# (ClinicalTrials.gov COVER PAGE)

**BOOST KIDNEY: A Multi-Centre 12 Month Parallel-Group Randomized Control Trial of BNT162b2 versus mRNA-1273 COVID-19 Vaccine Boosters in Chronic Kidney Disease and Dialysis Patients with Poor Humoral Response following COVID-19 Vaccination**

## NCT: 05022329

**Protocol Dated: 05-Nov-2021**

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## Protocol Number: 3750


**Principal Investigator:** Dr. Michelle Hladunewich



**Regulatory Sponsor:** Sunnybrook Research Institute

**Funding Agency:** COVID-19 Immunity Task Force (CITF)
Public Health Agency of Canada (PHAC)
Oreopoulos/Baxter Home Dialysis Grant (Division of Nephrology, University of Toronto)



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## SPONSOR STATEMENT OF COMPLIANCE

This study will comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements.

Personnel listed below are authorized to sign the protocol and any subsequent protocol amendments on behalf of the sponsor:

| | |
|---|---|
| Name:<br>*(Print)* | Dr. Michelle Hladunewich |
| Title:<br>*(Print)* | Principal Investigator |
| Signature: |  |
| Date of Approval:<br>*(yyyy-mmm-dd)* | 2021-Nov-09 |

# PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Qualified Investigator:

Name:
*(Print)* _____

Title & Institution:
*(Print)* _____

Signature: _____

Date of signature:
*(yyyy-mmm-dd)* _____

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## LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

| | |
|---|---|
| AE | Adverse Event/Adverse Experience |
| AEFI | Adverse Event Following Immunization |
| Anti-NP | Anti- nucleocapsid Protein |
| CC | Coordinating Centre |
| CIOMS | Council for international Organizations of Medical Sciences |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTO | Clinical Trial Ontario |
| CCTS | Centre for Clinical Trial Support |
| CKD | Chronic Kidney Disease |
| COVID-19 | Coronavirus 19 |
| EC | Ethics Committee |
| ELISA | Enzyme Linked Immunosorbent Assay |
| HD | Hemodialysis |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IP | Investigational Product |
| DSMB | Data Safety Monitoring Committee |
| DSPC | 1,2-distearoyl-sn-glycero-3-phosphocholine |
| eCRF | Electronic Case Report Form |
| pCRF | Paper Case Report Form |
| EDC | Electronic Data Capture |

| | |
|---|---|
| GCP | Good Clinical Practice |
| ICF | Informed Consent Form |
| MedDRA | Medical Dictionary for Regulatory Authorities |
| ORN | Ontario Renal Network |
| PD | Peritoneal Dialysis |
| PHI | Personal Health Information |
| PHIPA | Personal Health Information Protection Act |
| PI | Principal Investigator |
| PM | Product Monograph |
| QI | Qualified Investigator |
| RBD | Receptor-Binding Domain |
| REB | Research Ethics Board |
| RCT | Randomized Controlled Trial |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SC | Steering Committee |
| snELISA | Surrogate neutralization ELISA |
| SOP | Standard Operating Procedure |
| SRI | Sunnybrook Research Institute |
| SUADR | Serious and Unexpected Adverse Drug Reaction |
| TMF | Trial Master File |
| TDL | Task Delegation Log |
| USP | United States Pharmacopeia |

## *Protocol Summary*

| | |
|---|---|
| Full Title | BOOST KIDNEY: A Multi-Centre 12 Month Parallel-Group Randomized Control Trial of BNT162b2 versus mRNA-1273 COVID-19 Vaccine Boosters in Chronic Kidney Disease and Dialysis Patients with Poor Humoral Response following COVID-19 Vaccination |
| Short Title | BOOST KIDNEY |
| Phase | II/III |
| Protocol Number | 3750 |
| Version Date | Version 5.0, Nov 5, 2021 |
| Study Duration | 1 year |
| Principal Investigator | Dr. Michelle Hladunewich |
| Setting | Multicenter, 5 Dialysis Centres in Ontario and British Columbia, Canada |
| Number of Participants | 300 participants |
| Study Design | Four arm parallel randomized controlled trial of BNT162b2 versus mRNA-1273, third dose of the COVID-19 vaccine stratified by initial two dose vaccine type |
| Main Inclusion Criteria | Dialysis and non-dialysis chronic kidney disease (Stage 3b-5) |
| Primary Outcome(s) | Evaluate effect of third dose COVID-19 vaccine booster (BNT162b2 versus mRNA-1273) on serologic SARS-CoV-2 response (Anti-RBD) at 1 month following booster dose. |

| | |
|---|---|
| Secondary Outcome(s) | 1. Evaluate effect of third dose COVID-19 vaccine booster (BNT162b2 versus mRNA-1273) on Anti-Spike and SARS-CoV-2 viral neutralization at 1 month following booster dose.<br>2. Anti-Spike and Anti-RBD response at study enrolment, 3 months, 6 months and 12 months following booster dose.<br>3. Flow cytometry on PBMC, single-cell RNA sequencing and ELISPOT prior to, 1 month, and 6 months following booster dose to evaluate SARS-CoV-2 specific B and T-Cell response.<br>4. Evaluate adverse effects related to third dose of vaccine through a questionnaire 48 hours -14 days, and 30 days following third vaccine dose.<br>5. Differences in COVID-19 infections, symptomatic COVID-19 infections, hospitalization, and death between study groups. |
| Statistical Analysis | Intention to treat analysis for the primary outcome with two Chi-Squared test or Fisher's exact test for the primary outcome. Non-parametric testing for differences in antibody level between study groups. Mixed effects models will be used for comparison of longitudinal antibody levels. |

# 1 KEY ROLES AND CONTACT INFORMATION

| | |
|---|---|
| **Regulatory Sponsor:** | *Sunnybrook Research Institute (SRI)*<br>*2075 Bayview Avenue*<br>*Toronto, ON Canada M4N 3M5* |
| **Principal Investigator:** | *Michelle A. Hladunewich, MD, MSc, Sunnybrook Health Sciences Centre, University of Toronto* |
| **Academic Research Organization:** | *Centre for Clinical Trial Support, SRI*<br>*2075 Bayview Avenue*<br>*Toronto, ON Canada M4N 3M5* |

# 2 INTRODUCTION

This study document is the protocol for research involving human participants. This study is to be conducted according to Canadian and International standards, and in compliance with the protocol, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice E6 (GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements and research policies. This protocol was developed following the SPIRIT checklist for interventional trials.

## 2.1 BACKGROUND

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), emerged from Wuhan, China in December 2019, and has resulted in a devastating global pandemic. In Ontario, there have been nearly 546,000 confirmed cases and over 9000 deaths in Ontario as of July 4, 2021.[1] Rapid efforts have been untaken by the global scientific community to develop effective vaccines against SARS-CoV-2. On December 9, 2020 the *BNT162b2 mRNA* Covid-19 Vaccine (*COMIRNATY®/Pfizer-BioNTech*) was approved by Health Canada. This was followed by the approval of the *mRNA-1273* SARS-CoV-2 Vaccine (*SPIKEVAX®/Moderna*) on December 23, 2020. Both vaccines are lipid nanoparticle formulated, nucleoside-modified mRNA vaccines encoding the SARS-CoV-2 prefusion-stabilized full-length spike glycoprotein. Public health efforts are presently underway to quickly vaccinate the general population.

Patients on chronic dialysis have been recognized to be an at-risk population. In Ontario, over 15,000 patients require chronic dialysis treatment at over 100 in-centre hemodialysis units.[2] While the general population has been advised to stay at home, dialysis patients must visit dialysis treatment facilities minimally three times per week for life sustaining treatment. Shared transportation to dialysis, difficulty maintaining social distancing, and interactions with multiple healthcare providers, medical comorbidities and impaired immunity place dialysis patients at greater risk for acquiring infection nosocomially or in the community. Data from the Ontario Renal Network as of July 1, 2021 has demonstrated that 5.73% (1003 out of 176710 dialysis patients) have tested positive for COVID-19 compared to 1,545,181 out of 14,747,051 (3.69%) of the general Ontario population. Despite close adherence to screening protocols, usage of personal protective equipment, and social distancing measures, COVID-19 outbreaks have still occurred in Ontario dialysis units.[3]

As of July 1, 2021 there have been 1003 patients on chronic dialysis treatment who have been infected with COVID-19. Due to their comorbidities, patients on dialysis are at greater risk for severe COVID-19 disease. In Ontario, 63% of chronic dialysis patients with COVID-19 have required hospitalization, and the case fatality rate has been reported at 28.5%, which is almost 4 times higher than in the general population.[4] This is consistent with a recent meta-analysis of 3261 hemodialysis patients who contracted COVID-19 and identified an overall mortality rate of 22.4%.[5] Similarly, data from the European Renal Association–European Dialysis and Transplant Association Registry identified a COVID-19 attributable mortality of 20% in 3285 receiving dialysis.[6]

In general, dialysis patients are known to have decreased immune response to vaccination, including lower rates of seroconversion, lower antibody titers, and a less sustained humoral response after immunization compared with the general population. This is evident from routine Hepatitis B vaccination in dialysis patients wherein repeated series and booster doses are

required to maintain immunity.[7] The rate of seroconversion following the hepatitis B vaccine is only 44% in dialysis patients.[8] Furthermore, Hepatitis B antibody titers decline more rapidly in individuals who receive Hepatitis B immunization compared to individuals who acquire natural Hepatitis B infection.

Predictors of antibody levels against SARS-CoV-2 are under active investigation. A study in 98 dialysis patients infected with COVID-19 showed that COVID-19 specific antibody titers decreased significantly one month following seroconversion,[10] which is remarkably shorter than the healthy general population wherein durable humoral immunity may last at least 4-8 months.[11] Both the *BNT162b2 mRNA* Covid-19 Vaccine (*COMIRNATY®/Pfizer-BioNTech*) and the *mRNA-1273* SARS-CoV-2 Vaccine (*SPIKEVAX®/Moderna*) randomized placebo-controlled trials, included only limited patients with kidney disease and patients receiving immunosuppressive treatment were excluded.[12,13]

## 2.2 Clinical Data to Date

Given this significant knowledge gap, we conducted the SMASH-COVID-19 Study (Serial Measurement of Quantitative COVID-19 Antibodies in Hemodialysis and Peritoneal Dialysis Patients following COVID-19 Vaccination) in hemodialysis patients at Sunnybrook Health Sciences Centre to determine their humoral response to vaccination. In this prospective observational study, humoral response was compared in 66 hemodialysis patients sampled 28 days after receipt of one dose of vaccine to 76 patients who received two doses of vaccine sampled 14 days after the second dose. Among those receiving one dose, 6% had anti-RBD response above the median level of convalescent serum versus 41% who received two doses after 28 days. Given this finding, it was concluded that hemodialysis patients exhibit a poor humoral response to a single dose of BNT162b2 vaccine and the second dose should not be

delayed.[14] Furthermore, longitudinal follow-up at 13 weeks of our cohort of vaccinated hemodialysis patients has demonstrated that some individuals do not seroconvert and a significant proportion of individuals who attained convalescent serum levels of COVID-19 antibodies (anti-Spike and anti-RBD) exhibit declining antibody levels by 13 weeks as shown in Figure 1, which has not been observed in the general population. This single centre pilot study has led to a larger multi-centre study in Ontario and British Columbia entitled "Determining the Safety and Efficacy of COVID-19 Vaccination in the Chronic Kidney Disease Population" (CTO Protocol Number 3604) which is continuing to recruit patients with chronic kidney disease stage 3b-5. This study will follow serologic response to COVID-19 vaccination in patients with advanced chronic kidney disease including those on dialysis for a one year period to better understand the duration of humoral immunity in this patient population.

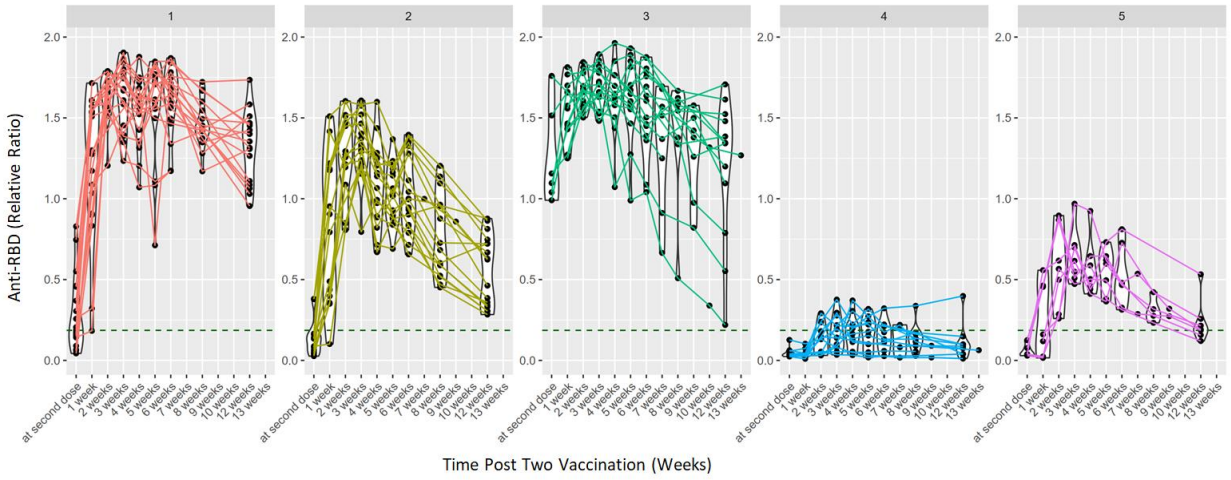


**Figure 1**: **SARS-CoV-2 IgG Anti-RBD Response Following BNT162b2 Vaccine in Hemodialysis Patients up to 13 weeks following second dose of vaccine.**

Patients have been divided into 5 clusters by k-clustering based on trajectory of anti-RBD response over time. Cluster 1 (orange) generally obtained robust response following vaccination

and maintains serologic response 13 weeks. Clusters 2 (yellow) had an Anti-RBD response but gradually exhibits declining titers, and 3 (green) was characterized by the presence of anti-RBD antibodies at the time of the second dose, either due to previous infection, response to the first dose, or both; in this group, most individuals retained antibodies at 13 weeks, similar to the Cluster 1 (orange), but some of the participants had more rapid decline in antibody levels. Cluster 4 (blue) generally did not achieve seroconversion following vaccination. Cluster 5 (purple) attained seroconversion but did not have an initial robust response defined as reaching convalescent serum levels and generally exhibits declining antibody levels over time. Antibody levels are reported as relative ratios to synthetic standards. Dots represent individual serum samples collected at the indicated times, and the samples from the same patients are connected by lines. Seroconversion threshold represents a positive test and is 0.186 and is indicated by the dashed line. The median level of antigen in convalescent serum taken 21-115 days post-symptom onset is considered a robust antibody response and is 1.25 for anti-RBD.

## 2.3 Rationale for Study

Given the concern that a proportion of dialysis patients do not reach convalescent serum antibody levels following two dose of COVID-19 vaccination, booster doses may represent a means of attaining improved humoral immunity analogous to what is currently practiced with Hepatitis B vaccines. At this time, there is limited data regarding humoral immunity in dialysis patients receiving booster doses and there are no studies examining cellular immunity after a booster dose. A study in France of 45 hemodialysis patients receiving a third dose of BNT162b2 COVID-19 vaccine one month following the second dose found that two out of five patients who did not respond to two doses of vaccine had a robust response following the third dose. It was also noted that the median increase in antibody titers was >580% following the third dose.[15]

Early studies of booster doses in other vulnerable patient populations including transplant patients on immunosuppression have also emerged. A case series in 30 solid organ transplant patients receiving a third dose of vaccine included 24 patients with negative antibody titers, and 6 with low-positive antibody titers. In this study, the third dose was provided a median of 67 days (IQR 59-81 days) following the second dose and different vaccine types were used for the third dose: Ad26.COV2.S vaccine (Johnson & Johnson/Janssen) in 15, *mRNA-1273* vaccine (*SPIKEVAX®/Moderna)* in 9, and the *BNT162b2* (COMIRNATY®/*Pfizer-BioNTech*) in 6. Antibody testing against the spike or RBD protein at 14 days post third dose found that in those with low positive antibody levels, all had high positive antibody levels following the third dose. Among those with initial negative antibody levels, 6/24 (25%) were able to attain high-positive antibody levels. Adverse reactions recorded 7 days following third dose the incidence of severe symptoms was low, and the investigators concluded that their finding warranted clinical trials on booster doses in this patient population.[16] Another recent study from France in solid organ transplant patients, including 78 kidney transplant candidates, also confirmed the utility of a third dose of the BNT162b2 vaccine in increasing the prevalence of patients with detectable SARS-CoV-2 antibody levels from 40% post second dose to 68% 4 weeks after the third dose. In this study, 44% of patients who were initially seronegative had seroconversion following the third dose. Notably those without antibody response were older and had lower GFR, which is typical of the hemodialysis population.[17] Limited studies have examined cellular immunity, however a study which included 41 hemodialysis patients, 4 peritoneal dialysis patients and 35 healthy controls, and 40 kidney transplant patients found impaired memory B cell formation in dialysis patients including RBD-specific plasmablasts and post-switch memory B-cells when measured 3-4 weeks after second dose of vaccine.[18]

Therefore, we propose a multi-site randomized, participant and investigator blinded controlled trial with four parallel arms stratified by initial two dose vaccine received in chronic

kidney disease stage 3b-5, and patients with end stage kidney disease to determine whether vaccine boosters with a third dose of vaccine *mRNA-1273* vaccine (*SPIKEVAX®/Moderna*) or the *BNT162b2* (*Pfizer/BioNTech*) will enhance the humoral and cellular immunity in patients with kidney disease who have not-responded well to vaccination (defined as levels that are below the median convalescent level of anti-RBD). This may mean that a patient never attained convalescent serum level of anti-RBD or that they initially obtained convalescent serum levels but exhibit declining levels over time.

The four study arms in this study will be as follows (as shown in Figure 2):

1. Group 1**:** First two dose *BNT162b2*, Third dose *BNT162b2*
2. Group 2**:** First two dose *BNT16b2*, Third dose *mRNA-1273*
3. Group 3**:** First two dose *mRNA-1273*, Third dose *BNT162b2*
4. Group 4**:** First two dose *mRNA-1273*, Third dose *mRNA-1273*

This study will evaluate both the humoral and cellular immune response in these patients. Serologic will be collected prior to booster dose, 1 month, 3 months, 6 months and 12 months following booster dose. Based on experience and high patient engagement from our prior pilot study measuring humoral response to COVID-19 vaccination, we anticipate >70% of participants approached for this study will agree to participate.

Studies have suggested that heterologous priming COVID-19 vaccination may result in improved immunogenicity although reactogenicity may be increased as demonstrated by Com-COV study from the United Kingdom, which examined heterologous schedules incorporating an adenoviral-vectored vaccine (ChAd) and an mRNA vaccine (BNT162b2), randomizing to eight groups: ChAd/ChAd, ChAd/BNT, BNT/BNT or BNT/ChAd, administered at 28- or 84-day intervals. The trial failed to meet pre-specified non-inferiority for the BNT/ChAd regimen, but did demonstrate that the Geometric Mean Concentration was higher in heterologous combinations than the licensed ChAd/ChAd schedule.[19,20] Another study from the United Kingdom in 88 health

care workers who received ChAd as their first dose and either a homologous boost with 9-12 weeks later with ChAd (n=37) or mRNA-1273 (n=51) found that 7-10 days following second dose Anti-RBD IgG levels were 5 times higher than pre-second dose with ChAd compared to 115 time higher with a mRNA-1273 boost. Similarly, this strong serologic response with heterologous vaccination was reflected in *in vitro* neutralizing antibody titers which were 20 times higher with heterologous vaccination with mRNA-1273 compared to approximately double following a second dose of ChAd compared to pre-second dose titers.[21] Therefore in this study, heterologous vaccination for the third dose will be explored in comparison to receiving the same vaccine (homologous) for all three doses with the hypothesis that the heterologous vaccination will result in higher antibody levels.

# 3 STUDY OBJECTIVES

## 3.1 Primary Objectives/Outcomes

Determine the effect of a third dose of COVID-19 vaccine (*mRNA-1273* or *BNT162b2*) on humoral immune response in patients with chronic kidney disease stage 3b-5 including end stage kidney disease receiving dialysis who did not attain convalescent serum levels or exhibiting declining antibody levels below convalescent serum levels of Anti-RBD through measurement of Anti-RBD at 1 month (30 days) following third dose of vaccine.

## 3.2 Secondary Objectives/Outcomes

1. Measurement of Anti-Spike, Anti-NP antibodies, and SARS-CoV-2 specific neutralization at 1 month (30 days) following third dose of vaccine.
2. Determine the effect of a third dose of COVID-19 vaccine on humoral immune response in hemodialysis patients who did not attain convalescent serum levels or exhibiting declining antibody levels below convalescent serum levels of Anti-RBD through measurement of Anti-Spike, Anti-RBD, and Anti-NP antibodies at 3 months, 6 months and 12 months following booster dosage.
3. In a subset of participants, assess cellular immunity through flow cytometry on PBMC and single-cell RNA sequencing prior to, one month, and 6 months following vaccine booster.
4. Evaluate adverse events related to third dose of vaccine through a questionnaire within 48 hours to 14 days and 30 days following third vaccine dose.
5. Differences in COVID-19 infections, symptomatic COVID-19 infections, hospitalization, and death between study groups.

# 4 STUDY DESIGN

## 4.1 General Design

The BOOST-KIDNEY study is a prospective, investigator and participant blinded randomized four parallel arm controlled study for CKD stage 3b-5 patients to evaluate the effect of a booster dose of vaccine on immunogenicity among those who did not respond defined as not reaching convalescent serum levels of Anti-RBD, or who exhibit declining antibody titers below the convalescent serum level of Anti-RBD. Enrolment will prioritize patients on dialysis but inclusion criteria will also include non-dialysis CKD stage 3b-5. Patients who are already participating in the study "Determining the Safety and Efficacy of COVID-19 Vaccination in the Chronic Kidney Disease Population" (CTO Protocol Number 3604) and have been found to have poor humoral response to COVID-19 vaccination will prioritized for recruitment. However, if a booster dose of COVID-19 vaccine is approved for the study population during the study period, patients will be eligible without serologic evaluation.

Patients will be randomized to *mRNA-1273* SARS-CoV-2 Vaccine (*SPIKEVAX®/Moderna*), or *BNT162b2 mRNA* Covid-19 Vaccine (*COMIRNATY®/Pfizer-BioNTech*) administered by a trained vaccine administrator. Information on prior vaccines received will be recorded, and patients may have received either *mRNA-1273* SARS-CoV-2 Vaccine (*SPIKEVAX®/Moderna*), or *BNT162b2 mRNA* Covid-19 Vaccine *(COMIRNATY®/Pfizer-BioNTech)* for their initial two doses of vaccine. Patients will be stratified by their initial vaccine type (*BNT162b2* or *mRNA-1273*) prior to randomization, which will result in four study groups as shown in Figure 2.

A placebo arm is not included in this study as it was not felt to be ethically justififed, but comparison will be made to participants not receiving a booster vaccine enrolled in CTO Protocol Number 3604 who choose not to participate. Similarly a primary outcome of COVID-19 infection

or hospitalizations was not chosen given the low incidence of COVID-19 infections in Canada due to high vaccination rates in the country.

Prior to receiving a third vaccine dose, quantitative SARS-CoV-2 IgG antibody levels against the full-length spike protein S1 domain, and Receptor Binding Domain (RBD) to assess humoral response will be measured and Anti-SARS-CoV-2 nucleocapsid protein to measure evidence of prior COVID-19 infection. In addition, we will isolate peripheral blood mononuclear cells in a subset to evaluate cellular immune response, however this will only be performed at University Health Network and Sunnybrook Health Sciences Centre as only these centres have the capacity for processing these samples. A neutralization antibody assay developed by the Gingras lab will also be used to assess for viral neutralization prior to booster dose at 1 month (30 days) post third dose of vaccine.

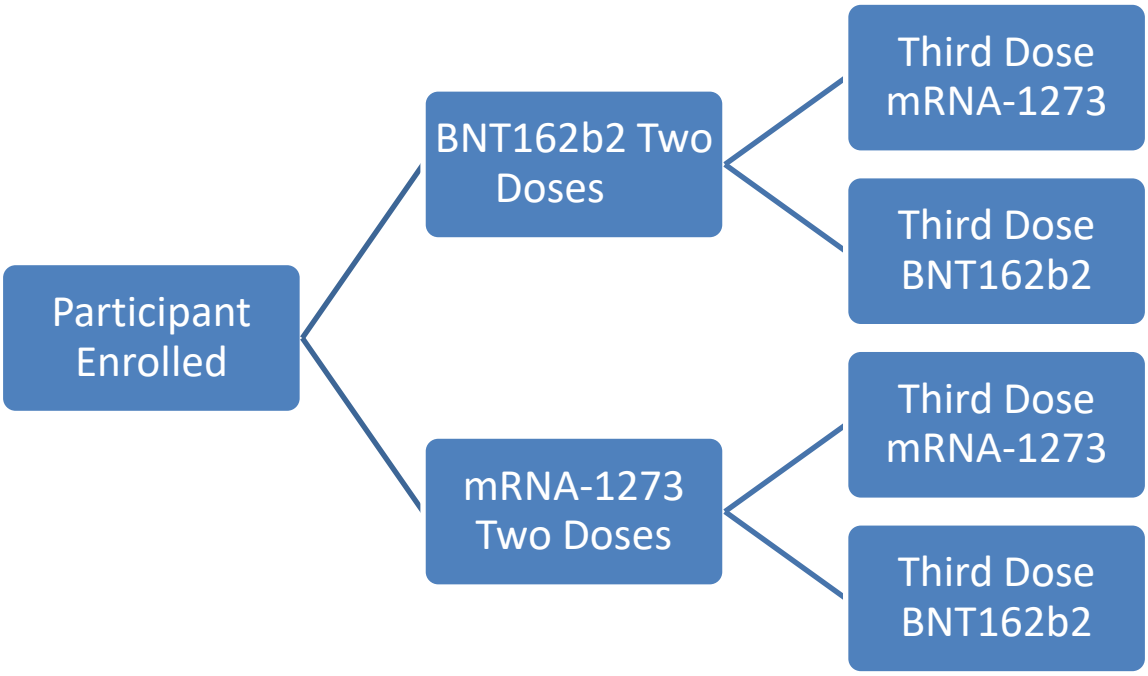


***Figure 2: Four study groups in the BOOST KIDNEY study. Study participants will be randomized 1:1 after stratification by initial vaccine type.***

Following the intervention, SARS-CoV-2 antibodies will be measured 1 month, 3 months, 6 months and 12 months post booster vaccination. Neutralizing antibodies will be measured at baseline and 1 month post third dose of booster vaccine. Cellular immunity in a subset will be evaluated at baseline, 1 month and 6 months post third dose of booster vaccine. Adverse events related to third dose of vaccination will be surveyed in the 14 day period following third dose of vaccine, and again 1 month following third dose. The study protocol may be altered if booster doses become available that are intended to target new SARS-CoV-2 variants. Furthermore, the study design will be adaptive, as if patients do not response to a third dose of vaccine the study protocol may be amended to consider other vaccine booster interventions. All study practices will follow social distancing measures currently recommended by Public Health authorities.

# 5 PARTICIPANT SELECTION and WITHDRAWAL

## 5.1 Study Population

Chronic kidney disease (CKD) patients including those on dialysis (in-centre hemodialysis, nocturnal hemodialysis, home hemodialysis, peritoneal dialysis) at the Toronto Academic Health Science Network (Sunnybrook Health Sciences Centre, University Health Network, and Unity Health Toronto), Scarborough General Hospital and University of British Columbia will be eligible.

## 5.2 Inclusion Criteria

Each participant must meet all of the following inclusion criteria to participate in this study:

1. Patients with CKD stage 3b-5 defined as an eGFR of less than 45ml/min/1.73m$^2$ or less will be eligible. Stage 5 CKD will include patients receiving in-centre hemodialysis, home dialysis (home hemodialysis or peritoneal dialysis), at Sunnybrook Health Sciences Centre, Unity Health Toronto, University Health Network, Scarborough General Hospital, or the University of British Columbia vaccinated with two doses of the COVID-19 vaccine will be eligible for a third dose to be given 2-12 months following the second dose. Patients may have participated in another COVID-19 study (CTO Protocol Number 3604) to assess humoral response .Patient not currently in CTO Study Number 3604 who are interested in the study are also eligible for recruitment into that trial.

2. All participants will be age ≥18 at the time of study enrolment.

3. The participants informed consent is obtained.

## 5.3 Exclusion Criteria

All participants meeting any of the following exclusion criteria at baseline will be excluded from participation in this study:

1. Patients not vaccinated against COVID-19 vaccination.
2. Patients who received heterologous first two doses of vaccine (expected to be a minimal number in this population as almost all patients received the same vaccine for both doses due to vaccination in dialysis units).
3. Patients with severe allergic reaction to prior COVID-19 vaccination or any of the ingredients.
4. New COVID-19 infection following study enrolment as determined by Anti-NP (drawn upon study enrolment) or new positive RT-PCR.

## 5.4 Participant Selection

Approximately 300 patients on dialysis, CKD stage 3b-5, will be recruited for the study. Serologic eligibility criteria for the study must be met following the screening period in the study.

## 5.5 Participant Recruitment

Participants will be recruited from participating renal centers within Canada from patients who have received two doses of COVID-19 vaccine. Eligible patients already participating in "Determining the Safety and Efficacy of COVID-19 Vaccination in the Chronic Kidney Disease Population" (CTO Protocol No. 3604) will be approached, but patients not in CTO Protocol No. 3604 will also be screened for eligibility and participation. Patients with known poor humoral response based upon their serum Anti-RBD levels will be prioritized for recruitment into the trial,

but if a booster dose of COVID-19 vaccine is approved for the study population during the study period, all participants meeting the inclusion and exclusion criteria will be approached.

### 5.5.1 Randomization Procedures

Stratified randomization will be performed centrally upon study enrolment with 1:1 receiving *BNT162b2* mRNA COVID-19 Vaccine (*COMIRNATY®/Pfizer-BioNTech*), and *mRNA-1273* SARS-CoV-2 Vaccine (*SPIKEVAX®/Moderna*) with stratification by baseline vaccine type *BNT162b2* or *mRNA-1273* given possible differences in vaccine immunogenicity in this population and heterologous priming.

The Participant whose written informed or preliminary verbal consent was obtained and eligible for the study will be randomized. Allocation will occur through identical, sequentially numbered, opaque, sealed envelopes. The two interventions will be the two COVID-19 vaccines which have been used predominantly in the dialysis population: the *BNT162b2 mRNA* COVID-19 Vaccine (*COMIRNATY®/Pfizer-BioNTech*) and *mRNA-1273* SARS-CoV-2 Vaccine *(SPIKEVAX®/Moderna*). The *BNT162b2* mRNA Covid-19 Vaccine (*COMIRNATY®/Pfizer-BioNTech*), is administered in 30 µg per dose while the *mRNA-1273* SARS-CoV-2 Vaccine (*SPIKEVAX®/Moderna*) is administered as 100 µg. Vaccines will be released from participating hospital pharmacies. Approval has been granted by the respective government agencies in in Ontario and British Columbia.

### 5.5.2 Blinding and Unblinding

Trial participants, study investigators, research team member, outcome assessors, and data analysts will be blinded to the intervention randomization. The individual dispensing and administering the vaccine will be aware of the vaccine being dispensed and administered but the patient will be blinded. Patients will be un-blinded to the vaccine they received following completing of adverse events following immunization reporting (30 days) and at that point will be provided with a vaccine receipt.

Un-blinding will only occur under exceptional circumstances where knowledge of the vaccine received is essential for further management of the study participant. Physicians are encouraged to discuss with the Qualified Investigator if un-blinding is necessary. If un-blinding is considered necessary, the Qualified Investigator will contact the randomization centre, who will do the code break as deemed necessary and communicate it directly to the attending physician. The Qualified Investigator will report all code breaks as they occur on the case report form.

## 5.6 Participant Withdrawal

At their own discretion, participants may withdraw from the study at any time and for any reason. Participants withdrawing from the study should be contacted by the study research team requesting a final visit and to follow up with any unresolved adverse events.

The participant may also be withdrawn from the study for the following reasons:

- Death: The participant died
- Protocol Deviation: The participant's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., failure to return for defined number of visits). The deviation must be discussed with Principal Investigator prior to the participant study withdrawal.

- Lost to Follow-up: The participant fails to attend study visits and study personnel are unable to contact the participant after repeated attempts.
- Physician Decision: The participant was terminated for a reason other than those listed above by the physician caring for the participant.
- Other: The participant was terminated for a reason other than those listed above and the reason will be recorded.

## 5.7 Data Collection and Follow-up for Withdrawn Participants

Once withdrawn from the study, no further study procedures or evaluations should be performed, or additional study data collected. Any data collected prior to the withdrawal of consent may be retained and used by the sponsor. However, every effort should be made to obtain permission to document the reason for withdrawal and to collect participant outcomes, such as survival data up to the protocol-described end of participant follow up period, where possible. Any data collected prior to the withdrawal of consent may be retained and used by the sponsor.

# 6 INTERVENTIONS

## 6.1 Investigational Product

The study exposure will be COVID-19 vaccination with a third dose (booster) of the *BNT162b2 mRNA* COVID-19 Vaccine (*COMIRNATY®/Pfizer-BioNTech*) or *mRNA-1273* SARS-CoV-2 Vaccine (*SPIKEVAX®/Moderna*).

### 6.1.1 Acquisition, Formulation and Packaging

#### *6.1.1.1 Acquisition and formulation*

The vaccine doses utilized in this study will be obtained at each site through the hospital supply of vaccine. Release of the vaccine for this research study has been approved by the Ontario and British Columbia Ministries of Health. The *BNT162b2 mRNA* Covid-19 Vaccine (*COMIRNATY®/Pfizer-BioNTech*) is a suspension for intramuscular injection which must be diluted prior to administration. After preparation, a single dose is 0.3 mL, while the mRNA-1273 SARS-CoV-2 Vaccine (*SPIKEVAX®/Moderna*) is administered as 0.5mL intramuscularly.

The *BNT162b2* vaccine includes the following ingredients: messenger ribonucleic acid (mRNA), ALC-0315 = ((4-hydroxybutyl) azanediyl), bis(hexane-6,1-diyl),bis (2-hexyldecanoate), ALC-0159 = 2-[(polyethylene glycol)-2000]-N, N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, cholesterol, dibasic sodium phosphate dehydrate, monobasic potassium phosphate, potassium chloride, sodium chloride, sucrose, and water for injection. The *mRNA-1273* vaccine contains the following ingredients: messenger ribonucleic acid (mRNA), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), Acetic acid, Cholesterol, Lipid SM-102,

PEG2000, DMG 1,2-dimyristoyl-racglycerol,methoxy-polyethyleneglycol, Sodium acetate tri-hydrate, Sucrose, Trometamol, Trometamol hydrochloride, and water for injection. Individuals with severe allergies to any of the components or who had a severe reaction to a previous dose of COVID-19 vaccine will be excluded from this study.

#### *6.1.1.2 Packaging*

*The BNT162b2* Pfizer-BioNTech COVID-19 Vaccine is packaged in a clear glass 2 mL vial with a rubber stopper (not made with natural rubber latex), aluminum overseal, and flip-off cap. The *mRNA-1273* vaccine (SPIKEVAX®/Moderna) is supplied in a multi-dose 10R type I glass vial (each of 5 mL) with a 20 mm Fluro Tec-coated chlorobutyl elastomer stopper, 20 mm flip-off aluminum seal. The vial stopper does not contain natural rubber latex. Vials are packaged in a secondary carton containing a total of ten (10) *mRNA-1273* vaccine vials per carton.

### 6.1.2 Treatment Assignment Procedures

All patients eligible for the study will receive a booster vaccine dose. Randomization will be stratified by initial two vaccines received *(BNT162b2* versus *mRNA-1273*) with 1:1 randomization to a third dose of *BNT162b2* or *mRNA-1273*.

### 6.1.3 Vaccine Allocation and Administration

The third dose of vaccine will be administered between 2 months to 12 months following second dose of vaccine to allow a reasonable window for eligibility, and to allow for the appropriate screening of study participants with suboptimal initial humoral serologic response for this study. Vaccine will be dispensed by the central pharmacies through concealed allocation prior to planned administration of the study intervention. The vaccine will be administered by an individual who

has been trained in COVID-19 vaccine administration. The individual administering the vaccine will not be blinded to the vaccine type. Vaccine receipt will be entered in the COVAX database, and receipt of a booster vaccine dose will be recorded in the Ontario Renal Network COVID-19 vaccine tracker after unblinding following reporting of the adverse events at 30 days.

Participants will be provided with documentation indicating that they have received a third booster dose and the date that this was received after unblinding following the completion of adverse event following immunization. As with standard vaccine administration, participants will sign additional informed consent to receive the vaccine and confirm that they do not have allergies to the components of either vaccine type. Participants will be monitored for 15 minutes following vaccine administration prior to being allowed to return home. For in-centre hemodialysis participants, the vaccine administration will occur during maintenance hemodialysis.

#### *6.1.3.1 Identification of Individuals with Suboptimal Humoral Response*

Patients enrolled in the pilot study “Determining the Safety and Efficacy of COVID-19 Vaccination in the Chronic Kidney Disease Population” (with Protocol CTO number 3604) or who are interested in the study who are found to have poor humoral response will be determined to be eligible for the trial by assessing their most recent antibody levels drawn at a minimum 1 month following their second dose of COVID-19 vaccine. Upon study enrolment SARS-CoV-2 antibodies against anti-Spike, anti-RBD, and anti-NP will be performed to exclude evidence of recent COVID-19 infection and confirm anti-RBD levels below convalescent serum levels.

Antibodies targeting the full-length spike protein (anti-spike) and its Receptor Binding Domain (anti-RBD) measured humoral response to SARS-CoV-2 vaccination and/or natural infection while antibodies to the nucleocapsid protein (anti-NP) detected natural SARS-CoV-2

infection, as this antigen is not targeted by the BNT162b2 vaccine. Antibody levels are reported as relative ratios to a synthetic standard included as a calibration curve on each assay plate.

Thresholds for positivity (seroconversion) were determined by aggregating data from negative controls and calculating the mean + 3 standard deviations. The median level of convalescent serum is determined by comparison to the median levels of convalescent serum taken 21-115 days post symptom onset in patients with COVID 19. The convalescent serum patients (n=211) were obtained from the Toronto Invasive Bacterial Diseases Network (REB studies #20-044 Unity Health, #02-0118-U/05-0016-C, Mount Sinai Hospital). had a median age of 59 years, 115/211 (55%) were male and included patients with mild (defined as not requiring hospitalization), moderate, and severe disease severity.

Seroconversion thresholds represent a positive serology test and are 0.19, 0.186, and 0.396 for anti-spike, anti-RDB, anti-NP antibodies respectively at a dilution of 0.0625. The median level of antibody in convalescent serum taken 21-115 days post-symptom onset in those infected with COVID-19 is considered a robust antibody response and is 1.38, 1.25, and 1.13 for anti-spike, anti-RBD, and anti-NP antibodies, respectively. All patients with anti-RBD below the level of convalescent serum at last serologic sampling will be eligible for the study which will be confirmed by serology taken upon enrolment in the study or already available due to registration in “Determining the Safety and Efficacy of COVID-19 Vaccination in the Chronic Kidney Disease Population” (CTO Protocol No. 3604).

### 6.1.4 Vaccine Dosage, Preparation and Administration

The following dosage, preparation and administration are summarized from the product monographs of the investigational products:

#### *6.1.4.1 mRNA-1273 (SPIKEVAX®/Moderna)*

COVID-19 Vaccine *SPIKEVAX®/Moderna* must not be reconstituted, mixed with other medicinal products, or diluted. The COVID-19 Vaccine *Moderna* should be administered intramuscularly as a 0.5mL dose. COVID-19 Vaccine *Moderna* is a white to off-white dispersion. It may contain white or translucent product-related particulates. Inspect COVID-19 Vaccine *Moderna* vials visually for foreign particulate matter and/or discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered. COVID-19 Vaccine *SPIKEVAX®/Moderna* should be administered by the intramuscular (IM) route only. Do not inject the vaccine intravascularly, subcutaneously or intra-dermally. The preferred site is the deltoid muscle of the upper arm. A needle length of ≥1 inch should be used as needles <1 inch may be of insufficient length to penetrate muscle tissue in some adults.

Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab. Withdraw each 0.5 mL dose of vaccine from the vial using a new sterile needle and syringe for each injection. Pierce the stopper preferably at a different site each time. The dose in the syringe should be used as soon as feasible, and no later than 24 hours after the vial was first entered (needle-punctured). COVID-19 Vaccine *Moderna* is preservative free. Once the vial has been entered, it should be discarded after 24 hours. Do not refreeze. Thawed vials and filled syringes can be handled in room light conditions. Any unused vaccine or waste material should be disposed of in accordance with local requirements. To help ensure the traceability of vaccines for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

#### *6.1.4.2 BNT162b2 (COMIRNATY®/Pfizer)*

*COMIRNATY®/Pfizer-BioNTech* COVID-19 Vaccine is a suspension for intramuscular injection which must be diluted prior to administration. After preparation, a single dose is 0.3 mL.

Dilution: Obtain sterile 0.9% Sodium Chloride Injection, USP,use only this as the diluent. Using aseptic technique, withdraw 1.8 mL of 0.9% Sodium Chloride Injection, USP into a transfer syringe (21-gauge or narrower needle), cleanse the vaccine vial stopper with a single-use antiseptic swab, add 1.8 mL of 0.9% Sodium Chloride Injection, USP into the vaccine vial. Equalize vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe, gently invert the vial containing the COMIRNATY®/Pfizer-BioNTech COVID-19 Vaccine 10 times to mix. Do not shake and inspect the vaccine in the vial.The vaccine will be an off-white suspension. Do not use if vaccine is discoloured or contains particulate matter.

Administration: Preparation of Individual 0.3mL doses of Pfizer-Biontech COVID-19 Vaccine: Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab, and withdraw 0.3 mL of the PfizerBioNTech COVID-19 Vaccine, preferentially using low dead-volume syringes and/or needles. Each dose must contain 0.3 mL of vaccine. If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume. Administer immediately, and no later than 6 hours after dilution. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. In order to ensure consistent withdrawal of 6 doses of 0.3mL, it is important to adhere to minimizing volume loss during dose extraction. Visually inspect each dose in the dosing syringe prior to administration. The diluted vaccine will be an off-white suspension. During the visual inspection: verify the final dosing volume of 0.3 mL, confirm there are no particulates and that no discolouration is observed, do not administer if vaccine is discoloured or contains particulate matter.

Administer COMIRNATY®/Pfizer-BioNTech COVID-19 Vaccine intramuscularly, preferably in the deltoid muscle. Do not inject the vaccine intravascularly, subcutaneously or intra-dermally. After dilution, vials of *Pfizer-BioNTech* COVID-19 Vaccine contain 6 doses of 0.3 mL of vaccine. Low dead-volume syringes and/or needles can be used to extract 6 doses from a single vial. In order to ensure consistent withdrawal of 6 doses of 0.3 mL, it is important to adhere to minimizing volume loss during dose extraction. If standard syringes and needles are used, there may not be sufficient volume to extract a 6th dose from a single vial. Irrespective of the type of syringe and needle: each dose must contain 0.3 mL of vaccine, if the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume, do not pool excess vaccine from multiple vials.

### 6.1.5 Dose Modification

No modification will be made to the vaccine doses in the study.

### 6.1.6 Receiving, Storage, Dispensing and Return

#### *6.1.6.1 Receipt of Investigational Product*

Upon receipt of the investigational product and/or study supplies, an inventory must be performed and a receipt log filled out and signed by the research team member accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable product in a given shipment will be documented in the study files. The site must notify the study sponsor of any damaged or unusable product that was supplied to the site.

#### *6.1.6.2 Vaccine Storage and Stability*

All the sites involved in this study have resources and capacity for the storage of both vaccines. The *BNT162b2* vaccine is stored -80°C and must be thawed prior to dilution. Vials must reach room temperature before dilution. Undiluted vials may be stored at room temperature for no more than 2 hours. After dilution, the vials are stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution. The *mRNA-1273* multi-dose vials are stored frozen between -25º to -15ºC (-13º to 5ºF). Once thawed, unpunctured vials may be kept at 2 º C to 8 ºC in a refrigerator for up to 30 days, or at 8º C to25ºC for up to 24 hours. After thawing, the vial is allowed to stand at room temperature for 15 minutes before administering. Alternatively, thaw at room temperature between 15°C to 25°C (59°F to 77°F) for 1 hour. Once the vial has been entered (needle-punctured), it can be stored at room temperature or refrigerated, but must be discarded after 24 hours.

### 6.1.7 Prior and Concomitant Medications/Treatments

Information regarding receipt of COVID-19 vaccination will be documented to determine study eligibility with stratification determined by receipt of *BNT162b2* and *mRNA-1273*. In addition, a booster dose of vaccine will not be administered within 14 days of another vaccine (e.g. Hepatitis B or Shingle vaccination).

### 6.1.8 Procedures for Intervention Training and Monitoring

Individuals providing the COVID-19 vaccine will have undergone standardized training for administration of both the *BNT162b2* and *mRNA-1273* vaccines.

# 7 STUDY SCHEDULE AND PROCEDURES

## 7.1 Study Procedure

Participants who meet study eligibility criteria and consent to participate will be enrolled in the study. At study enrolment baseline, serum will be collected for SARS-CoV-2 serology, neutralizing antibodies and in a subset determined by the Investigator, PBMC will be collected for assessment of cellular immunity at Sunnybrook Health Sciences Centre or University Health Network prior to receiving the booster dose. Patients who are already participating in the study "Determining the Safety and Efficacy of COVID-19 Vaccination in the Chronic Kidney Disease Population" (CTO Protocol Number 3604) and have been found to have poor humoral response to COVID-19 vaccination will prioritized for recruitment. However, if a booster dose of COVID-19 vaccine is approved for subsets of the study population or the study population at large during the study period, patients remain eligible for randomization without serological confirmation of low antibody titres.

Vaccine will be administered by an individual trained in vaccine administration at the site.

Following vaccination, participants will be asked about adverse symptoms related to COVID-19 vaccination through a questionnaire at 48 hours -14 days either in person in the dialysis unit or by telephone and at 1 month post third dose.

Following the intervention with either third dose of booster vaccine, the participant will have blood collection for Anti-SARS-CoV-2 IgG antibodies targeting the full length spike protein, RBD, nucleocapsid protein at 1 month, 3 months, 6 months, and 12 months following receipt of the booster dose. For feasibility, neutralizing antibodies will only be performed at 1 month following third dose. Non-dialysis participants may have bloodwork testing as part of routine

clinical care at each time point to determine if the booster vaccine dose has impacted kidney function including a serum creatinine and a spot urine micro-albumin creatinine ratio.

## 7.2 Study Assessments

### 7.2.1 Anti-SARS-CoV-2 IgG Antibody Assays

Anti-SARS-CoV-2 IgG antibodies targeting the full-length spike protein trimer and its receptor binding domain will be measured to assess humoral response to vaccination. Anti-SARS-CoV-2 IgG antibodies to the nucleocapsid protein will indicate likely prior SARS-CoV-2 infection as this is the antigen with the strongest immune-dominance in the coronavirus family, and this antigen is not targeted by the current COVID-19 vaccines available in Canada.

Dr. Anne-Claude Gingras has developed in-house SARS-CoV-2 Receptor Binding Domain (RBD) and nucleocapsid protein ELISA test on a robotic platform that can be scaled up to test up to 10,000 samples/day. She currently is performing highly reproducible, in-house, quantitative and highly specific assays of serum IgG, IgA, and IgM to SARS-CoV-2 Spike, nucleoprotein, and RBD domain. She has also developed a surrogate assay that can predict neutralization ability of serum to SARS-CoV-2.[22,24] These tests have been validated on cohorts of laboratory confirmed positive and negative specimens. Levels of antibodies to each of the antigens will be normalized to reference standards included on each plate (in collaboration with the National Research Council of Canada), and expressed as relative ratios. All assays are also calibrated to the international standard from the National Institute for Biological Standards and Control (NIBSC).

Assessment of viral neutralization will be performed using a viral neutralization assay developed by the Gingras laboratory and may be adapted to test neutralization against novel

variants of concern. The Gingras laboratory has a surrogate neutralization assay which is performed on the same platform as the ELISA for the antibody testing and was well correlated with the gold standard plaque reduction neutralization test.[22]All testing on serum will be performed by the Gingras Lab at Mount Sinai Hospital.

### 7.2.2 Cellular Immunity Testing

To assess cellular immunity flow cytometry will be performed in peripheral blood mononuclear cells (PBMC) in a subset of participants to examine SARS-CoV-2 specific B and T-cell lymphocyte subsets prior to and following booster dosage of vaccine. Based upon baseline serologic levels individuals will be categorized as non-responders (who never attained convalescent level of anti-RBD) or those with waning antibody levels. In total approximately 50 participants at University Health Network and Sunnybrook Health Sciences Centre are anticipated to have samples drawn for this sub-study. PBMC will be collected prior to third dose booster, 1 month, and 6 months following booster dose. ELISpot (enzyme-linked immunospot) assays to evaluate SARS-CoV-2 specific cellular immunity will be harmonized with protocols with other CITF studies.

### 7.2.3 Evaluation for COVID-19 Infection

To avoid potential contamination of the study result by participants who develop COVID-19 during the study period , natural COVID-19 infection will be detected by serologic assessments with Anti-NP which has a sensitivity of approximately 79%. Participants who present with any signs or symptoms of COVID-19 will be swabbed with SARS-CoV-2 nasopharyngeal swabs as per current screening protocols. Participants who develop COVID-19 infection during the study will be excluded from the analysis.

### 7.2.4 SARS-CoV-2 Variants of Concern

Given the emergence of novel SARS-CoV-2 variants of concern, additional neutralization assays may be considered to evaluate effectiveness against variants of concern including the B.1.1.7, B.1.351, P.1, and B.1.617.2 (Delta) variant. Additionally, if any breakthrough infections are reported in patients in this study, whole genome sequencing will be performed in order to identify the viral lineage. Table 1 provides summary of study assessments.

***Table 1: Schedule of Study Assessments for BOOST KIDNEY Protocol***

| **Study Visit** | **Screening for Eligibility and Informed Consent** | **Baseline Study Assessment** | **Adverse Event Questionnaire** | **Serum SARS-CoV-2 Antibodies (Spike, RBD, NP)** (5mL SST Tube) | **SARS-CoV-2 Neutralizing Antibodies** (5mL SST Tube) | **PBMC** (20mL Na Heparin blood) (n=50) | **Vaccine Receipt and Participant Unblinding** |
|---|---|---|---|---|---|---|---|
| Study Enrolment | X | X | | X | | | |
| Prior to Booster | | | | | X | X | |
| Booster Vaccine Administration | | X | | | | | |
| 48 hours -14 days post-booster | | | X | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 month | | | X | X | X | X | X |
| 3 months | | | | X | | | |
| 6 months | | | | X | | X | |
| 12 months | | | | X | | | |

## 7.3 Specimen Collection, Transportation, Bio-banking

For serum, blood will be collected in a single SST tube, and allowed to clot for 30 minutes and centrifuged for 10 minutes at 3000 x g at room temperature. Aliquots are made in 1 or 2 mL -80°C stable cryo-vials each with a volume of 300µL. Testing for three antigens (Anti-NP, Anti-Spike, and Anti-RBD) and surrogate SARS-CoV-2 pseudo-neutralization assay requires a minimum volume of 200µL. Tubes are labelled with the study code, participant ID, date of collection, and appropriate time point. Samples are transferred on dry-ice to the Gingras Lab. A paper copy of list of samples sent is emailed using the template for data collection including labelled information in addition to vaccine type received and vaccination dates. Samples will not be collected if a participant has active COVID-19 as determined by Infection Control and Prevention but may resume when precautions have been discontinued. If a study participant has active COVID-19, clinical surplus if available at Sunnybrook may be processed into serum as part

of the Sunnybrook COVID-19 Biobank REB2109 and released to this study for serological analysis.

All study procedures will be in compliance with current Public Health guidelines for COVID-19 including the use of personal protective equipment, masking, and social distancing by all study personnel. If a study participant becomes infected with SARS-CoV-2, confirmed by RT-PCR during the course of the study, a study sample will not be collected from the participant with active COVID-19, but the participant will resume in the study once deemed safe by Public Health and their quarantine period is complete.

All infected patients will be referred for appropriate clinical care. Policies and procedures are already in place for in-center dialysis patients at each participating site to manage patients who have COVID-19 including ensuring appropriate isolation, droplet/contact precaution procedures, and informing Public Health authorities as well as local hospital Infection Prevention and Control. Non dialysis patients that become infected will also be referred for appropriate clinical follow-up and will be reported to Public Health Authorities per provincial mandates. All participating sites are experienced managing infected patients with established services to follow remotely and recommend admission when necessary. These services will be involved in each case to provide symptom assessment, develop an appropriate monitoring plan with regular severity assessments, and treatment plan for the patients.

For PBMC, 20 ml of heparinized blood will be separated into a mononuclear fraction by Ficoll-Paque or SepMate tube methodology. Blood samples will be separated into peripheral blood mononuclear cells and plasma within four hours of collection. Mononuclear cells will be viably frozen and plasma samples will be frozen for future use. Mononuclear cells with be frozen in 10% DMSO in alpha-MEM with 50% fetal bovine serum. Storage concentration is 1-10 x $10^7$ cells/aliquot. Viable PBMC will be cryopreserved in vapor-phase liquid nitrogen.

## 7.4 Baseline Data Collection

The Ontario Renal Reporting System (ORRS) and British Columbia's PROMISE databases will be used to obtain demographic information on all participants enrolled in the study. The Ontario Renal Network has already mandated provincial data collection regarding symptoms/adverse events related to vaccination and COVID-19 infection confirmed by SARS-CoV-2 RT-PCR in hemodialysis and peritoneal dialysis patients. Specifically the following variables will be collected in all participants: age, sex, prior COVID-19 (NP Swab), vascular access, cause of kidney disease, current immunosuppressive medications (defined as taking any of the following: antimetabolite agent, calcineurin inhibitor, cytotoxic medications, rituximab in prior 6 months, tumor necrosis factor alpha monoclonal antibodies, or glucocorticoids greater than prednisone 5 mg daily), autoimmune disease, diabetes mellitus, cancer, coronary artery disease, congestive heart failure, chronic obstructive lung disease, hypertension, obesity, hepatitis B non-responder status (defined as <10mIU/mL), and ABO blood type. In non-dialysis patients serum creatinine and proteinuria will be recorded.

# 8 ASSESMENT OF SAFETY

The safety of research participants is foremost and should always be considered throughout the conduct of research.

## 8.1 Definitions

### 8.1.1 Adverse Events

An adverse event (AE) means any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment, and includes an adverse drug reaction (ADR).An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

### 8.1.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward occurrence that at any dose:

Results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or in significant disability/incapacity, is a congenital abnormality or a birth defect. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

### 8.1.3 Unexpected Adverse Event

An unexpected adverse event is any AE that is not identified in nature, severity or frequency in the current Investigator's Brochure or Product Monograph.

### 8.1.4 Unexpected Adverse Drug Reaction (ADR)

An ADR is an adverse reaction, the severity of which is not consistent with the applicable Investigator's Brochure or Product Monograph. All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. The expression "causal relationship" is meant to convey that in general there are facts, evidence or arguments to suggest a reasonable causal relationship. All serious and unexpected ADRs will have expedited reporting to regulatory agencies following ICH-GCP and local regulatory requirements.

## 8.2 Assessment of an Adverse Event

### 8.2.1 Relationship (Causality/Relatedness)

The causality assessment is the determination, according to the investigator's clinical judgment, of the existence of a reasonable possibility that the study drug (IP) caused or contributed to an adverse event. If the investigator or delegated sub-investigator is unsure about whether or not the study drug caused or is related to the event, then the event will be handled as "related" to the study drug for reporting purposes of the trial. If the causality assessment is

"unknown but not related" to the study drug, this should be clearly documented in the source documents.

### 8.2.2 Expectedness

Events are classified as unforeseen or unexpected if the nature, severity or frequency is not consistent with the risk information set out in the Product Monograph (PM) or label.

### 8.2.3 Seriousness

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant.

### 8.2.4 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. The terms “serious” and “severe” are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

## 8.3 Adverse Event Recording

Investigations into potential adverse events should be done during each contact with a participant. Investigations may be done through specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly in the source document, and assessed by an investigator in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and SUADRs if needed. Adverse event CRFs should be completed using source documents by a delegated research team member in a timely manner/within 15 days of site awareness. All clearly related signs, symptoms, and abnormal diagnostic procedures should be recorded in the source document, though should be grouped under one diagnosis.

The following are not considered AEs and therefore do not require recording: Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency, at the discretion of the investigator; events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of IP exposure, and elective medical or surgical procedures.

## 8.4 Reporting of SAEs and Unanticipated Events

### 8.4.1 Investigator reporting: Notifying the REB:

Serious adverse events and unanticipated events should be recorded and reported to the REB in accordance with local reporting requirements and timelines.

### 8.4.2 Investigator reporting: Notifying the Sponsor

The investigator is responsible for reporting serious adverse events and serious and unexpected adverse drug reactions (SUADRs) to the sponsor in accordance with applicable

regulations and reporting requirements and timelines. Events that are assessed to be serious and unexpected and related or cannot be ruled out as related to the investigational product are considered SUADRs. Reporting for SUADRs should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable participant, one identifiable reporter, one serious reaction, and one suspect product.

Additionally, a Suspect Adverse Reaction Report – CIOMS I Form (see appendix B) must be completed by the investigator and forwarded to the Sponsor within 24 hours of site awareness. Information on other possible causes of the event, such as concomitant medications and illnesses should also be provided as soon as is made available.

### 8.4.3 Sponsor Reporting of SUADRs: Notifying Health Canada

The regulatory sponsor is responsible for reporting SUADRs to regulatory authorities in accordance with local expedited reporting requirements and timelines. In addition, the Sponsor will complete the ADR Expedited Reporting Summary Form and submit this form in conjunction with the completed CIOMS Form to the appropriate Health Canada directorate.

### 8.4.4 Sponsor Reporting of SUADRs: Notifying Sites

The regulatory sponsor is responsible for distributing blinded expedited reports of SUADRs to each investigator for submission to local Ethics Committees within 15 days of sponsor awareness.

### 8.4.5 Events of Special Interest

Events of Special Interest in relation to COVID-19 are derived from the Public Health Ontario Report of Adverse Event Following Immunization (AEFI): Vaccine-associated enhanced disease, acute respiratory distress syndrome, acute cardiovascular injury, coagulation disorder, acute kidney injury, acute liver injury, anosmia and / or ageusia, chilblain-like lesions, single organ cutaneous vasculitis, erythema multiforme.

## 8.5 Type and Duration of Follow-up for Adverse Events

AEs occurring as of the first administered dose of the investigational product and 30-days after the last administered dose, will be collected. AEs recorded during this period will be followed through to resolution, or until the event is assessed as chronic or stable.

## 8.6 Reporting and Entry Timelines

Study investigators will report SAEs to the sponsor within the following timelines: All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the sponsor within 24 hours of site awareness. Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported to the sponsor within 72 hours of site awareness. Adverse event information will be entered into the CRF in a timely manner and no later than 15 days from the time the investigator becomes aware of the event. Serious adverse event information will be entered into the CRF in a timely manner/within 72 hours from the time the investigator becomes aware of the event.

## 8.7 Evaluation of Adverse Events and Safety Questionnaires

Local and systemic AE will be evaluated within 48 hours to 14 days and 1 month post third dose. Local adverse events include pain at the injection site, redness, and swelling. Systemic adverse events include fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain. Serious adverse events (SAE) will be recorded and investigated and questions will be adapted from the report of Adverse Event Following Immunization (AEFI) from Public Health Ontario, including local reactions at the injection site, symptoms (fever, chills, fatigue, nausea/vomiting, diarrhea, muscle pain, joint pains and other adverse events). Participants will be advised that acetaminophen may reduce vaccine side-effects but will not actively be counselled to medicate, but usage will be recorded. Due to kidney disease, anti-inflammatory medication will be discouraged. A recent study of heterologous prime-boost found increased adverse events with heterologous vaccination but no hospitalizations were recorded, and most adverse events occurred within 48 hours of vaccination.[20]

In Ontario, all chronic dialysis patients are currently being tracked for serious adverse events using the COVID-19 vaccine tracker although this had not detected any serious adverse events to date. This customized Excel spreadsheet is pre-populated by the Ontario Renal Network (ORN) and completed by renal programs monthly (submitted securely via Tumbleweed systems). Adverse events related to vaccination are also tracked in PROMIS (BC) which has detailed clinical records on their patients. Coordinators will conduct a questionnaire to inquire about local and systemic symptoms related to the vaccine. Other rare adverse events will be captured using detailed descriptions. Questionnaires will be conducted 48 hours -14 days, and 1 month after the booster vaccination dose. Individuals participating in the pilot study have had side effects after the first two doses of vaccine recorded. SAEs are defined using the Health Canada definition as

those resulting in hospitalization admission or prolongation of existing hospitalization, resulting in persistent or significant disability or incapacity, is life-threatening, or resulting in death and definitely or probably associated with vaccination in the opinion of their nephrologist. The provincial data collection includes reasons for vaccine hesitancy or refusal which could inform education for specific groups. In addition, renal programs in Ontario are currently tracking all infections, including the 3 reported variants (B117, B1351, P1, and others).

## 8.8 Data Safety Monitoring Committee (DSMB)

The data safety monitoring committee will include Nephrologists, an infectious disease specialist, Public Health Specialist, and experts in clinical trials. The DSMC will review summary data and adverse events several times early in the trial and subsequently will meet at approximately 6 months and 12 months following the third dose. The purpose of the DSMC will be to review safety concerns and review external data that may have bearing on the design of or decision to continue the trial.

## 8.9 General Trial Conduct Considerations

### 8.9.1 Protocol Deviation

We will allow a 7 day window for collection of blood samples for the primary outcome at 1 month. During the later blood collection period, we will allow a 15 day window for collection of blood samples or the blood collection will be deferred until the next scheduled time point. It is the responsibility of the investigator to ensure that only investigative procedures, as outlined in this

protocol are performed on study participants; the occurrence of deviations from the protocol or SOPs are limited; and compliance with the regulations is maintained. Planned deviations from the protocol must not be implemented without prior agreement from the sponsor and approval from the local REB/ethics committee (EC), as required, unless to eliminate an immediate hazard to a participant. Planned or unplanned deviations may occur on the part of the participant, the investigator, or study research team. In resolution to a deviation, corrective/preventative actions are to be developed and implemented in a timely manner. Protocol deviations will be documented and reported as required and assessed where necessary during analysis.

# 9 SITE MONITORING, AUDITING AND INSPECTING

## 9.1 Site Monitoring Plan

Site monitoring is conducted to ensure the safety of human study participants and the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation and that the study is conducted in accordance with the protocol and operating procedures.

Monitoring for this study is the responsibility of the sponsor. The delegated monitor will evaluate study processes and documentation based on the approved protocol/amendment(s), Part C, Division 5 of the Food and Drug Regulations, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), E6: Good Clinical Practice guidelines (GCP) and institutional policies.

The extent and nature of monitoring is outlined in the Monitoring Plan. The monitoring plan specifies the frequency of monitoring, monitoring procedures, the level of site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Monitoring activities will be performed both in person and remotely. Reports of findings identified during monitoring activities will be provided to sites detailing any required actions. Documentation of monitoring activities and findings will be provided to the site study team and the study QI. The institution and/or local REB reserves the right to conduct independent audits as necessary.

The Investigator is responsible for ensuring monitors and/or quality assurance reviewers are given access to all study-related documents noted above and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and have adequate space to conduct the monitoring visit or audit.

## 9.2 Auditing and Inspecting

The investigator will provide direct access to source data/documents for the purposes of study-related monitoring, audits, and inspections by the REB, the sponsor, and applicable regulatory bodies. The investigator will permit the review of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) and will ensure access to applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Study Hypotheses

Based on evidence from the transplant population, we hypothesize that patients who did not initially attain an initial robust immune response to two dose COVID-19 vaccination, a substantial proportion may attain improved humoral and cellular immunity against COVID-19 following a third vaccine booster with acceptable tolerability. We hypothesize that heterologous vaccination (e.g. a different vaccine from the first two doses) for the third dose may result in increased serologic response.

## 10.2 Sample Size Considerations

Approximately 500 patients with chronic kidney disease are presently enrolled in the study entitled “Determining the Safety and Efficacy of COVID-19 Vaccination in the Chronic Kidney Disease Population”, but this number is rapidly increasing. We have limited information to guide our sample size, but in the case series published in transplant patients 25% of patient who were seronegative responded to a booster vaccine, while 100% of those with “low positive” antibody levels responded to a booster vaccine. Similarly in a study from France the prevalence of positive SARS-CoV-2 antibodies increased 28% after the third dose.

Our sample size is based on serologic response for Anti-RBD as this measure may be a better correlate with neutralizing antibodies than Anti-Spike.[22,23] In our pilot study we found that 60% of patients had attained convalescent serum levels of Anti-RBD by two weeks after post-second dose and therefore we expect no issues with finding eligible participants. For our sample size calculation, to achieve 80% power to detect 25% difference in individuals reaching convalescent serum levels of Anti-RBD receiving a COVID-19 from *mRNA-1273* versus

*BTN162b2* at a two sided alpha of 0.05 assuming 25% response in the *BNT162b2* group based on the limited studies to date, we would require 58 participants in each study group. The 25% difference was determined by consensus by the Principal Investigators to represent a clinically important difference. Given the stratification by baseline vaccination received, there will be four study groups, requiring a sample size of 232 participants as shown in Table 2. A Bonferroni adjustment for the alpha will not be used. A similar sample size calculation is obtained if the nested (two) chi-squared tests for the primary outcome of this study are considered the equivalent of a logistic regression equation with the baseline initial vaccine received as the two covariates. Assuming approximately 25% response to a booster dose, and the general rule that 10 outcome events are required per covariate, and 10% drop out during the one month period of the primary outcome, a total sample size of 89 would be required. Capacity to enroll is higher, therefore the target sample size will be 300 participants to avoid under-powering the study, and will account for up to 10% participant loss to follow-up due to death or new COVID-19 infection during the 1 month follow-up period for the primary outcome.

*Table 2: Potential sample size calculations based upon differences in Anti-RBD response observed between BNT162b2 and mRNA-1273 vaccines at a Power (1-β) of 80% and ∞ 0.05*

| Clinically Significant Difference | BNT162b2 Response[a] | mRNA-1273 Response[a] | Power (1-β) | Alpha (∞) | Required Sample Size Per Group | Required Total Sample Size (4 Groups) |
|---|---|---|---|---|---|---|
| **30%** | 25% | 55% | 80% | 0.05 | 41 | 164 |
| **30%** | 50% | 80% | 80% | 0.05 | 39 | 156 |
| **30%** | 65% | 95% | 80% | 0.05 | 27 | 108 |
| **25%** | 25% | 50% | 80% | 0.05 | 58 | 232 |
| **25%** | 50% | 75% | 80% | 0.05 | 58 | 232 |
| **25%** | 65% | 90% | 80% | 0.05 | 43 | 172 |
| **20%** | 25% | 45% | 80% | 0.05 | 82 | 328 |
| **20%** | 50% | 70% | 80% | 0.05 | 93 | 372 |
| **20%** | 65% | 85% | 80% | 0.05 | 73 | 292 |
| **15%** | 25% | 40% | 80% | 0.05 | 152 | 608 |
| **15%** | 50% | 65% | 80% | 0.05 | 170 | 680 |
| **15%** | 65% | 80% | 80% | 0.05 | 138 | 552 |

[a]Defined as reaching median convalescent serum levels of anti-RBD.

## 10.3 Planned Analyses

The primary outcome will be evaluated at 30 days (1 month ) following the study intervention. Subsequent analyzes will be planned at other time points in the study (3 months, 6 months, and 12 months) following study intervention.

### 10.3.1 Safety Review

Adverse event questionnaires completed following the study intervention will be reviewed continuously with planned safety reviews at 30 days by the Data Safety Monitoring Board.

## 10.4 Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse events that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

## 10.5 Final Analysis Plan

The final analysis plan will be developed by the biostatistician in conjunction with the Principal Investigator. The targeted sample size for this study will be 300 due to feasibility, although a lower number are estimated to be required based upon sample size calculations above, and the final sample size may be adjusted by the Principal Investigator dependent upon study recruitment. If the final sample size is adjusted, a Clinical Trial Amendment will be filed. The proportion of patients receiving BNT162b2 and mRNA-1273 will be reported.

Quantitative Anti-SARS-CoV-2 IgG targeting the spike protein, RBD, nucleocapsid, and neutralizing antibodies will be reported at each time point as relative levels. Descriptive statistics will be used to describe baseline characteristics of patients in all four arms of the study. Mean

and median timing between first, second, and third (booster) vaccine dosage will be reported. Differences in the cell-mediated immunity as measured through flow cytometry on PBMC will be exploratory. Pre-specified clinical outcomes will include COVID-19 infections, COVID-19 related hospitalizations, and death.

### 10.5.1 Statistical Analysis of the Primary Outcome

An intention-to-treat analysis will be followed for the primary outcome. The primary outcome will be the proportion of patients who attain convalescent serum levels of Anti-RBD at 1 month (30 days) following third dose of vaccine. Two Chi-Squared test or Fisher's exact test will be used, one for those who received first two doses of *BNT162b2* and the second for those who received *mRNA-1273* for the first two doses. This study is powered to determine differences between the use of *mRNA-1273* vaccine and *BNT16b2* vaccine as the booster dose on the primary outcome based on a clinically significant difference of 25% as described above in the sample size considerations. An adjusted analysis with logistic regression modelling will be performed if imbalance in baseline characteristics is found to between study groups following stratified randomization. Individuals who develop new COVID-19 infection as determined by a positive Anti-NP serologic test or positive SARS-CoV-2 RT-PCR nasopharyngeal swab during the study will be excluded from analysis of the primary outcome.

### 10.5.2 Statistical Analysis of Secondary Outcomes

Secondary outcomes will include the proportion of patients who attain Anti-Spike median convalescent serum at 1 month (30 days) following third dose of vaccine. Differences in relative antibody levels (Anti-Spike and Anti-RBD) and neutralizing antibodies between study groups will be assessed through the Mann-Whitney test. The relative levels of antibodies will be tracked

longitudinally for each patient permitting analysis of SARS-CoV-2 antibody kinetics following vaccination and will be assessed through a mixed-effects repeated measures model with random intercepts and fixed covariates following log transformation of relative ratios, which will be exploratory. Differences in serial levels in relative antibody levels will be compared through a mixed effects model as above. Similar to the primary outcome, those with a new positive Anti-NP serologic test or COVID-19 nasopharygneal swab during the study will be excluded from analysis. An intention to treat analysis will be followed, although an exploratory per protocol analysis may also be reported.

### 10.5.3 Subgroup Analyses

Pre-specified subgroup analyses will be exploratory and are not included in the sample size calculation and are as follows:

1. Hemodialysis versus peritoneal dialysis patients.
2. Non-dialysis CKD patients.
3. Participants who do not seroconvert following two doses of vaccine.
4. Patients who initially obtain convalescent serum levels but exhibit declining titers.
5. Patients who never attained convalescent serum levels.

## 11 Data Handling and Record Keeping

### 11.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Personal Health Information Protection Act of 2004 (PHIPA) and the Research Ethics Board. PHIPA outlines the rules for the collection, use and disclosure of personal

health information. The Act requires each participant to consent to the collection, use and access of personal health information (PHI), unless consent is waived by the REB. Where consent is required, each participant must be informed of the following:

- What PHI will be collected during this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator may use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period. The study staff may communicate with participants via E-mail. No PHI (Personal Health Information will be communicated via E-mail. E-mail transmission cannot be guaranteed to be secure or error-free as information could be intercepted, corrupted, lost, destroyed, or incomplete. To the best of our abilities, the research team will take the necessary precautions to transmit emails in a secure manner, by using a secure network. To ensure participant confidentiality and safety, all transmitted emails will include the following disclaimer:

This email and any attachments are confidential and may contain privileged or confidential information. If you are not the intended recipient, any transmission, distribution, replicating, or disclosure by you is prohibited and may be illegal and you must not use or rely on this email for any purpose.

## 11.2 Source Documents

Source data/documents are original documents, data and records in a clinical study that are necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to worksheets, hospital records, medical records, memorandum, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments (i.e. ECGs), copies or transcriptions certified after verification as being accurate and complete, participant files and records kept at the pharmacy, entries entered directly into the printed CRF.

The following data points will be recorded directly on the CRFs, and will be considered source data as no prior written or electronic record of data is available: SARS-CoV-2 Antibody Levels, neutralizing antibodies, adverse event questionnaires.

Each participating site will maintain appropriate medical and research records for this study, in addition to regulatory and institutional requirements for the protection of confidentiality of participants. If electronic source data documents are printed it should be signed and dated by the investigator to confirm content and filed with other source documents.

The investigator(s) and research team members listed on the Task Delegation Log (TDL) will have access to participant medical records and will collect only the information needed for the study. Sponsor delegated monitors, representatives of institutional committees and regulatory authority representatives of the country in which the study is being conducted will also have access to examine records for the purposes of quality assurance reviews, audits and evaluation of study safety and progress.

## 11.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study personnel under the supervision of the investigator. All source documents and applicable laboratory reports should be reviewed as needed and used to ensure that data collected for the purposes of the study are accurate and complete. Contemporaneous review of laboratory results and the assessment of clinical significance for those results considered out of range should be documented by means of dated signature by the reviewing investigator. Study personnel, including data entry team members, should use source documents to complete case report forms (CRFs).

As part of the safety plan for this study, the investigator will review individual study participant records to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Participant records include, but are not limited to: consent forms, case report forms, data forms, laboratory specimen records, inclusion/exclusion forms, and medical charts. All study data will be collected by a member of the study research team and recorded in accordance with applicable procedures.

Data in the (COVID-19 Immunity Task Force ) CITF Database may be used by researchers in Canada or in other countries following Data Access Committee (DAC) approval. These transfers will also be made in compliance with Canadian law and research ethics. A DAC will be responsible for reviewing applications for access to data and for approving applications that respect the privacy and access policies of the CITF. The data will be used to perform research concerning COVID-19 and related health outcomes. Data may be used alone or in combination with other data, including other health data. The DAC will ask researchers to confirm that their intended research activities have received necessary ethics approvals. Data may also be shared

with other COVID-19 research databases that follow similar protections and procedures as the CITF Database.

Participation in the CITF Database is not likely to provide a direct benefit to participants' health or well-being. Participation in the CITF will help collect accurate data about COVID-19 immunization that will potentially help in the creation of treatments or otherwise improve the quality of COVID-19 healthcare delivery. No directly identifying information will be provided to the CITF, nor included in the CITF Database. Participants' identifiers, such as name and civic address, will be replaced with a code. By agreeing to participate in this research, patients do not give up any legal rights against the CITF.

## 11.4 Data Capture

### 11.4.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. Electronic/Paper case report forms (eCRFs/pCRFs) will be used to collect data for this study. CRFs are to be completed by data capture personnel and signed off by the investigator in a timely manner. Good documentation practices should be implemented according to standard operating procedures. All data requested on the CRF must be recorded and verifiable by source document.

## 11.5 Records Retention

It is the responsibility of the REB, investigator and regulatory sponsor to retain study essential documents as per local regulatory requirements and GCP Guidelines. Study essential documents must be maintained in a secure and confidential manner for participating Canadian sites for a period of 25 years. For the purposes of this study, the start date of the retention period is the date of the final report of the trial. Exceptions may be made for sites which close prematurely, wherein the start date for the retention period will be the date of notification to Health Canada of the sites closure. Sites conducting this study outside of Canada must maintain study records for the required retention period as stipulated by local regulatory authorities. All study records are then to be destroyed according to local and national policy and requirements. It is the investigator's responsibility to request authorization for destruction at the completion of the retention period and/or for the sponsor to inform the investigator/institution when these documents may be destroyed.

## 11.6 Clinical Trial Registration

In accordance with Health Canada's Notice "Registration and Disclosure of Clinical Trial Information, November 30, 2007", the sponsor will be responsible for registering the study on Clinicaltrials.gov (www.clinicaltrials.gov), a publically available registry that conforms to international standards for registries.

## 12 QUALITY CONTROL AND QUALITY ASSURANCE

As per ICH-GCP and local regulations, the sponsor is responsible for ensuring the implementation and maintenance of systems that support quality assurance and quality control. The study must be conducted in compliance with the study protocol and all data collected must be accurate and verifiable by source document(s). For the purpose of monitoring and auditing by the Sponsor, and inspection by regulatory authorities, the site will provide direct access to all study related source data/documents. The sponsor will verify that the study is conducted and data has been collected, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Data for the study will be centrally stored and managed by the Centre for Clinical Trial Support (CCTS). To ensure the quality of study data, quality assurance and control systems will be implemented using validated electronic quality control checks within the electronic data capture system. These verification measures will identify missing data, inconsistencies and/or data anomalies. Both electronic and manual queries will be generated for resolution and review by sites. Access to secure and validated electronic systems used for the purposes of this study will be controlled by the sponsor. Access will only be granted to individual research team members upon review of training and qualification and authorization by delegation of the investigator.

Quality assurance and control measures will be implemented to ensure training for specific trial–related tasks beyond the usual scope of practice. Only administration of the booster vaccine is considered potentially a study specific procedures requiring additional training, and will be reviewed for documentation of training and/or qualification.

## 12.1 Steering Committee

The steering committee (SC) will include: Dr. Hladunewich, Dr. Yau, Dr. Levin, Dr. Leis, Dr. Bolotin, Dr. Perl and Dr. Chan. The SC will meet once monthly to discuss and emerging scientific or logistical issues related to the conduct of the study.

# 13 ETHICS CONSIDERATIONS

## 13.1 Ethical Standard

The investigator will ensure that this study is conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, and codified in the Tri-Council Policy Statement and/or the ICH E6. The Principal Investigator will be responsible for ensuring that this trial will be conducted in accordance with the protocol, the applicable regulations and guidelines for Good Clinical Practice (GCP), Health Canada's regulations, the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2.0) and the principles in the Declaration of Helsinki.

## 13.2 Research Ethics Board (REB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study, unless to eliminate an immediate hazard

## 13.3 Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Informed consent will be obtained from in-centre hemodialysis patients to participate in this study while they are attending maintenance hemodialysis or via telephone. CKD and home dialysis patients will be consented during clinic appointments or via telephone. A consent form describing in detail the study procedures and risks

will be reviewed with and given to each participant. Consent forms will be REB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The informed consent process could be over the phone or initially verbally obtained, then when the participants present for their first study related visit, they will sign the informed consent form (ICF). Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records.

Prior to involvement in any study-related activities, consent must be obtained in writing for each participant using the current REB approved informed consent from. It is the responsibility of the investigator to ensure that all advertisements and written information, including the informed consent form, disseminated to participants has been approved by the local REB prior to use. The ethics approved Informed Consent Form (ICF) and any other written information, must be provided to each participant, allowing ample time to ask and have answered any questions prior to making a decision regarding participation. Neither the investigator nor study staff should unduly influence or coerce a participant to participate in the study.

The ICF will be signed and dated by the participant and individual obtaining consent. The consent process will be documented in the clinical or research record. The original ICF, in its entirety, will be maintained by the site, and a complete copy of the signed ICF provided to the participant. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The provision of consent is an ongoing process

and should be maintained throughout the duration of the study. Participants may withdraw consent at any time throughout the course of the study. Patients may request access to their study results from their primary nephrologist or the study coordinator. Results will not appear on their electronic medical record. Risks and benefits to participations in the study are outlined below.

### 13.3.1 Benefits

Benefits to participants include the potential for increased immunity following a booster dose of vaccine. Results from this study will provide evidence to help determine whether a booster vaccination may be beneficial in this patient population, if a specific vaccine is more beneficial for boosting, and may inform policy change at the provincial and/or national level for patients with chronic kidney disease.

### 13.3.2 Risks

All potential risks will be explained to the participants. The greatest risks to this study include the possibility for increased reactogenicity or adverse effects following a booster dose of vaccine that may make the patient feel unwell. Larger studies on safety of a third dose are not widely available, but early studies in solid organ transplant patient have demonstrated acceptable tolerability and generally low incidence of severe adverse effects, therefore we expect that this risk will be present but not high. The risk of phlebotomy is low as the blood volume obtained from patients is minimal, and does not require additional blood draws from hemodialysis patients as these blood samples will be collected during routine hemodialysis care through pre-existing vascular access. Peritoneal dialysis and CKD patients have a small risk of bruising due to blood draws.

## 14 PUBLICATION/DATA SHARING POLICY

Given the urgency for timely knowledge dissemination, findings of study will be rapidly submitted for peer reviewed publication. Authorship on study publications will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors. These requirements state “Authorship credit should be based on:

1) Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2) Drafting the article or revising it critically for important intellectual content; and
3) Final approval of the version to be published.

# 15 CONFLICT OF INTEREST

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Oreopoulos/Baxter Home Dialysis Grant is an unrestricted research grant from the Division of Nephrology, University of Toronto and Baxter has no role in the design or conduct of the study.

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## *APPENDICES:*

### *Appendix A: Schedule of Study Assessments for BOOST KIDNEY Protocol*

| **Study Visit** | **Screening for Eligibility and Informed Consent** | **Baseline Study Assessment** | **Adverse Event Questionnaire** | **Serum SARS-CoV-2 Antibodies (Spike, RBD, NP)** (5mL SST Tube) | **SARS-CoV-2 Neutralizing Antibodies** (5mL SST Tube) | **PBMC**(20mL Na Heparin blood) (n=50) | **Vaccine Receipt and Participant Unblinding** |
|---|---|---|---|---|---|---|---|
| Study Enrolment | X | X | | X | | | |
| Prior to Booster | | | | | X | X | |
| Booster Vaccine Administration | | X | | | | | |
| 48 hours-14 days post-booster | | | X | | | | |
| 1 month | | | X | X | X | X | X |
| 3 months | | | | X | | | |
| 6 months | | | | X | | X | |
| 12 months | | | | X | | | |

## *Appendix B : CIOMS FORM*

CIOMS FORM

| SUSPECT ADVERSE REACTION REPORT | |
|---|---|

### I. REACTION INFORMATION

| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH Day | Month | Year | 2a. AGE Years | 3. SEX | 4-6 REACTION ONSET Day | Month | Year | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | ☐ PATIENT DIED<br>☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION<br>☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY<br>☐ LIFE THREATENING |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) | | | | | | | | | | |

### II. SUSPECT DRUG(S) INFORMATION

| 14. SUSPECT DRUG(S) (include generic name) | | 20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA |
|---|---|---|
| 15. DAILY DOSE(S) | 16. ROUTE(S) OF ADMINISTRATION | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA |
| 17. INDICATION(S) FOR USE | | |
| 18. THERAPY DATES (from/to) | 19. THERAPY DURATION | |

### III. CONCOMITANT DRUG(S) AND HISTORY

| 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) |
|---|
| 23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.) |

### IV. MANUFACTURER INFORMATION

| 24a. NAME AND ADDRESS OF MANUFACTURER | | |
|---|---|---|
| | 24b. MFR CONTROL NO. | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL | |
| DATE OF THIS REPORT | 25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP | |