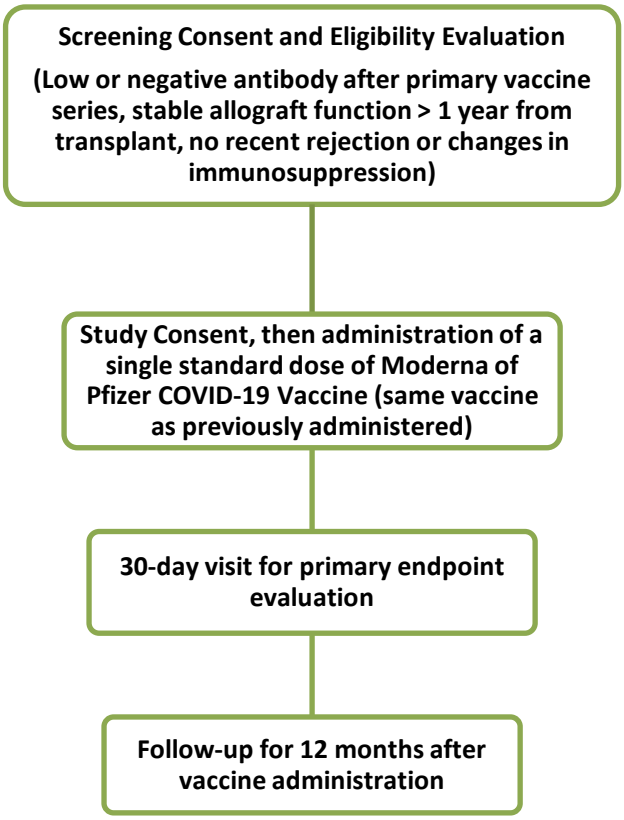


Figure 1. *Study Design Diagram*

3.2 Primary Endpoint

The primary endpoint is the proportion of participants who achieve an antibody response >50 U/mL measured at 30 days after the third dose of vaccine using the Roche Elecsys® anti-RBD assay. All subjects with detectable antibody will in addition have neutralizing antibody titers and further quantification and characterization of antibody using the best available assay.

3.3 Secondary Endpoints

3.3.1 Secondary Safety Endpoints

- Local and systemic vaccine reactogenicity and/or allergy
- Serious adverse events occurring during the 30 days following the third dose of vaccine

- Treated acute cell-mediated and/or antibody-mediated allograft rejection (clinical or biopsy-proven) within 60 days following the third dose of vaccine
- Development of de novo donor-specific anti-HLA antibody within 90 days of the vaccine
- Graft loss within 60 days of the vaccine
- Death within 60 days of the vaccine

3.3.2 Exploratory Mechanistic Immunogenicity Endpoints

- Range of antibody responses and other measures of immunologic protection
- Anti-S1 and anti-RBD serology
- Additional serological panels and correlates of neutralizing antibody
- Neutralizing antibody assays
- SARS-CoV-2 virology, diagnostics, and sequencing, including novel variants of concern
- Antigen-specific B cell response
- Antigen-specific T cell response
- Evidence of immune activation and metabolic profile by transcriptomics and cytokine signaling
- Durability of de novo donor-specific anti-HLA antibody

4. Selection of Participants and Clinical Sites/Laboratories

4.1 Rationale for Study Population

Participants who received two prior doses of mRNA vaccine but have a negative test for antibody or have very low antibody titers (≤50 U/mL) will be enrolled in this study. This group of patients is at high risk for severe COVID-19 disease due to pharmacologic immunosuppression and a high prevalence of non-transplant risk factors such as obesity and diabetes.

4.2 Inclusion Criteria

Individuals who meet all the following criteria are eligible for enrollment as study participants:

1. Able to understand and provide informed consent.
2. Individual ≥ 18 years of age.
3. Recipient of kidney transplant ≥12 months prior to enrollment, without treated allograft rejection in the 6 months preceding enrollment.
4. Received 2 doses of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine as specified in the respective FDA EUAs, >30 days and <8 months prior to study entry.
5. Negative (titer <0.8U/mL) or low (antibodies detected at titer ≤ 50 U/mL) response to the vaccine at ≥ 30 days from dose 2 of the Moderna COVID-19 vaccine or the Pfizer BioNTech vaccine, using the Roche Elecsys® anti-RBD assay.

4.3 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Recipient of any number of doses of any COVID vaccine product other than the Moderna COVID-19 vaccine or the Pfizer-BioNTech COVID-19 vaccine.
2. Known history of severe allergic reaction to any component of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine.
3. Thrombotic events, myocarditis, or pericarditis temporally associated with prior dose of COVID-19 vaccine.
4. Any change in transplant immunosuppression regimen (drug or dose) in response to suspected or proven rejection within the last 6 months.
5. Significant graft dysfunction (see Study Definitions for further details).
6. Receipt of any cellular depleting agent (e.g. ATG, Rituximab, Alemtuzumab, Cyclophosphamide) within 12 months preceding enrollment.
7. Receiving systemic immunomodulatory medication(s) for any condition other than transplant.
8. Any untreated active infection including BK viremia $>10^4$ copies.
9. Infection with HIV.
10. Maintenance immunosuppressive regimen that includes belatacept or abatacept.
11. Recent (within one year) or ongoing treatment for malignancy.
12. Any past or current medical problems, treatments, or findings which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the candidate's ability to comply with study requirements or may impact the quality or interpretation of the data obtained from the study.

4.4 Selection of Clinical Sites

4.4.1 Selection of Clinical Site

This is a single site study that will be carried out at the Johns Hopkins University. Vaccine administration will take place at the Bayview Clinical Research Unit (CRU) and Broadway Adult Outpatient Clinical Research Unit (CRU). CRU personnel are trained in and currently engaged in COVID-19 vaccine administration in other clinical research studies. Johns Hopkins has a large cohort of kidney transplant recipients, who have received the 2-dose COVID-19 mRNA vaccine series.

5. Known and Potential Risks and Benefits to Participants

Information related to administration of a third dose of vaccine to immunocompromised transplant recipients is scarce and anecdotal. The risks cited below reflect the experience in immunocompetent persons receiving 2 doses of the Moderna or Pfizer-BioNTech vaccine.

5.1 Risks of the Investigational Products as cited in the Full FDA EUA Prescribing Information

5.1.1 Risks of Moderna COVID-19 Vaccine

The most common side effects reported include injection site reactions (pain, redness and swelling), axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, and nausea/vomiting. Severe allergic reactions, including anaphylaxis, have been reported following the administration during mass vaccination outside of clinical trials. Severe allergic reactions included difficulty breathing, swelling of the face and throat, rash, dizziness, and weakness.

5.1.2 Risks of Pfizer-BioNTech COVID-19 Vaccine

The most common side effects reported include non-severe allergic reactions (rash, itching, hives and facial swelling), injection site reactions (pain, redness and swelling), fatigue, headache, myalgia, arthralgia, chills, fever, lymphadenopathy, vomiting, diarrhea, arm pain and general malaise. Severe allergic reactions that include difficulty breathing, swelling of the face and throat, rash and dizziness or weakness have been reported post authorization but are less common.

5.1.3 Risks of Moderna COVID-19 Vaccine and Pfizer-BioNTech Vaccines in adults as cited in Medical Literature

The Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine are being administered under an Emergency Use Authorization. Adverse Events that occur outside of clinical trials as a result of the mass vaccination effort are reported to each manufacturer and included in a Fact Sheet for Healthcare Providers.[33,34]

In a recent cohort of 741 organ transplant recipients who received two doses of either the Moderna or Pfizer-BioNTech vaccine, reactogenicity was similar to what has been reported in immunocompetent people: pain at injection site, fatigue, and headache were common. Severe reactogenicity (defined as preventing daily activity) occurred in 1-2% of study participants. Systemic reactogenicity was more common after the second dose of vaccine. There was an increased risk of local reactogenicity among recipients who were maintained on an immunosuppressive regimen that included corticosteroids or mTOR inhibitors, and also among those who received the Moderna vaccine. There were no cases of anaphylaxis. There was one case of acute allograft rejection after the second dose of vaccine.[36]

5.1.4 Potential Risks to Study Population

There may be an increased risk of low-to-moderate reactogenicity to trial participants who receive a third dose of vaccine. Based on currently available information, the risk of serious allergic events is likely to be extremely low, equal to or less than has been seen in the immunocompetent population. There is no evidence that the COVID-19 vaccine will result in new alloimmune events, and none are expected.

5.2 Risks of Other Protocol Specified Medications

There are no other protocol specified medications.

5.3 Risks of Study Procedures

5.3.1 Risk of Blood Draw

Collection of blood may cause slight discomfort, pain, bleeding or bruising at the injection site. Rarely, fainting or infection may occur.

5.3.2 Risks Associated with Nasopharyngeal Swab Collection

Nasal swab collection may cause localized discomfort. Rarely, mild epistaxis may occur.

5.3.3 Risk of Internet Based Data Collection

Data from this study will be entered into a computerized database through a secured web site. All information will be saved and transmitted in a coded form. Only authorized personnel requiring a password will be permitted to enter data. There is risk, although minimal, of unauthorized persons obtaining confidential information.

5.4 Potential Benefits

There may be no benefit to participants in this study. If a participant achieves a protective level of antibody against SARS-CoV-2 as a result of participating in this study, there will likely be associated benefit. However, whether any participant will achieve this is unknown. The results of this study will inform larger scale studies designed to promote vaccine response in transplant recipients.

6. Investigational Agents

6.1 Investigational Agent #1: Moderna COVID-19 Vaccine

The Moderna COVID-19 Vaccine is authorized for use under FDA EUA for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The FDA EUA specifies a 2-dose series and this study will include a third dose, which is not currently included in the FDA EUA.

6.1.1 Formulation, Packaging, and Labeling

Moderna COVID-19 Vaccine is provided as a white to off-white suspension for intramuscular injection. Each 0.5 mL dose of Moderna COVID-19 Vaccine contains 100 mcg of nucleoside-modified messenger RNA (modRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus.

Each dose of the Moderna COVID-19 Vaccine also contains the following ingredients: a total lipid content of 1.93 mg (SM-102, PEG 2000 dimyristoyl glycerol [DMG], cholesterol, and DSPC), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.12 mg sodium acetate, and 43.5 mg sucrose.

Moderna COVID-19 Vaccine will be supplied in cartons containing 10 multiple-dose vials per carton (10 doses per vial); the vial stoppers are not made with natural rubber latex.

Moderna COVID-19 Vaccine should be stored frozen between -25° to -15°C (-13° to 5°F) in the original carton to protect from light. Product should not be stored on dry ice or below -40°C.

6.1.2 Dosage, Preparation, and Administration

The Moderna COVID-19 Vaccine multiple-dose vial contains a frozen suspension that does not contain a preservative and must be thawed prior to administration, per the Full FDA EUA Prescribing Information.[33] Additional details are included in the Pharmacy Manual.

The booster dose level in this trial will be 100mcg (0.5 mL) Moderna COVID-19 Vaccine administered intramuscularly in the deltoid. Vaccine administration details will follow FDA EUA fact sheet instruction and be recorded on a case report form.

6.2 Investigational Agent #2: Pfizer-BioNTech COVID-19 Vaccine

The Pfizer-BioNTech COVID-19 Vaccine is authorized for use under FDA EUA for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. This protocol is currently only enrolling participants 18 years of age and older.

6.2.1 Formulation, Packaging, and Labeling

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple-dose vials; each vial must be diluted with 1.8 mL of sterile non-bacteriostatic 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2.

Each dose of the Pfizer-BioNTech-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate),

0.05 mg 2[PEG-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection, USP) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine does not contain preservative. The vial stoppers are not made with natural rubber latex.

Pfizer-BioNTech COVID-19 Vaccine will be supplied in cartons containing 25 multiple-dose vials per carton (6 doses per vial) in thermal containers with dry ice. Once received, the vial cartons must be removed immediately from the thermal container and stored in an ultra-low temperature freezer between -80°C to -60°C (-112°F to -76°F). Vials must be kept frozen between -80° C to -60°C (-112°F to -76°F) and protected from light until ready to use.

6.2.2 Dosage, Preparation, and Administration

The Pfizer-BioNTech COVID-19 Vaccine multiple-dose vial contains a volume of 0.45 mL supplied as a frozen suspension that does not contain preservative. Each vial must be thawed prior to dilution with 1.8 mL of sterile non-bacteriostatic 0.9% Sodium Chloride Injection, USP and vaccine administration, per the Full FDA EUA Prescribing Information.[34] Additional details are included in the Pharmacy Manual.

The dose level in this trial is 30 mcg (0.3 mL) Pfizer-BioNTech COVID-19 Vaccine administered intramuscularly in the deltoid. Vaccine administration details will follow FDA EUA fact sheet instruction and be recorded on the Vaccine Administration eCRF. The Pfizer-BioNTech COVID vaccine is administered intramuscularly as a single (third) dose to study participants.

6.3 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

6.4 Assessment of Participant Compliance with Investigational Agent

Not Applicable; one time dose administration of COVID-19 vaccine.

6.5 Toxicity Prevention and Management

The vaccine will be administered by qualified personnel in dedicated observation rooms. Participants will be monitored for allergic reactions or other intolerance for 30 minutes following vaccine administration. Appropriate medications to address allergic reactions will be supplied by the investigational pharmacy (i.e.,

epinephrine, anti-histaminergic medications) and there is access to local rapid response team support in case of serious adverse events.

6.6 Premature Discontinuation of Investigational Agent

Not Applicable

7. Other Medications

7.1 Concomitant Medications

7.1.1 Protocol-mandated

None

7.1.2 Other permitted concomitant medications

Transplant immunosuppression as determined by the treating transplant physician may include tacrolimus or cyclosporine, corticosteroids, MMF and/or azathioprine.

7.2 Prophylactic Medications

Infectious disease prophylaxis will be determined by the treating transplant physician.

7.3 Prohibited Medications

There are no prohibited medications.

7.4 Rescue Medications

Not applicable

8. Study Procedures

8.1 Enrollment

Potential study participants may be identified by medical chart review and initially contacted by a member of the study team in person or over the phone. During this initial contact, the potential participant will be provided information on the study and asked about their interest in study participation. If they elect to continue, they will be appropriately consented and move to the screening portion of the study.

During the consent process, potential participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures.

8.2 Screening Visit

The purpose of the screening period is to confirm eligibility prior to the study intervention. During the screening period for study eligibility, the study personnel will review the participant's medical record for previous and current medical history.

The following procedures, assessments, and laboratory measures will be conducted to determine participant eligibility:

1. Review medical history and immunosuppression to confirm eligibility.
2. Blood drawn locally for anti-RBD Igg (using Roche Elecsys® assay). A prior result may be used for eligibility if it was obtained at least 30 days following the second COVID-19 vaccine administration.

8.3 Study Visits or Study Assessments

8.3.1 Vaccination Visit (Day 0)

Participants who meet inclusion and do not meet any exclusion criteria will be scheduled for a vaccination visit. Baseline blood, nasopharyngeal, and urine samples will be collected per the Schedule of Events in Appendix 1.

Following sample collection, the participant will proceed to the administration location and receive their third dose of COVID-19 vaccine (see Section 6.1 for vaccine details). Participants will be observed for 30 minutes post vaccine administration.

8.3.2 Follow-up Visits

Follow-up will occur on Days 3, 7, 14, 30 (month 1), 90 (month 3), 180 (month 6), 210 (month 9) and 365 (year 1) following vaccine administration. The Day 30 visit is the primary endpoint visit. During these visits, participants will be asked about their general health, any new events, immunosuppression medication changes and their transplanted kidney.

In addition, blood will be collected for assessments to be run in the clinical and research laboratories per the Schedule of Events in Appendix 1. Nasopharyngeal swab for SARS-CoV-2 PCR testing will be collected at baseline and Days 30, 90 (month 3), 180 (month 6), 210 (month 9), 365

(year 1) following vaccine administration, and in any case of suspected COVID-19 infection. Participants will be instructed to contact the study team if they receive any COVID-19 testing at an outside lab during the course of the study. All instances of COVID-19 infection will be reported on a case report form.

8.3.3 Suspected or Confirmed Cases of COVID-19 Infection

If participants suspect they have contracted COVID-19 infection, they will be directed to follow-up with their local transplant physician or primary care provider to obtain the appropriate clinical care. Information related to their illness will be collected for the study and reported in the clinical database.

8.3.4 5-Month COVID-19 Booster

The CDC currently recommends a COVID-19 booster at 5 months following completion of the primary series (3 doses for immunocompromised patients). The study team will remotely contact participants monthly, beginning 5 months following their study dose of vaccine to encourage them to get a COVID-19 booster dose and inform the study team when this occurs.

Participants who receive the 5-month COVID-19 booster will be followed on a separate schedule (Appendix 2) at 30 days and 90 days following the 5-month booster. Data will be collected regarding their booster dose of vaccine and research specimens (blood, nasal swabs) will be collected at these timepoints. Their participation will be complete at 90 days post-booster or study Month 12, whichever occurs first. Participants who do not receive a 5-month COVID-19 booster by Month 11 will remain on their original study schedule per Appendix 1.

8.4 Unscheduled Visits

If there is a change in immunosuppressive medications, new medical events or a diagnosis of rejection between regularly scheduled visits, participants will be instructed to contact study personnel and may be asked to return to the study site for an “unscheduled” visit.

8.5 Visit Windows

Study visits should take place within the time limits specified below: the designated visit windows *(i.e. +/- n days)* for each scheduled visit are also indicated on the Table of Events.

Visits 1-2 (Day 3, Day 7)	+/- 1 day
Visits 3-4 (Day 14, Day 30)	+/- 3 days
Visits 5-7 (Day 90, Day 180, Day 365)	+/- 2 weeks

9. Mechanistic Assays

9.1 Introduction

Effective vaccinations induce potent protective humoral and cellular immunity and promote development of robust T and B cell memory, together preventing infection and accelerating viral clearance following pathogen exposure. Current concepts are that vaccination results in activation of both T cells and B cells. Vaccine antigen-activated B cells can differentiate into low affinity IgG- or IgM-secreting plasma cells (PCs). Alternatively, vaccine antigen-activated B cells can interact with antigen-activated CD40+ CD4+ (Th1) helper T cells to undergo an isotype switch and enter germinal center (GC) reactions wherein they undergo affinity maturation. Positive selection of the highest affinity B cells in the GC requires cognate interactions with antigen specific IL-21-producing follicular helper CD4+ T cells (Tfh). The positively selected high affinity B cells then can differentiate into long lived antibody-secreting PCs, can become memory B cells (Bmem), or can reenter the GC to undergo further affinity maturation. Crucial features of the antibody repertoire relevant to pathogen clearance include antibody specificity, affinity, titer, isotype class, and glycosylation patterns, among others. Antigen-reactive CD4+ and CD8+ T cells that expand and differentiate following vaccination are also crucial mediators of pathogen clearance independent of their functions as helper cells for effective humoral immune responses. Important characteristics of these induced T cell responses include epitope specificity, cytokine secretion patterns, and cytotoxic function, among others. Effective anti-pathogen immunity also involves activation of innate immune cells, including dendritic cells, macrophages, and natural killer cells that can interact with an enhance the adaptive immune responses and have been recently shown to exhibit cellular and molecular features consistent with memory.

As noted in the background section, emerging evidence indicates that the overwhelming majority of transplant recipients taking immunosuppressant medications do not produce effective antibody responses to SARS-CoV-2 spike protein mRNA vaccinations. Whether these patients develop and maintain protective T cell responses after the same vaccines is not known. A detailed kinetic analysis of innate and adaptive immunity following SARS-CoV-2 mRNA vaccination, particularly comparing responders to non-responders, is thus essential in order to interpret the clinical trial outcome and to guide design of follow up studies aimed at overcoming identified defects. Moreover, if it were possible to identify an early post vaccine molecular signature that correlates with vaccine success vs failure, such a biomarker could be used to guide subsequent strategies aimed at enhancing induction protective immunity in each transplant patient.

Thus, the overall goals of the proposed mechanistic studies are to a) characterize the vaccine-induced innate and adaptive immune responses in each study subject, b) define the durability of the responses over 1-year post vaccination, c) provide insight into immune mechanisms that prevent formation and/or durability of the induced responses, d) identify molecular markers of successful vaccination.

To this end we will serially collect serum, plasma and PBMC samples over the entire study period. Using these samples we will a) quantify spike protein production in serum, b) provide a detailed kinetic characterization of the vaccine induced antibody repertoire (specificity, isotype, titer, neutralization capacity), c) perform a kinetic phenotypic and functional analysis of antigen specific Bmem (frequency, antigen specificity, surface markers, metabolomics, gene expression patterns, single cell sequencing) and PC, d) perform a kinetic, analysis of antigen specific CD4+ and CD8+ T cells (frequency, epitope specificity, surface markers, metabolomics, gene expression patterns single cell sequencing), e) assess phenotypic,

functional and gene expression patterns of innate immune DC, monocyte/macrophage and NK cell subsets in peripheral blood, and f) perform genomic profiling of peripheral blood cells that will provide a biomarker for an effective response.

9.2 Objective 1: To quantify spike protein production in serum or plasma after vaccination.

Transient expression of a modified spike protein using mRNA vaccines (Moderna and Pfizer-BioNTech) has been crucial in global effort to control the SARS-CoV-2 pandemic. This platform offers the flexibility for rapid modification to control variants. Given the requirement for effective protein expression of immunogen the extremely poor responses for transplant recipients, particularly those on mycophenolate mofetil raises the question whether the anti-metabolite properties of MMF may impair the transient expression of spike poor response of transplant patients and thereby contribute to the impaired response of transplant patients. Using a recently developed ultrasensitive molecular assay to detect spike protein in serum we will assess expression at baseline and 3 days post vaccination.

9.3 Objective 2: To provide a detailed kinetic characterization of the vaccine induced antibody repertoire (specificity, isotype, titer, neutralization capacity).

While relative contributions of vaccine induced humoral and T cell immunity in the protection from severe SARS-CoV-2 disease are not fully understood, the development of a critical level of SARS-CoV-2 Ab are emerging as a correlate of protection. A detailed understanding of the profile of Ab responses in transplant recipients after vaccination is crucial step toward understanding what population benefits from an additional dose of vaccine. The primary endpoint of this study focuses on the candidate correlate of protection MSD 3-plex (S-2P, RBD and N protein +BSA) assay. This objective will provide a deeper mechanistic characterization of to support hypothesis generating observations to understand the mechanisms underlying vaccine failure and to identify candidate humoral biomarkers to predict vaccine response. This includes surrogate and live virus neutralization titers including versus novel variants of concern.

9.4 Objective 3: To perform a kinetic phenotypic and functional analysis of antigen specific Bmem (frequency, antigen specificity, surface markers, metabolomics, gene expression patterns, single cell sequencing) and PC.

To identify and characterize SARS-CoV-2 memory B cells we will use fluorescently labeled multimerized probes for targets of the vaccine (spike receptor-binding and ectodomain) and as well as non-vaccine expressed SARS-CoV-2 antigens (e.g. Nucleocapsid). The magnitude and differentiation of anti-specific IgM+ and IgG+ memory B cells will be assessed at each time point. We will use flow cytometry, CyTOF, single B cell multi-omics (cell surface CITE-seq profiling using tagged antibody and multimerized probes for vaccine targets), transcriptomics, and B cell receptor VDJ repertoire analysis to characterize antigen specific B cells. We will perform in vitro ELISPOT assays to determine frequencies of antigen specific PCs in peripheral blood.

9.5 Objective 4: To perform a kinetic, analysis of antigen specific CD4+ and CD8+ T cells (frequency, epitope specificity, surface markers, metabolomics, gene expression patterns single cell sequencing).

While the requirements for sustained protection against SARS-CoV-2 are not yet known, effective control of viral pathogens often depends on the development of both humoral and cellular immunity.

We will assess the strength, breadth and character of the anti-spike T cell response in study participants using flow-cytometry based, ELISPOT, and single cell-multi-omics assays. Antigen-specific cells will be interrogated using a rapidly evolving set of peptide and MHC multimer reagents using flow-cytometry, CyTOF, and or ELISPOT readouts. For flow-based analysis we will utilize 1) antigen specific functional assays (activation-induced marker (AIM), intracellular cytokine secretion assays and novel T cell metabolic profiling assays and, 2) phenotypic characterization of spike-specific T cells MHC-peptide multimer staining. We will use single T cell multi-omics (cell surface CITE-seq profiling using tagged antibody and tetramers, transcriptomics, and T cell receptor VDJ repertoire analysis.

Exploratory analysis of associated of these deep immune profiling assessments with protective immunity will be performed.

9.6 Objective 5: To assess phenotypic, functional and gene expression patterns of innate immune DC, monocyte/macrophage and NK cell subsets in peripheral blood.

We will characterize the kinetics of peripheral blood immune landscape of mononuclear leukocyte lineage and phenotypic markers to broadly assess the immunological cellular profile of transplant recipients before and after vaccination, focusing on the absolute and relative frequency of T, B, NK and APC subsets.

We will characterize these cells types in peripheral blood using flow cytometry and or CyTOF assays. We will test function using in vitro assays that include in vitro stimulation of DC subsets with TLR ligands (cytokine and surface marker readouts as measures of activation), in vitro stimulation of macrophages with LPS (cytokine readouts as a measure of trained immunity, which would then be followed up with epigenetic analyses), in vitro functional analyses of NK cells.

9.7 Objective 6: Exploration of molecular biomarkers of early responders to vaccination

We will collect serial blood samples for RNA profiling (RNAseq) and/or proteomics in addition to characterization of cytokine signaling early after vaccine intervention.

10. Biospecimen Storage

Biological specimens obtained under this protocol may be used in future assays to reevaluate biological responses as additional research tests are developed over time. These may include, but are not limited to, tests examining aspects of host immunology, cell biology, or human genetics as it relates to any of these aspects. Appropriate informed consent will be obtained for both the collection and storage of samples. The specimens from these evaluations will be labeled with a coded ID and may be stored beyond the funding period.

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1 Participant Completion

All participants will be followed for 12 months post vaccine administration.

11.2 Participant Stopping Rules and Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.

11.3 Participant Replacement

Participants who withdraw or are withdrawn will not be replaced.

11.4 Follow-up after Early Study Withdrawal

If a participant is withdrawn from the study for any reason, the participant may be asked to complete a final visit and/or final assessments.

12.5. Study Pausing Rules

The third vaccine doses will be administered over a very short period at the beginning of the study, and there are no further interventions. There will therefore be a very brief window for the implementation of pausing rules. Pausing rules will only remain in effect until all study participants have received their third dose of vaccine.

If the following occur, enrollment may be temporarily halted and an expedited DSMB review take place:

Reactogenicity: Two Grade 4 or higher reactogenic adverse events (AEs) that are definitely or possibly related to the vaccine

Allergy: Five participants in the first 100 participants vaccinated, or 5% of all participants thereafter experiencing a Grade 3 systemic allergic reaction that is definitely or possibly related to the vaccine

12. Safety Monitoring and Reporting

12.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, Reporting of Serious Adverse Events and Adverse Events) to the sponsor, DAIT/NIAID. Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version [enter 5.0 or correct version applicable to trial] : http://ctep.cancer.gov/reporting/ctc.html.

12.2 Definitions

12.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, an adverse event will include the following associated with the third dose of vaccine and study mandated procedures.

Vaccine Administration (Moderna COVID-19 Vaccine or Pfizer-BioNTech COVID-19 Vaccine)

- All AEs occurring within 30 days following vaccine administration and SAEs up to 6 months post vaccine administration.

Study mandated procedures:

- Any AE occurring within 24 hours of a protocol mandated blood draw
- Any AE occurring within 24 hours of a protocol mandated nasopharyngeal swab

12.2.2 Solicited Adverse Events

For the purposes of this study, the following specific local and systemic reactogenicity events, as well as symptoms of a potential allergic reaction, will be solicited from the participant through a remote contact on Day 7 post-vaccination. Any other adverse events reported during the course of this remote contact will be reported on the AE eCRF. Study clinicians will follow all adverse events to resolution.

- Local reactions at the injection site including erythema/redness, swelling/induration (hardness), and pain.
- Systemic reactions including fever, myalgia, arthralgia, fatigue, headache, nausea, vomiting, diarrhea, and chills.
- Potential allergic reaction, which includes the following symptoms:
- Skin: hives, swelling other than injection site, itching, redness other than injection site, rash
- Respiratory: wheezing, shortness of breath, coughing, tightness in the throat or chest, sneezing, nasal stuffiness or congestion
- Gastrointestinal: trouble swallowing, abdominal cramps, diarrhea, nausea, vomiting
- Dizziness or lightheadedness

12.2.3 Unsolicited Adverse Events

Participants will be instructed to contact the study site and report any adverse events up to 30 days post vaccine administration. This will include any delayed onset local reactions.

12.2.3.1 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the SARS-CoV-2 vaccine caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.4 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Package Insert or FDA Emergency Use Authorization or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the IND.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)*]*

12.2.5 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor DAIT/NIAID, it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor [add DAIT/NIAID or other Sponsor, *if applicable],* its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the NIAID Medical Monitor and Protocol Chair and has been deemed appropriate for the subject population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ADL: Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)
Grade 4 = Life-threatening consequences; urgent intervention indicated.
Grade 5 = Death related to AE.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

12.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE/SAE eCRF. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.3.2.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 12.3.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

12.4 Collection and Recording of Adverse Events

12.4.1 Collection Period

Adverse Events temporally associated (24 hours) with the research blood draws and nasopharyngeal swabs will be collected from the time of the screening visit until a subject completes study participation.

Adverse Events as defined in Section 12.2.1 will be collected for 30 days following COVID-19 vaccine administration. Serious Adverse Events will be collected for 6 months following vaccine administration.

12.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.].
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, *Definitions)* on the appropriate electronic case report form regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 Reporting of Serious Adverse Events to DAIT/NIAID

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor via the AE/SAE eCRF. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report all serious adverse events (see Section 12.2.3, *Serious Adverse Event)*, regardless of relationship or expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE eCRF provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the AE/SAE eCRF will be updated and submitted. Initial SAE eCRFs should include as much information as possible, but at a minimum:

- AE term
- Relationship to study vaccination
- Relationship to study procedure
- Reason why the event is serious
- Supplementary eCRF pages that are current at the time of the SAE reporting e.g. medical history and vaccine administration

12.5.2 Reporting to Health Authority

After an adverse event requiring 24 hour reporting (per Section 12.5.1, *Reporting of Serious Adverse Events to Sponsor*) is submitted by the site investigator and assessed by DAIT/NIAID*,* there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities:

12.5.2.1 Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.1.1, *Suspected Adverse Reaction,* and Section 12.2.2, *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 12.2.2, *Suspected Adverse Reaction*).
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

12.5.2.2 Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious and unexpected suspected adverse reaction** [**SUSAR]** (see Section 12.2.1.1, *Suspected Adverse Reaction* and Section 12.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Category 2: **Any findings from studies that suggests a significant human risk**
The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the FDA and all participating investigators of expedited Safety Reports within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

12.5.3 Reporting of Adverse Events to IRBs/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All Safety Reports to the FDA shall be distributed by DAIT/NIAID or designee to all participating institutions for site IRB/IEC submission.

12.5.4 Mandatory reporting to Vaccine Adverse Event Reporting System

Per the FDA EUA for the Pfizer-BioNTech COVID-19 Vaccine and the FDA EUA for the Moderna COVID-19 Vaccine, the site investigator, or designee, is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):

- vaccine administration errors whether or not associated with an adverse event,
- serious adverse events (irrespective of attribution to vaccination),
- cases of Multisystem Inflammatory Syndrome in adults, and
- cases of COVID-19 that result in hospitalization or death.

The site investigator, or designee, is also responsible for recording vaccination information in the state/local jurisdiction's Immunization Surveillance System or other designated system.

12.6 Reporting of Other Safety Information

An investigator shall promptly notify the site IRB as well as the SACCC when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event.

12.7 Review of Safety Information

12.7.1 Medical Monitor Review

The NIAID Medical Monitor shall receive monthly reports from the SACCC compiling new and accumulating information on AEs and SAEs recorded by the study site(s) on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE and pregnancy reports received by the SACCC (See Sections 12.5.1, Reporting of Serious Adverse Events to Sponsor, and 12.6, Pregnancy Reporting).

12.7.2 DSMB Review

12.7.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data one month after all study participants have received study vaccine, unless a safety event requires earlier review. They will review the study again when the database is locked after the last patient's last visit. Interim DSMB reviews may occur at any time at the discretion of the medical monitor or the protocol chair. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

The DSMB will be informed of any Expedited Safety Reports within one week of submitting such reports to the FDA..

12.7.2.2 Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death that occurs in the study which is possibly or definitely related to study treatment regimen.
- A Pausing Rule (outlined in Section 11.2) is met.

After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.7.2.2.1 Temporary Suspension of enrollment for ad hoc DSMB Safety Review

See Section 11.2 for Participant Stopping Rules and Withdrawal Criteria

13. Statistical Considerations and Analytical Plan

13.1 Overview

The goal of the study is to assess antibody response to a third dose of vaccine against SARS-CoV-2 in kidney transplant recipients who have failed to respond to two doses of either the Moderna COVID-19 vaccine or Pfizer-BioNTech COVID-19 vaccine. The study population will consist of kidney transplant recipients who have received two doses of the Moderna or Pfizer-BioNTech vaccine and subsequently shown a negative or weakly positive antibody response. The study is a single-arm, non-randomized intervention study in which all participants receive a third dose of the vaccine for which they have previously received two doses.

13.2 Endpoints

The primary endpoint is protective antibody response measured at 30 days after the third vaccine dose, measured using the FDA validated MSD 3 plex (Wu-1 full length spike, RBD and N proteins) assay. Key secondary endpoints include vaccine reactogenicity, treated acute allograft rejection within 60 days of the dose, serious adverse events within 30 days of the dose, graft loss within 60 days, and death within 60 days.

13.3 Measures to Minimize Bias

This is an unrandomized, unblinded, single-arm study. To minimize measurement bias, baseline exposures will be measured before the third dose is received. To minimize bias in ascertainment of outcomes, all outcome definitions will be standardized and all assays will be processed in a centralized laboratory.

13.4 Analysis Plan

13.4.1 Analysis Populations

Analysis will be per-protocol. All individuals who receive the intervention and have antibody response measured at 30 days after the intervention will be included in the analysis of the main outcome. For secondary and exploratory outcomes, all individuals who receive the intervention and have that outcome measured will be included. In the event that data for any outcome are missing for more than 20% of individuals who receive the intervention, we will use a weighting approach to estimate the distribution of that outcome among all individuals (measured and unmeasured) who receive the intervention.

13.4.2 Primary Analysis of Primary Endpoint

The primary outcome is binary: whether or not a positive response is detected at 30 days after the intervention. We will calculate an exact binomial confidence interval around this proportion. In the event that outcome data are missing for more than 20% of individuals, we will use a weighting approach to estimate the distribution of the outcome among all individuals (measured and unmeasured) who receive the intervention. Specifically, we will use logistic regression to model the probability of a positive response adjusting for age, years since transplant, antimetabolite usage, and type of vaccine (Moderna vs Pfizer-BioNTech) among individuals with a measured response. This model will be applied to individuals with no measured response to predict the number of those individuals who would have had a positive response had it been measured. We will use a bootstrap to derive an empirical 95% confidence interval around this estimate. This procedure will be run using the entire sample of 200 individuals, and also separately in the two strata (negative response vs weak prior antibody response).

13.4.3 Supportive Analyses of the Primary Endpoint

We will characterize risk factors associated with the primary outcome using logistic regression. Risk factors (age, sex, race/ethnicity, years since transplant, antimetabolite usage, vaccine type) will analyzed individually using univariable logistic regression. Additionally, we will analyze all risk factors in a single multivariable logistic regression model.

13.4.4 Analyses of Secondary and Other Endpoints

Secondary endpoints will be analyzed using exact binomial confidence intervals and logistic regression as per the methods described in 13.4.2 and 13.4.3. We will analyze exploratory mechanistic and other endpoints by reporting proportion with binomial exact confidence interval for binary variables, proportions for categorical variables, and median (IQR) for continuous variables. We will also report these outcomes stratified by the primary outcome, with Fisher exact tests for binary and categorical variables and ranksum tests for continuous variables.

13.4.5 Descriptive Analyses

We will describe demographics and other baseline (pre-intervention) characteristics (medication use, time since transplant, type of vaccine) in the study population by reporting proportion for binary and categorical variables, and median (IQR) for continuous variables. We will report these overall and stratified by the primary outcome.

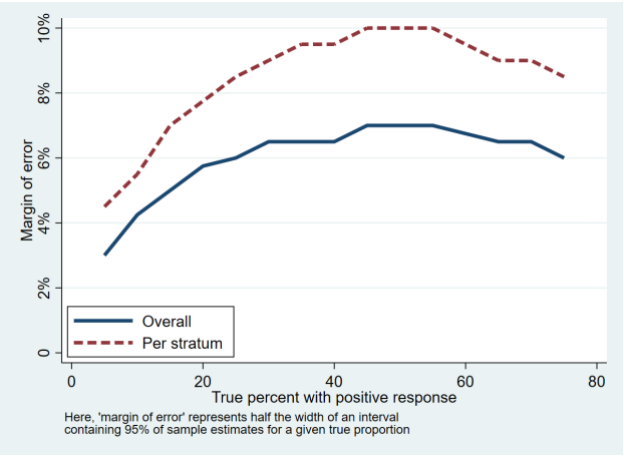
13.5 Interim Analyses

No interim analyses are planned for this study.

13.6 Statistical Hypotheses

This is a single-arm pilot study to estimate the proportion of individuals with a positive antibody response to a third dose of vaccine. For the primary endpoint, we do not test any specific hypothesis. Rather, our goal is to estimate the proportion of individuals with a positive response. We will estimate this proportion, with 95% confidence interval, using an exact binomial confidence interval.

13.7 Sample Size Considerations



In the context of estimating a single proportion, the relevant consideration for sample size is the difference between the true proportion (what proportion of all individuals would have a positive response if our sample size was infinite) and the observed proportion (what proportion in the actual study have a positive response). For a range of true proportions (5%-75%), we ran 20,000 simulations of the study, and calculated the "margin of error": that is, half of the difference between the 2.5th percentile of the observed proportion and the 97.5th percentile of the observed proportion. Depending on the true proportion, the margin of error thus defined ranged from 3% to 7% overall (N=200), and from 5% to 10% per stratum when the two strata are the same size (N=100) (figure). If the smaller stratum has only 50

participants, the margin of error will range from 6% to 14%. Our sample size, therefore, will be sufficient to provide an accurate estimate of the true proportion.

14. Identification and Access to Source Data

14.1 Source Data

Source documents and source data are the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations, and other activities during a clinical trial.

14.2 Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID and their representatives as well as to relevant health authorities (Food and Drug Administration). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15. Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

16. Protocol Deviations

16.1 Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance with the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy, and reliability of the study data.

16.2 Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

17. Ethical Considerations and Compliance with Good Clinical Practice

17.1 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by Institutional Review Board (IRB). Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

17.2 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the FDA Form 1572 will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in the participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing, and any new findings will be communicated to the participants. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

17.3 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

18. Publication Policy

The publication guidelines and policies stipulated in the grant will apply to this protocol.

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Appendix 1: Schedule of Events

Study Schedule	Day										
Time points	**Screen**	**0**	**3[1]**	**7**	**14**	**30**	**90**	**180**	**210**	**365**	**For Cause[2]**
Visit #	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**FC**
Visit Windows (+/-)		**-**	**1d**	**1d**	**3d**	**3d**	**2w**	**2w**	**2w**	**2w**	**-**
General Assessments											
Informed Consent	X	X[3]									
Medical History[4]	X										
Remote Contact [5]	X			X		X	X	X	X	X	X
Immunosuppressive Medications[6,7]	X	X	X	X	X	X	X	X		X	X
Adverse Event/Serious Adverse Event Assessment	X	X	X	X	X	X	X	X		X	X
Clinical Laboratory Assessments											
Complete Blood Count		X			X	X	X	X		X	
Metabolic Panel[8]		X			X	X	X	X		X	
Quantitative Immunoglobulins		X						X			
Anti-RBD Igg (Roche Elecsys®)	X				X	X	X	X		X	X[9]
Urine Pregnancy Test[10]		X									
Investigational Intervention											
COVID-19 mRNA Vaccine		X									
Central Laboratory Assessments											
Antibody/Neutralization assays[11]		X			X	X	X	X		X	X
Spike Protein		X	X								
Nasopharyngeal SARS-CoV-2 PCR		X				X	X	X	X	X	X
Proteomics		X				X					
Transcriptomics		X	X								
T and B Cell Assays[7]		X	X		X	X	X	X		X	X
Donor Specific Antibodies (DSA)		X				X	X	X		X	

[1] May be a home draw.
[2] Unscheduled "for cause" visit for breakthrough infection, rejection, and reactogenicity. If the unscheduled visit is for breakthrough infection, a nasopharyngeal swab for SARS-Cov-2 PCR will be collected.
[3] Reconfirm eligibility by history at the time of the main study consent.
[4] Review medical history to confirm eligibility.
[5] Starting at 5 months post the CPAT study vaccine dose, monthly remote contact should take place to encourage the participant to receive the 5-month COVID-19 booster. Once they receive the 5-month booster, the participant will follow Appendix 2.
[6] Ensure the participant has not received any medications since the time of transplant that make them ineligible.
[7] Immunosuppressive medications will be collected for 90 days post vaccine. Following 90 days, immunosuppressive medications will be collected in cases of allograft rejection and SAEs.
[8] Comprehensive metabolic panel at baseline, basic metabolic panel all other timepoints.
[9] If a participant contracts COVID-19 during the study, a sample should be collected as close as possible to the diagnosis and 30 days post diagnosis within a +/-7 day window. A scheduled visit draw may be used if it falls within the +/-7 day window.
[10] Results are not required prior to vaccination.
[11] Not all assays will be performed at each time point. Please refer to the lab manual for specific details.

Appendix 2: Schedule of Events (5-Month COVID-19 Booster)

Study Schedule	**Day**		
Time points	**0**	**30**	**90[12]**
Visit #	**B1**	**B2**	**B3**
Visit Windows (+/-)	**-**	**3d**	**2w**
General Assessments			
Informed Consent (reconsent)	X		
Remote Contact	X	X	X
Immunosuppressive Medications	X	X	X
Collect Data re: COVID-19 Booster Injection	X		
Clinical Laboratory Assessments			
Complete Blood Count		X	X
Metabolic Panel		X	X
Anti-RBD Igg (Roche Elecsys®)		X	X
Central Laboratory Assessments			
Antibody/Neutralization assays		X	X
Nasopharyngeal SARS-CoV-2 PCR		X	X
Proteomics		X	
T and B Cell Assays		X	X
Donor Specific Antibodies (DSA)		X	X

[12] This will be the last study visit for participants who received a COVID-19 booster injection.