BEEHIVE
Booster Epidemiological Evaluation of Health, Illness and Vaccine Efficacy

# Booster Epidemiological Evaluation of Health, Illness and Vaccine Efficacy (BEEHIVE) Study

*Randomized Trial to Compare the Clinical Efficacy of Novavax vs. mRNA COVID-19 2023-2024 updated vaccines among adults 18-49 and 50+ years in the United States*

**Protocol Version: June 24, 2024**

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# 1. Abstract/Executive Summary

Novavax's (NVX-CoV2373) protein based, novel but traditional immunizations have potential scientific advantages to the population through enhanced cross-reactivity which may facilitate activity against Coronavirus disease 2019 (COVID-19) variants.[1,2] This technology also provides significant safety assurances to those wishing to utilize traditional immunization technology for their vaccination.[3] There are two main challenges thought to largely explain the development of COVID-19 breakthrough infections: combination of variant mutations in the spike protein along with declines in antibodies.[4]

This randomized controlled trial (RCT) is comparing recipients of the 2023-2024 updated COVID-19 vaccines vs. non-recipients and Novavax (NVX) vs. mRNA 2023-2024 updated vaccines. The primary study hypothesis is to compare vaccine efficacy (VE) between participants who receive a 2023-2024 updated vaccine (mRNA or NVX) and participants who are recommended by the Advisory Committee on Immunization Practices (ACIP) to be vaccinated but decline the updated vaccine. The secondary hypothesis is to determine the relative vaccine efficacy (rVE) of the mRNA and the NVX 2023-2024 updated vaccines in preventing SARS-CoV-2 infection to confirm non-inferiority for NVX. This RCT may show evidence of the superiority of a blended vaccination approach of combining vaccines with different platforms.[5]

The trial will be conducted at the University of Utah (UT) Health for the upcoming SARS-CoV-2 virus circulation from Fall of 2023 to Spring of 2024. We aim to enroll 1500 participants who previously received at least two doses of the mRNA COVID-19 vaccine at least 90 days prior to enrollment. Upon enrollment, participants will be asked to describe their intention to receive a COVID-19 2023-2024 updated vaccines or not. Those who decide not to receive a vaccine during the study period will be placed in a non-randomized comparison group (n=300). Participants who intend to get vaccinated (n=1200) will be randomized into the NVX vaccine group or the mRNA vaccine group. Eligible participants will be randomized 1:1 to receive 1-dose of the NVX vaccine versus mRNA vaccine during November 2023 through February 2024. All eligible participants will be stratified by their age and sex within the respective groups.

Study team members who will have direct contact with participants as well as involvement with data collection and analysis will be blinded to the study arm assignment. Designated study staff who are aware of the randomization assignments will manage the logistics of the injections and the preparation of the vaccines but will have no other role in trial conduct. Participants assigned to the vaccinated groups will be blinded to the specific vaccine product which will blind their personal medical providers. All vaccinated group participants will be unblinded as to their study arm assignment upon the completion of all data collection activities.

All participants, both those who do and do not elect to get a 2023-2024 updated vaccine, will be followed with surveillance for COVID-like illness (CLI)-associated SARS-CoV-2 virus infection. Similar to previous studies and CDC's updated list of COVID-19 symptoms, COVID-like illness will be defined as symptoms in the past 7 days: fever, chills, malaise, fatigue, headache, cough, shortness of breath, sore throat, runny nose or nasal congestion, nausea or vomiting, diarrhea, muscle or body aches, and change in smell/taste.[6,7,8] All participants will immediately begin active surveillance activities after their

enrollment visit. During this active surveillance, participants will self-collect respiratory specimens and use home antigen tests for SARS-CoV-2 infection weekly from Fall 2023 to Spring 2024 during the anticipated wintertime SARS-CoV-2 virus circulation, which we estimate to be 24 weeks. Participants will respond to weekly online surveys asking about new onset of CLI symptoms and complete weekly home rapid antigen tests (RATs). For participants who report CLI symptoms or who test positive on their weekly test, they will complete additional home RATs for SARS-CoV-2 virus and will complete follow up questionnaires to provide detailed information about their illnesses. Electronic surveillance and testing will continue to allow each participant to complete 24 weeks of surveillance.

# 2. Investigators

## 2.1 University of Utah

| | | |
|---|---|---|
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## 2.3 Novavax

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|---|---|---|
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## 2.4 Roles

The Investigator/Sponsor of the study is University of Utah (UT). Novavax is providing funding for the study and contributing the Novavax 2023-2024 updated COVID-19 vaccine. Novavax, UT and Westat will collaborate to carry out this study. Novavax will not be involved with human subjects or their identifiable data and will receive a de-identified dataset for analysis at the end of the study. UT is responsible for serving as the IRB of record and entering into an agreement for Westat to rely on UT for human subjects oversight; identifying potential participants, recruiting, screening, consenting, and enrolling study participants; supplying participants with at-home rapid antigen tests for SARS-CoV-2 infection; and coordinating with Westat to implement the study. UT will also oversee all IND submissions, including adverse event reporting. Westat is responsible for assisting UT and Novavax with protocol and study materials development; developing and maintaining an online participant portal and study tracking system; producing weekly dashboards detailing study progress; administering study messages and surveys and providing helpdesk IT support; and serving as the data coordinating center to collect, manage, and prepare to deliver identifiable datasets to UT and de-identified datasets to Novavax.

The Steering Committee (SC) for the BEEHIVE study will provide high level input into this project and sign off on any decisions made. The SC will consist of representative(s) from University of Utah, Westat, and Novavax. The SC will be consulted on over-arching project issues including final protocol decisions, adjudicating any protocol deviations or adverse events that might occur, reviewing and confirming analysis plans, and making final decisions on analyses, manuscripts, and authorship as needed.

# 3. Background

The reduced vaccine effectiveness of COVID-19 vaccines against the B.1.1.529 (omicron) and its sub-lineages indicate a need for new vaccine strategies against emerging SARS-CoV-2 variants. Several studies report the decreasing protection of 2- and 3-doses of Pfizer-BioNTech and Moderna monovalent messenger RNA COVID-19 vaccines (mRNA) against immune evasive omicron and its sub-lineages despite earlier studies demonstrating high vaccine effectiveness against mild disease against ancestral and delta variants.[9-14]

As protection from the monovalent vaccines started to wane and the immune-evasive omicron became the predominant variant in circulation in the U.S., the Food and Drug Administration (FDA) recommended an update to the vaccine strain composition to contain the ancestral SARS-CoV-2 strain component and the omicron BA.4/5 spike protein components. [15] This omicron-containing vaccine is also known as the BNT162b2 (Pfizer-BioNTech) and mRNA-1273.214 (Moderna) bivalent vaccines. As of April 18th, 2023, the FDA announced that the Pfizer-BioNTech and Moderna monovalent vaccines are no longer authorized for use in the U.S. and only a 1-dose of Pfizer-BioNTech and Moderna bivalent vaccine is authorized for use under varying conditions based on age, immune status, and prior vaccination status.[16]

There is limited data on the bivalent vaccines. At the time of bivalent vaccine arrival, the omicron variant BA.1 was no longer circulating in the U.S. and had evolved (e.g. BA.4, BA.5). These mutated strains are reported to have increased transmissibility and evasiveness against vaccine-induced immunity.[9,11,12]

RCTs have yet to report the vaccine efficacy of the bivalent vaccine.[17] Phase 2 and 3 clinical trials report that the bivalent vaccine enhanced neutralizing antibody response and cross-reactivity against multiple variants.[18,19] However, vaccine experts are not unified on their opinion on the efficacy and immunogenicity of bivalent vaccines and their clinical significance in healthy individuals.[20] Large observational studies estimated vaccine effectiveness of bivalent vaccines to be 28-56% in preventing symptomatic disease, 32-54% from preventing medically attended COVID-19 (including emergency department/urgent care encounters, and hospitalizations), 72-74% in hospitalized adults ≥65 years, and 68% for COVID-19 related death in adults ≥65 years.[17,21-23] A large pharmacy and community-based study reported bivalent vaccine effectiveness of 52% and 48% against symptomatic BA.5 and XBB/XBB1.5 infections, respectively.[24] Overall, there are limited studies on the available bivalent vaccines and more information will be needed for the upcoming 2023-2024 updated vaccines and potential considerations for targeted vaccination.

The Novavax NVX-CoV2373 vaccine (NVX) is a traditional protein-based vaccine, which is a novel approach amongst COVID vaccines. The vaccine has been available in the U.S. since July 2022, and has been shown to be efficacious and safe in RCTs. Instead of the mRNA platform, Novavax uses traditional vaccine technology which consists of recombinant spike (rS) proteins of the SARS-CoV-2 virus and a saponin-based adjuvant, Matrix-M that assists with immune system's response to the spike protein.[25] One phase 2a—b trial in South Africa reported preliminary results of 49% vaccine efficacy during the predominant circulation of the B.1.351 variant in their region with majority of infections as mild-moderate COVID-19.[26] Three phase 3 trials of healthy and medically stable adults in the U.S., U.K., and Mexico sites demonstrated that a 2-dose series of NVX had approximately 83-90% vaccine efficacy against any severity COVID-19 and 79-100% efficacy against moderate-to-severe COVID-19 during periods prior to high circulation of omicron.[27-29] Interestingly, the UK cohort found vaccine efficacy was 76% against laboratory confirmed asymptomatic infections, which was higher than other vaccine types.[29] In a phase 2 immunogenicity trial a third and fourth monovalent dose (administered in 6-month intervals from last dose) resulted in cross-reactive immunity to SARS-CoV-2 variants with enhanced neutralization against omicron and its sub-lineages with a third dose.[1,30] A phase 2 heterologous study of COVID-19 vaccines in the UK had NVX administered after primary series of ChAdOx1nCoV-19 AstraZeneca) or BnT162b2 (Pfizer-BioNTech) and found increased antibody and neutralization activity.[31] A phase 2 homologous study in the US and Australia administered NVX as a first additional dose 6 months after a 2-dose series of NVX found enhanced immunogenicity.[32]

The FDA designated Emergency Use Authorization to the monovalent NVX vaccine on July 13, 2022, for prevention of COVID-19 in adults 18 years and older. In October 2022, FDA and CDC recommended the monovalent NVX vaccine as a first additional dose under conditions where the patient is unable or unwilling to receive a mRNA bivalent vaccine.[33,34] As of October 2023, Pfizer-BioNTech, Moderna, and Novavax COVID-19 vaccines (2023-2024 formula) have been recommended by the CDC for use in the United States.[35] The 2023-2024 updated COVID-19 vaccines targets the XBB lineage of the Omicron variant. The Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines (2023-2024 formula) are FDA-approved, and the Novavax COVID-19 vaccine (2023-2024 formula) is FDA-authorized for use in the United States.

Having multiple vaccine platforms may help maintain robust immunity and increase access and uptake of vaccines. Though the mRNA vaccines are the dominant option in the U.S., the Johnson & Johnson's Janssen (J&J/Janssen) COVID-19 vaccine single dose viral vector vaccine was initially approved for primary vaccination but now is limited use due to risk of serious adverse events (e.g. recommended to use in cases of severe allergic reaction to mRNA vaccines).[33] The addition of the Novavax vaccine to the portfolio of vaccines may be an additional tool to protect against variants. In addition to its high efficacy against symptomatic disease and an acceptable safety profile similar to other vaccine types, it has demonstrated effectiveness against asymptomatic infections which may be important to control transmission, the logistical benefit in areas where maintaining freezing temperatures is difficult (NVX is stable at refrigerated temperatures 2 to 8$^{o}$C), as well as the utilization of traditional technology which may increase uptake in those hesitant on newer platforms and its side effects, and be a resource in case of supply shortages.[36]

Currently, clinical trials have reported minimal vaccine efficacy data on the available COVID-19 vaccines that are given as additional doses to the primary series and results available on effectiveness data are from a handful of large observational studies which suggests further investigation is needed on the upcoming variant-specific vaccines and heterologous vaccines. The objectives of this study are to compare, in participants 18-49 years and 50+ years and previously vaccinated with at least 2-doses of mRNA vaccine, the vaccine efficacy of the Novavax COVID-19 vaccine, adjuvanted, 2023-2024 formula (monovalent, Omicron XBB.1.5 containing) (NVX) or Pfizer-BioNTech COVID-19 vaccine, mRNA 2023-2024 formula (monovalent, Omicron XBB.1.5 containing) (mRNA) to those who decline a 2023-2024 updated vaccine and to determine the relative vaccine efficacy between the mRNA and NVX updated vaccines. Also, this study would be the first real-world efficacy trial on the mRNA and the NVX 2023-2024 updated vaccines. Furthermore, the study will also be able to compare protection of heterologous and homologous schedules of mRNA and NVX updated vaccines.

## 3.1 Abbreviations

| | |
|---|---|
| AEFI | Adverse Events Following Immunization |
| BEEHIVE | Booster Epidemiological Evaluation of Health, Illness and Vaccine Efficacy |
| CLI | Covid-like Illness |
| COVID-19 | Coronavirus disease 2019 |
| CRSO QA | Clinical Research Support Office Quality Assurance Group |
| CTSI | Utah Clinical & Translational Science Institute |
| DUA | Data Use Agreement |
| EUA | Emergency Use Authorization |
| EW | Essential workers |
| FAQs | Frequently Asked Questions |
| FDA | U.S. Food and Drug Administration |
| FR | First responders |
| HCP | Healthcare personnel |

| | |
|---|---|
| HIPAA | Health Insurance Portability and Accountability Act |
| IIS | Immunization Information System |
| IRB | Institutional Review Board |
| J&J/Janssen | Johnson & Johnson's Janssen |
| KAP | Knowledge, attitudes, and practices |
| mRNA | Messenger RNA |
| NVX | Novavax |
| PCC | Post-COVID Conditions |
| PPE | Personal Protective Equipment |
| PROTECT | Pediatric Research Observing Trends and Exposures in COVID-19 Timelines |
| QA/QC | Quality Assurance and Quality Control |
| RAIVEN | Randomized Participant- and Investigator-Blinded Trial to Compare the Clinical Efficacy of Recombinant Influenza Vaccine to Standard Dose Egg-Based Inactivated Influenza Vaccine among Adults Aged 18-64 Years in the United States |
| RAT | Rapid Antigen Test(s) |
| RCT | Randomized Controlled Trial |
| RECOVER | Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel |
| rS | Recombinant Spike |
| RT-PCR | Real time Reverse Transcription Polymerase Chain Reaction assay |
| rVE | Relative vaccine efficacy |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SMART | Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform |
| SMS | Short message service |
| US | United States |
| USIIS | Utah Statewide Immunization Information System |
| UT | University of Utah |
| VE | Vaccine efficacy |

# 4. Objectives

## 4.1 Primary Objectives

1. Compare the VE between participants who receive a single dose of Novavax (NVX) vaccine (Novavax COVID-19 Vaccine, Adjuvanted, 2023-2024 formula (monovalent, Omicron XBB.1.5 containing)) or mRNA vaccine (Pfizer-BioNTech COVID-19 Vaccine mRNA, 2023-2024 formula (monovalent, Omicron XBB.1.5 containing))) and a group of non-randomized participants who are recommended to be vaccinated by CDC/ACIP but decline the updated vaccine to prevent CLI-associated SARS-CoV-2 infection, confirmed by COVID-19 rapid antigen test (RAT).
2. Determine the relative vaccine efficacy (rVE) of a single dose of NVX vaccine (Novavax COVID-19 Vaccine, Adjuvanted, 2023-2024 formula (monovalent, Omicron XBB.1.5 containing)) and a single dose of the mRNA vaccine (Pfizer-BioNTech COVID-19 Vaccine mRNA, 2023-2024 formula (monovalent, Omicron XBB.1.5 containing))) to prevent CLI-associated SARS-CoV-2 infection,

confirmed by COVID-19 RAT, to confirm non-inferiority for NVX.

## 4.2 Secondary Objectives

1. Evaluate the effect of prior number of doses of COVID-19 vaccination during the preceding 3 years on the relative efficacy of a single dose of NVX.
2. Assess the vaccine efficacy against asymptomatic or any (asymptomatic or symptomatic) RAT-confirmed SARS-CoV-2 infections.
3. Examine the individual, occupational, and environmental predictors of SARS-CoV-2 infection and compare these predictors between asymptomatic infection versus symptomatic COVID-19 illness.
4. Describe the clinical characteristics and outcomes associated with COVID-19.[37]
    a. Determine the duration and severity of illness and examine the socio-demographic and health characteristics associated with prolonged or severe illness.
    b. Determine the impact of COVID-19 on indicators of functioning, including missed work, ability to complete normal work and home activities, and working while ill.
    c. Determine the proportion of COVID-19 illnesses that are medically attended and examine the factors associated with seeking medical care and treatment.
5. Compare illness characteristics and duration with primary vs. re-infection with SARS-CoV-2 during the study window.
6. Examine if VE is modified by socio-demographic characteristics, occupation, health status, or other risk factors.
7. Examine if 2023-2024 formula (monovalent, Omicron XBB.1.5 containing) vaccines modifies illness severity and duration among participants with breakthrough infection despite vaccination.
8. Assess the incidence of post-COVID conditions (PCC) and factors associated with PCC symptoms.
9. Determine if PCC symptoms differ among vaccinated and participants who decline the 2023-2024 updated vaccine.
10. Determine if PCC symptoms are modified by vaccination status (e.g. 2-, 3-, and 4+ doses) prior to infection.
11. Characterize the knowledge, attitudes, and practices (KAPs) of participants related to new COVID-19 2023 vaccine variant vaccines and examine the associations between KAP and subsequent vaccination behaviors (including vaccine refusal, hesitancy, or incomplete adherence to vaccination recommendations).

# 5. Methods

## 5.1 Overview of Study Design

Approximately 1,500 adults 18 years and older from Salt Lake City, UT and surrounding areas (60-mile radius) will be enrolled in a randomized trial to be followed until Summer 2024. This trial will employ a stratified recruitment approach to ensure there is sufficient variability in sex and age within the cohort. For those that are in the intervention group, their randomization occurs at their vaccination appointment. Information on socio-demographics, employment information, occupational responsibilities, exposure to SARS-CoV-2 virus, history of SARS-CoV-2 infection, COVID-19 and flu vaccine history, health status and conditions, PPE use, pre-vaccination intention, and knowledge and attitudes about SARS-CoV-2 infection control practices will be collected by self-report through an enrollment survey. Information on previous COVID-19 vaccination history and concomitant medications will be collected at enrollment by study staff.

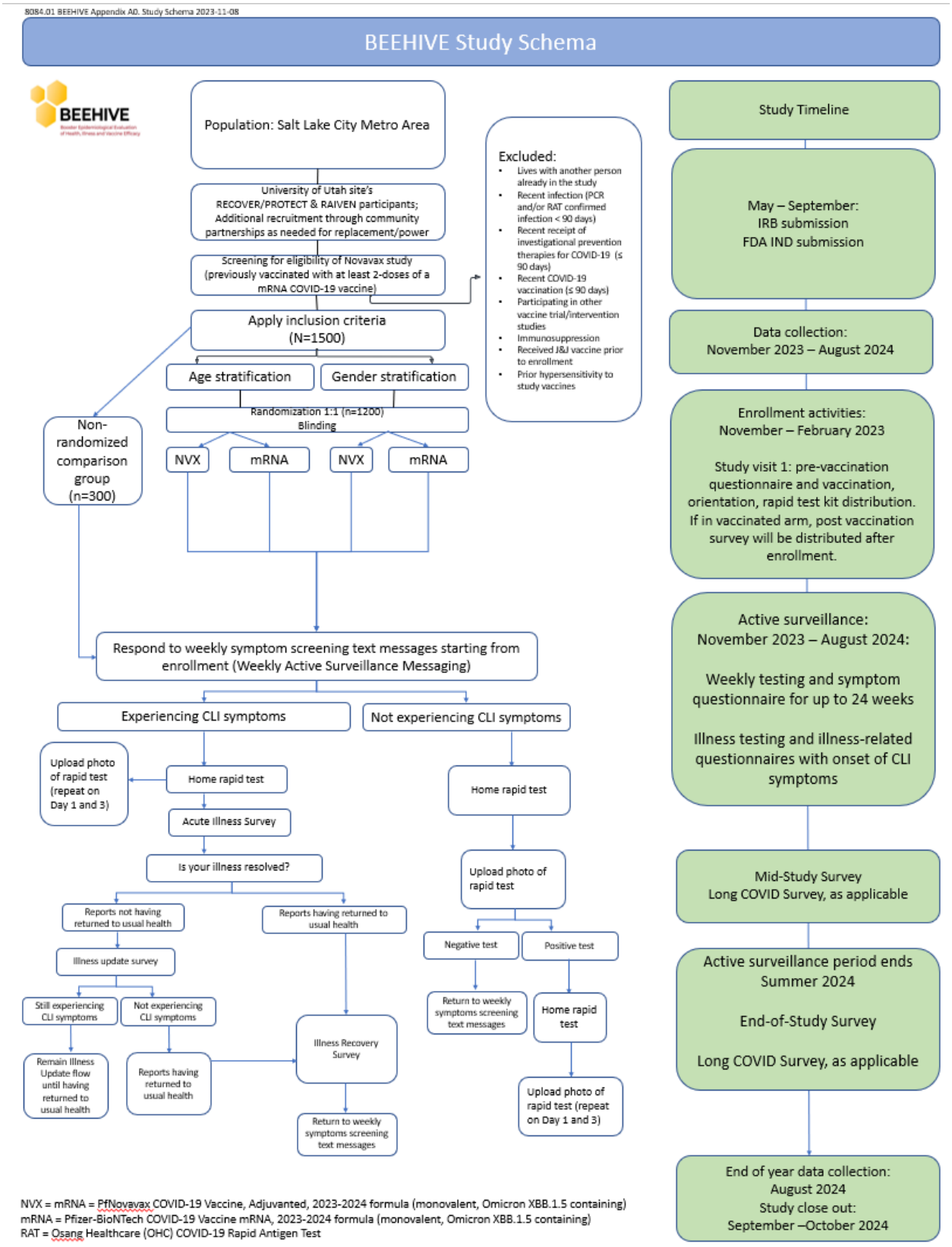
Following participant enrollment, active surveillance will be conducted weekly to identify acute illness symptoms via secure short message service (SMS) text messages. Participants will also be asked to proactively notify study staff if they develop symptoms during the week. To determine acute illness, participants will be asked if they developed subjective COVID-like illness (CLI) symptoms since the day of their last scheduled surveillance. CLI symptoms include fever, chills, malaise, fatigue, headache, cough, shortness of breath, sore throat, runny nose or nasal congestion, nausea or vomiting, diarrhea, muscle or body aches, and change in smell/taste. Each week, regardless of symptoms, participants will self-test with an at-home COVID-19 rapid antigen test (RAT) and upload a photo of the results to the database platform. When an acute illness and/or a positive COVID-19 test is identified, participants will self-test with an at-home COVID-19 antigen test on day 0, day 1, and test again on day 3. When illnesses are identified, participants will describe their symptoms, illness severity, duration, impact on functioning through resolution of their illness, and report any treatments/interventions and medical visits for SARS-CoV-2 infection.

All participants will be asked to complete additional brief surveys, such as asking KAP and vaccine-intention related questions prior to vaccine availability, obtaining influenza or non-study SARS-CoV-2 vaccine documentation post-vaccination, updating information on participant health, work responsibilities, and attitudes and practices associated with infection control and prevention measures, reporting PCC symptoms at enrollment, mid-study, and end of the study time points. Appendix Q provides an overview of the study activities described above. Figure 1 provides a schematic of the study components (Appendix A0. Study Schema).

**Appendix Q. Schedule of Activities**

| **Study Period** | **Screening** | **Full enrollment** | **COVID-19 circulation** | | **Study End** |
|---|---|---|---|---|---|
| | | | | | |
| Approximate calendar month | Nov 2023-Feb 2024 | Nov 2023-Feb 2024 | Fall 2023-Summer 2024 | | Sep-Oct 2024 |
| Study week | <=8 | 0 | 1 | 26 | |
| Study day | -62 to -1 | 0 | 7 | 182 | |
| Acceptable window (days) | | 0 | 6-9 | 180-190 | |
| | | | | | |
| **Eligibility Assessment (Inclusion/Exclusion)** | **X** | **X** | | | |
| **Consent** | **X** | **X** | | | |
| **Enrollment questionnaire** | **X** | **X** | | | |
| | | | | | |
| **Enrollment visit** | | | | | |
| Pre-Vaccination Questionnaire* | | **X** | | | |
| Randomization* | | **X** | | | |
| Vaccination (participant and investigators blinded; vaccination staff unblinded) * | | **X** | | | |
| Rapid test kit distribution and instruction review | | **X** | | | |
| | | | | | |
| **Surveillance** | | | | | |
| Post Vaccination Survey* | | **X** | | | |
| Weekly rapid test self-collection and uploading digital photo of results | | | **X** | | |
| Weekly text or email screening questions | **X** | **X** | **X** | | |
| Illness rapid test self-collection and uploading digital photo of results (Day 0, 1, 3) | | | **X** | | |
| Acute illness, update, and recovery questions | | | **X** | | |
| Mid-Study survey | | | **X** | | |
| Long COVID survey | | | **X** | | **X** |
| Follow-up of non-responsive participants | | | **X** | | **X** |
| SARS-CoV-2 results reporting per local requirements | | | **X** | | **X** |
| Rapid test kit replenishment (as needed) | | | **X** | | |
| | | | | | |
| **COVID-19 vaccine verification for preceding 3 years** | | | | | **X** |
| **End-of-Study survey** | | | | | **X** |
| **End-of-Study vaccine status unblinding*** | | | | | **X** |

**Figure 1. Schematic of Major Study Components (Appendix A0)**



## 5.2 Study Population

**Study Population:** Individuals aged 18 years and older who: 1) reside in Salt Lake City, Utah and surrounding areas and 2) have previously received at least 2-doses of mRNA COVID-19 vaccine before joining the trial. Those from the greater Salt Lake City community partners, including participants from previously established cohorts who have consented to be contacted for future studies, will be invited to participate in the trial. The use of existing cohorts of college and graduate students, healthcare personnel (HCP), first responders (FR), and other essential workers (EW) has several advantages:

- We will only contact individuals from previous studies who gave permission to re-contact them about future studies. These studies include: the 2020-2023 "Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER)" study; the 2021-2022 "Pediatric Research Observing Trends and Exposures in COVID-19 Timelines (PROTECT)" study; and the 2022-2023 "Randomized Participant- and Investigator-Blinded Trial to Compare the Clinical Efficacy of Recombinant Influenza Vaccine to Standard Dose Egg-Based Inactivated Influenza Vaccine among Adults Aged 18-64 Years in the United States (RAIVEN)" study. Given their existing relationship with the research team, we anticipate these participants will be more likely to agree to participate.
- Enrollment of many participants within the same work facility and/or community facilitates estimation of incidence among individuals with similar exposures.
- Recruitment from closed systems such as healthcare facilities opens the opportunity to calculate participation rates and examine potential participation biases related to age, gender, occupation, location, or other basic socio-demographic information.
- Vaccination status for some participants can be documented via a review of existing study records or other vaccine registries.

**Study Duration:** Study activities will commence following Institutional Review Board (IRB) approval. We aim to begin recruitment activities, i.e., identifying and screening potential participants, in November 2023. We anticipate initiating enrollment in November 2023 and start data collection immediately after enrollment. The vaccine campaign is estimated to begin in November 2023 and end in February 2023. All participants will start active surveillance immediately following their enrollment visit. Participants will complete all surveillance activities for a total of 24 weeks from the date of enrollment/vaccination. Surveillance activities are estimated to end Summer 2024. Close-out activities will begin in September 2024.

## 5.3 Eligibility Criteria

Inclusion criteria

- Age ≥18 years
- Previously received ≥ 2-doses of US FDA-authorized mRNA vaccines
- Comfortable reading and responding to text messages and emails sent in English or having an interpreter assist them
- Plan to remain in the greater Salt Lake City area for the next 12 months
- Daily access to the internet (via cell phone, laptop, desktop, or tablet) and a phone with text messaging capabilities

- Willingness to complete weekly symptom and illness surveillance surveys sent via text and email
- Willingness to complete an online survey at enrollment, mid-study, and end-of-study surveys
- Willingness to be contacted periodically by study staff via text, email, and/or telephone as part of study activities
- Willingness to self-collect rapid antigen tests (RAT; approved by FDA EUA for COVID-19 detection) weekly and when prompted for study purposes, and to send results via the study portal
- Willingness to self-collect additional rapid antigen test (approved by FDA EUA for COVID-19 detection) if experiencing a qualifying symptomatic illness or upon RAT-confirmation of an asymptomatic infection
- Willingness to attend in-person visit to receive supply of rapid antigen tests and training on their use (all participants) and to receive a COVID-19 2023-2024 updated vaccine (if in randomized group)

Exclusion criteria

- Lives with another person who is already enrolled in this study as reported by the subject on the Eligibility Survey (Appendix C. Eligibility Survey)
- Previous hypersensitivity reaction to COVID-19 vaccines as reported by the subject on the Eligibility Survey (Appendix C. Eligibility Survey)
- Recent COVID-19 infection [Real time Reverse Transcription Polymerase Chain Reaction assay (RT-PCR) and/or RAT confirmed infection ≤ 90 days of trial vaccine administration
- Receipt of a COVID-19 vaccine within ≤ 90 days of trial vaccine administration
- Participation in other vaccine or investigational product trials
- Medical history of immunosuppression
- Receipt of J&J vaccine prior to study enrollment
- Receipt of any investigational prevention therapies for SARS-CoV-2 infections, such as prophylactic antiviral medications or other immune system modifying interventions within ≤ 90 days of trial vaccine administration
- Unwillingness to provide electronic consent
- Unwillingness to self-report occupation, work responsibilities, and prior COVID-19 illness.

Withdrawal criteria

- As deemed necessary by the principal investigator for noncompliance or other reasons.
- Withdrawal of consent.

Discontinuation criteria

- Termination of study

## 5.4 Recruitment

Recruitment and attrition prevention activities will occur at the trial site. This trial will employ a stratified recruitment approach to ensure there is sufficient variability in sex and age. This approach will open the opportunity to improve the ability to compare the non-randomized comparison group and the vaccinated groups. This systematic approach is also intended to minimize convenience sampling, which can introduce known and unknown biases.

The study will use a combination of methods to recruit adults in the 18-49 age group and 50+ age group, including engagement of previously established cohorts that have consented to be contacted for future studies, such as RECOVER, PROTECT, and RAIVEN.

To reach potential participants within the study catchment area, the recruitment team will also engage in the following outreach activities: joining occupational health vaccination campaigns and other existing mass-vaccination outreach events; advertising through social media and local news outlets (Appendix A1. Recruitment Ad); sharing flyers (Appendix A2. Recruitment Flyer); holding booths at community events; hosting community vaccination stations; collaborating with Community Faces of Utah to engage communities of color (to approximate the racial and ethnic composition of Utah based on census data); and partnering with University of Utah Health, community clinics, Utah businesses, senior centers, and local fire and police departments.

Utah ranks #27 for percent of the population who received a COVID primary vaccine series (62.2%) demonstrating good balance of potential participants. The study will monitor the recruitment rate of both vaccinated and non-vaccinated participants on a weekly basis. If recruitment of the non-vaccinated group is lagging behind the other arms, the study team will consider the following: 1) adding additional venues that may have people who are less likely to want to receive an updated vaccine, 2) modify recruitment advertisements and language to stress recruitment in this group, 3) provide more flexible scheduling and locations, 4) partnering with healthcare providers, 5) receiving and implementing iterative feedback to identify barriers and improve recruitment process, and 6) cultivate transparency and trust-building among these particular subsets of the population.

### 5.4.1 Identify Potential Participants

A brief, online pre-screening interest survey (Appendix A3. Pre-Screening Interest Survey) will be offered to potential participants from the previous study cohorts and to interested individuals during the outreach activities, though this survey will not be required. Through these efforts, we will produce a list of all potential participants for internal site-specific use to identify interested participants.

Recruitment efforts will focus on achieving a minimum number of participants by age group and sex to ensure representation of each group (Table 1. Illustration of Recruitment Goals by Strata). Aggregate counts of potential participants will be recorded in the database platform to track invitations, acceptance, and refusal counts.

**Table 1. Illustration of Recruitment Goals by Strata**

| | Female | | Male | |
|---|---|---|---|---|
| | Ages 18-49 | Ages 50+ | Ages 18-49 | Ages 50+ |
| Randomized vaccinated group (N=1200) | ≥300 | ≥300 | ≥300 | ≥300 |
| Non-randomized comparison group (N=300) | ≥75 | ≥75 | ≥75 | ≥75 |

### 5.4.2 Screening

In accordance with the recruitment approach detailed above, study staff will email (Appendix B. Invitation Email) or share a link to the study website with potential participants to invite them to complete an online eligibility survey to determine whether they meet the inclusion/exclusion criteria (Appendix C. Eligibility Survey). Study staff will contact potential participants who do not respond up to two times. The end of the survey will communicate individuals' eligibility status.

### 5.4.3 Informed Consent

Following completion of the eligibility survey, potential participants who are deemed eligible for the study will be prompted to read and electronically sign the consent and HIPAA authorization form (Appendix D. Consent HIPAA Form) from the study website. The electronic signature and date will be maintained in the study database. The electronic consent form will explain study details, risks, and benefits and emphasize the voluntary nature of participation. A list of Frequently Asked Questions (FAQs) (Appendix E. FAQs) will also be available on the study website. Participants can call to ask questions about the consent process by calling/texting (801) 203-0320 and/or emailing BEEHIVEStudy@utah.edu at any time prior to their in-person enrollment visit. Next, participants who electronically sign the consent and HIPAA authorization form will enter their contact information, create a study portal account, complete the enrollment survey, and schedule an in-person enrollment visit. A copy of the consent form with the participant's e-signature will be available on the participant's dashboard.

When participants check-in for their in-person enrollment visit, participants will have the opportunity to ask questions and discuss the consent and HIPAA authorization form with the study with staff. If they are interested in joining the study, the study staff will download the consent form with the participant's e-signature and co-sign the form. Participants will be given a copy of the signed document and a copy will be kept on file with the research team.

This consent will include authorization to provide the following:

- Permission to be contacted for completing acute illness surveillance and study surveys.
- Self-collected respiratory specimens using rapid antigen tests, as appropriate for SARS-CoV-2 detection in accordance with FDA guidance and approval.

- Participants who elect to be in the vaccinated group give permission to be randomly selected to receive the Novavax or mRNA COVID-19 2023-2024 updated vaccines.
- Permission to retrieve applicable COVID-19 and flu immunization records, as available in the state immunization registry, Utah Statewide Immunization Information System (USIIS).

The consent also informs potential participants that confirming their COVID-19 and flu vaccination history may be accomplished by checking records from previous participation in other COVID-19 or flu vaccine studies. This may apply to participants recruited from the University of Utah in the 2020-2023 cohort studies titled RECOVER, PROTECT, and RAIVEN.

## 5.5 Data Collection

Most research activities will occur through electronic communications (email, text, and internet-based surveys), telephone contacts, or via postal or express mail. All surveys are designed to be self-administered electronically and online (via cell phone, laptop, desktop, or tablet). In-person contacts will occur as needed to train participants for respiratory self-swab specimen collection procedures and for the administration of a COVID-19 vaccine, if in the vaccinated group, by licensed study staff. For participants in prior research studies at the University of Utah, additional data collection of demographic characteristics, medical history, medical utilization, clinical SARS-CoV-2 and influenza lab testing results and vaccination history will be accessed through records from prior studies, in accordance with the consent forms from those studies.

### 5.5.1 Enrollment Activities

#### 5.5.1.1 Enrollment Survey

Those who electronically sign the consent and HIPAA authorization form to join the study will receive a follow up email and text asking them to complete an enrollment survey (Appendix F. Enrollment Survey) and schedule an in-person enrollment visit. Participants are required to complete the enrollment survey in order to be able to schedule the enrollment visit.

The Enrollment Survey can be completed on a computer, tablet, or mobile phone, and will assess the following through self-report:

- Socio-demographic characteristics (sex, age, race, ethnicity, marital status, household composition, and socio-economic status)
- Health status and behaviors (smoking history, self-rated health, and sleep quality)
- Occupation status and employment history
- Self-reported chronic medical conditions (for participants without medical records)
- Self-reported COVID-19 and influenza vaccination history
- Participants who enter the study with a previous SARS-CoV-2 infection (identified by self-report at enrollment) will receive questions to gather information on symptoms and illness

#### 5.5.1.2 Orientation and Test Kits

At the enrollment visit, study staff will verify that the participant has read and understood the consent and HIPAA authorization, that they have had all of their questions and concerns about the study

answered, and that they have consented to participate. Participants who indicated on the consent form that they agreed to receive a 2023-2024 updated COVID-19 vaccine will receive one of the two COVID-19 vaccines at random. All participants, regardless of whether they receive the COVID-19 vaccine, will receive a supply of at-home rapid antigen test (RAT) kits and get set up for completing future online study surveys in the study portal. Participants will receive enough supplies for weekly and illness specimen collection during the active surveillance period. Participants will also receive written and/or visual detailed instructions for using the RATs and uploading test results to the study portal. If additional testing supplies are needed, participants may contact the study team to request that supplies be mailed to them.

The study will provide all participants with the OSANG Healthcare (OHC) COVID-19 Antigen Self Test. The OHC COVID-19 Antigen Self Test is the sole test for the study. The OHC Self Test is authorized for non-prescription of home use with self-collected anterior nasal swab samples from individuals 14 years or older.[38]

### 5.5.2 Active Surveillance for Acute Illness

Surveillance for acute illness will be conducted throughout the study period.

Participants will be prompted to begin active surveillance immediately following their enrollment visit. The participant dashboard will contain video instructions reminding them about how to store the RATs, self-collect the nasal specimen, interpret the results on the cassette (Table 2. Interpretation of results based on status of first day of testing), and submit their results. A contact number and email address will be provided to call, text, or email with questions or to talk to a study staff member.

To determine acute illness, participants will be asked if they developed subjective COVID-like illness (CLI) symptoms since the day of their last scheduled surveillance. The primary means for detecting acute illnesses during the study period will be through a Weekly Active Surveillance system (conducted in English) using a text message platform. The online surveys for weekly surveillance, specimen collection and self-testing, and illness assessments, are outlined in Appendix G1: Surveillance and Illness Messaging Surveys. These are also illustrated in Appendix G2. Messaging and Survey Flow Diagram. Procedures for capturing weekly surveillance will include SMS response, a link to a response-specific online survey, spontaneous reporting of CLI symptoms by participants clicking a button on their participant dashboard, or in special circumstances, an email or phone call may be used as well. Each week, all participants will be contacted to ascertain the development of symptoms and be reminded to collect a weekly specimen and upload the photo of the RAT result (Appendix G1: Surveillance and Illness Messaging Surveys). Participants will have an assigned routine day for communication and specimen collection and self-testing.

CLI will be defined as an episode that includes at least one subjective (i.e. participant-reported) CLI symptoms. Specifically, the participant is asked if they have experienced one or more of the following CLI symptoms in the past 7 days:

- Fever
- Chills
- Malaise

- Fatigue
- Headache
- Cough
- Shortness of breath
- Sore throat
- Runny nose or nasal congestion
- Nausea or vomiting
- Diarrhea
- Muscle or body aches
- Change in smell or taste

If a participant reports they are not ill, they will be asked 1-4 additional questions and be reminded to submit their weekly self-test results (Appendix G1: Surveillance and Illness Messaging Surveys).

An acute illness can be identified by responding/selecting "Yes" to CLI symptoms in the past 7 days question on the Weekly Messaging Survey or reporting their symptoms on the Acute Illness Survey which will be posted in the participant dashboard. If a participant develops an acute illness in between their designated days for weekly surveillance contacts, Acute Illness Survey will be posted in the participant dashboard for the participant to launch the survey (Appendix H: Acute Illness Survey).

Once an acute illness is identified, participants will be asked to identify qualifying symptoms from a more detailed symptom checklist, confirm date of onset, and if symptoms are still ongoing (Appendix H: Acute Illness Survey). If the participant does not confirm CLI symptoms, they will return to weekly surveillance. If the symptoms are currently ongoing, participants will be prompted to collect a specimen using the Illness Specimen Kit (Appendix G1: Surveillance and Illness Messaging Surveys), rapid antigen test for COVID-19 and submit results per study procedures. Regardless of illness, participants should collect their weekly surveillance specimen on their assigned day. If the participant reports illness and/or collects the Illness Specimen Kit on their assigned routine specimen day or outside their assigned day (Day 0), they will be asked to collect a 2$^{nd}$ specimen on the next day (Day 1) and a 3$^{rd}$ specimen on Day 3 in order to confirm the results of the rapid test. Participants will be asked to upload a digital photo of the results of the 2$^{nd}$ and 3$^{rd}$ rapid test as well.

In the informational materials provided to the participant and on the participant dashboard, there will be a instructions on how to interpret their test results. For this study, the interpretation of results (Table 2: Interpretation of results based on status of first day of testing) is based on the participant's status on the first day of testing (e.g. asymptomatic or has CLI symptoms). If a participant does not have any CLI symptoms and tests negative on their weekly test, they do not have to perform a retest. If a participant is asymptomatic but tests positive on their weekly test and they then test positive either on day 1 or day 3, they are considered a positive COVID-19 case. If a participant is asymptomatic or has non-CLI symptoms and tests positive but two subsequent tests are negative, then this is considered a false positive. If a participant is symptomatic with CLI symptoms, any positive result is considered a positive COVID-19 case. To be considered a true negative case, all three tests must result as negative.

**Table 2. Interpretation of results based on status of first day of testing**

| Status on First Day of Testing (Day 0) | Result Day 0 | Result Day 1 | Result Day 3 | Interpretation | IT team |
|---|---|---|---|---|---|
| Has CLI Symptoms | Positive | Positive | Positive | Positive for COVID-19 | If a participant is symptomatic, any positive result is considered a positive COVID-19 case. To be considered a true negative case, all three tests should be negative. |
| | Negative | Positive | Positive | Positive for COVID-19 | |
| | Negative | Negative | Positive | Positive for COVID-19 | |
| | Negative | Positive | Negative | Positive for COVID-19 | |
| | Negative | Negative | Negative | Negative for COVID-19 | |
| Without Symptoms | Positive | Positive | Positive | Positive for COVID-19 | If a participant is asymptomatic and they test positive either 2nd or 3rd, they are considered a positive COVID-19 case. |
| | Positive | Negative | Positive | Positive for COVID-19 | |
| | Positive | Positive | Negative | Positive for COVID-19 | |
| | Positive | Negative | Negative | Negative for COVID-19 | False positive |
| | Negative | N/A | N/A | Negative for COVID-19 | If a participant does not have any CLI symptoms and tests negative on their weekly test, they do not have to perform a retest. |

Weekly messaging for ill participants will be modified to assess continuing illness, ability to conduct normal activities, and a reminder to contribute their weekly specimen. This message will continue every week until the participant reports they are no longer experiencing illness symptoms or until a new unrelated illness is reported. A new illness would be identified as a new onset of CLI symptoms and/or positive rapid test greater than 90 days from the previous illness and/or infection.

Participants who report continuing illness symptoms on the first weekly messaging that is ≥7 days after illness onset will be asked to complete the Illness Update Survey (Appendix I: Illness Update Survey) which assesses symptom onset and severity for this persistent illness.

Once the participant reports they are no longer experiencing illness symptoms, participants will also be prompted to complete the Illness Recovery Survey (Appendix J) via web-survey to assess symptoms and additional illness information. Until a participant reports ≥90% recovery progress, the weekly Follow-Up Messaging Survey will continue to ask about recovery progress (Appendix G1). Once a participant reports ≥90% recovery, the weekly messaging will return to the standard questions in the Weekly Messaging Survey (Appendix G1).

As a measure of response rate to the weekly routine surveillance contacts, research staff will track and report:

- The response rate to symptom screening messaging, defined as the proportion of weeks for which the participant provided an appropriate number of valid responses.
- The adherence rate to digital photo submission of results during periods of SARS-CoV-2 virus circulation as the proportion of weeks for which the participant provided an appropriate number of valid photos.
- The adherence rate to illness messaging and digital photo submission of results during period of illness defined as the proportion of reported CLI episodes during which the participant collected and submitted their results.

### 5.5.3 Vaccination

**Enrollment visit**

- Participants who elect to get the 2023-2024 updated COVID-19 vaccine will be able to self-schedule a future vaccination visit immediately after they have given consent. Study staff will confirm their appointment approximately 7-14 days before the start of study vaccine administration if participants are enrolled before study vaccine is available on site. Participants will be able to re-schedule or cancel appointments using the self-scheduling application. Participants may “walk-in” to vaccination sites and complete pre-vaccination activities on the same day as vaccination. At the vaccination visit, study staff will complete a brief questionnaire to determine if a COVID-19 vaccine can be given (Appendix K. Pre-Vaccination Questionnaire) to the participant. If it is determined that administration of the COVID-19 vaccine may need to be delayed a follow-up appointment will be made. Participants will have the option at this visit of changing their minds and participating in the non-vaccinated arm of the study if they wish and if there is still space available.

- Participants who decline to get the 2023-2024 updated COVID-19 vaccine but consent to take part in the study will also come in for the enrollment visit. These participants will be able to self-schedule their Study Visit immediately after they have given consent. Study staff will confirm their appointment approximately 7-14 days before their enrollment visit. Participants will be able to re-schedule or cancel appointments using the self-scheduling application. Participants

may “walk-in” to vaccination sites and enroll in the study even if they decline to get the vaccine. At the enrollment visit, study staff will distribute weekly and illness surveillance kits and provide instruction. Participants will have the option at this visit of changing their minds and participating in the vaccinated arm of the study if they wish and if there is still space available.

**Randomization**

- Randomization will be stratified by age group (18-49 years and 50+ years) and sex. If participants do not report a sex, they will be stratified in the male category. Randomization will be done after completing the Pre-Vaccination Questionnaire (Appendix K) that confirms that the participant is able to receive study vaccine on the same day. Participants will be randomized within each age and sex stratum 1:1 to receive NVX or mRNA. The randomization list will be generated before enrollment starts using a computerized random-number generator to select randomly permuted group blocks of size 6 with 3 of each vaccine type in each block for 1:1 assignments. The next available sequential randomization slot number within the appropriate stratified age and sex group will be assigned to each enrolled participant upon completion of the Pre-Vaccination Questionnaire. These block slots will be designated A-F, with three letters representing mRNA vaccines and the other three representing NVX. This structure is used to limit the potential for blinded staff or participants becoming fully unblinded to the study vaccines. Even if a blinded staff or study participants is inadvertently made aware of what one of the six block letters represents, they will not then automatically be aware of what all other letters represent.

**Vaccine administration**

- Prior to receiving the 2023-2024 updated COVID-19 vaccine, study participants in the vaccinated group will receive NVX and mRNA vaccine-specific EUA fact sheets or package insert (Appendix V1. Novavax COVID-19 Vaccine Fact Sheet and Appendix V2. Pfizer COVID-19 Vaccine Fact Sheet) outlining the potential risks, side effects, and benefits of the vaccine. Participants will receive a single dose of study vaccine administered in the deltoid muscle of the arm (0.3 ml for Pfizer and 0.5 ml for Novavax). Vaccine administration will be performed by a qualified HCP trained in the delivery of study vaccines and documented on the Vaccine Administration Form (Appendix L). Detailed information on the vaccine administration process developed in collaboration with the University of Utah are available in the Vaccine Administration Standard Operating Procedures (SOP) (Appendix X). This administration process includes an observation step to monitor vaccine recipients for 15 minutes after vaccination for any allergic reactions. Participants will be provided with contact information for the Investigator should they have any questions or adverse effects that arise after leaving the vaccination site.

**Surveillance Instruction**

- All participants will receive a study orientation including an overview of the weekly text message surveillance, instructional material that explains how to use the rapid antigen test, and how to submit the test results (Appendix V3. Test Instructions Video Script and Appendix V4. Test and Upload Instructions). Participants will be asked to participate in weekly text message surveillance at the study visit. Participants will be asked to self-test weekly following their enrollment visit. It is anticipated that self-testing will span approximately 24 weeks. Participants will receive a full supply of rapid antigen testing kits that include written and pictorial instructions on how to use the kit and submit the test results to the study team. If needed, study staff will re-supply the participant with rapid tests upon request.

**Blinding**

- Participants will elect whether they are in the vaccinated group or decline to be in the vaccinated group. So, all participants will be aware of their group assignment. However, those participants in the vaccinated group as well as study investigators will be blinded to study arm assignments within the vaccinated group. A limited number of study staff handling and administering the vaccines will be aware of vaccine assignment and will be trained not to divulge vaccine assignment information to the investigator team. Study staff administering vaccine will not be involved with study surveillance to avoid involvement with measurement of study outcomes. The study will provide electronic documentation confirming that participants received one of the study vaccines (without indicating which vaccine) with date of vaccine administration (Appendix M: Documentation of Vaccine Administration). The electronic documentation of vaccine administration will be password protected to maintain blinding.

- At the completion of the trial, a designated group of investigators may be unblinded to the vaccine assignment groups to conduct analyses to address objectives related to vaccine efficacy.

- At the completion of study data collection (defined as following the administration of Appendix O. End Study Survey), all participants will be unblinded as to which study arm they were assigned to within the vaccinated group. This information will be provided via their secure study dashboard and is anticipated to take place in June-July 2024. Should a participant elect to terminate their study participation prior to the end of data collection, they will still receive their vaccine unblinding information in June-July 2024.

**Emergency Unblinding**

- Unblinding of vaccine assignment for a participant may be necessary due to a medical emergency or other significant medical event. Study participation will be discontinued for participants whose vaccine has been unblinded. In the event that an emergency unblinding is necessary, the unblinded statistician at Westat will work with Utah staff to provide the unblinded vaccine status to the Investigator who initiated the emergency unblinding. This unblinding will be accomplished by using the crosswalk and randomization list generated by the unblinded statistician and utilized only by unblinded study staff.

**If unblinding is required:**

- Only the Investigator or delegated co-investigator or sub-investigator will make the decision to unblind the vaccine assignment.
- Only the affected participant will be unblinded.
- The designated study pharmacist(s)/designee at the study site will provide the unblinded vaccine assignment to the Investigator.
- The Investigator will notify the Novavax or Pfizer as soon as possible but no later than 24 hours after unblinding the participant.

**Post Vaccination Safety Monitoring**

- Per the Advisory Committee on Immunization Practices' General Best Practice Guidelines, all vaccine recipients will be observed for 15 minutes after vaccination for syncope. If the pre-vaccination survey reveals prior history of possible allergic reaction, the post-vaccination observation time-frame may be extended further to 30 minutes to further monitor for allergic reactions. Participants will be provided with contact information that can be utilized should they have any questions or adverse effects that arise after leaving the vaccination site. Additionally, 24 hours, 48 hours, and 6 days after receiving the vaccine, participants will be asked to complete a Post-Vaccination Survey (Appendix W) which will allow for monitoring events for 168 hours following vaccination.
- All study 2023-2024 updated COVID-19 vaccines have received EUA or approval from the FDA to be provided as a single dose, and data on reactogenicity events and adverse events will be documented. Study staff will provide participants with a phone number and email to call in case they have any questions after vaccination.
- Please note that due to changes in recommended language from the FDA, references to the vaccines in this protocol have been changed from "booster" to "2023-2024 updated COVID-19 vaccines". However, we have maintained the booster reference in participant-facing documentation given that concept of a "booster" continues to be well recognized by the general public at this time, and much of the advertising for the study (including the study name itself) incorporates references to a booster.

#### 5.5.3.1 Immunization Information Systems

Study staff will query the state immunization information system (IIS) or registry to obtain COVID-19, and influenza vaccination status or history. Participants will be asked to consent to this data collection in the consent form and may opt out of having their vaccine records obtained by the study. Administration of COVID-19 vaccines may need to be documented by public health jurisdictions within 24 hours of administration. Study staff will work with IIS personnel to determine the appropriate procedures to document COVID-19 vaccination receipt. The process for collection of vaccine record data will be outlined in Appendix N1: Vaccine Abstraction Verification and Appendix N2: Vaccine Abstraction Verification End-of-Year.

#### 5.5.3.2 Vaccination Reporting

Influenza vaccination status will be reported by the participants (including type of vaccine, location, and date of vaccination) through the Mid-Study and End-of-Study (Appendix O) Surveys. Receipt of 2023-2024 updated COVID-19 vaccine outside of the study during the study period will similarly be self-reported through the Mid-Study and End-of-Study Surveys. Should a participant in the non-vaccinated arm of the study receive an updated COVID-19 vaccine during the study period, that information will be captured via the Mid-Study Survey & End-of-Study Surveys (Appendix O), or the Vaccine Abstraction Verifications (Appendix N1-N2) but the participant will remain in the study. Participants will also be asked to provide their COVID-19 and influenza vaccination history through self-report and the upload of vaccine documentation to their participant dashboard. Examples of documentation include a digital photo of the vaccination receipt or immunization records. These documents can be uploaded only via the participant dashboard.

In addition to the responses provided in the eligibility and enrollment surveys, previous COVID-19 vaccination data will be retrieved through USIIS by study staff or provided by the participant (vaccine card or immunization records) to determine eligibility. The study team will collect the vaccine manufacturer information. This information is important due to the exclusion criteria centered around receipt of the J&J vaccine. There were a small proportion of Utah residents who received the J&J Vaccine (<8%, 166581/2082443). The vaccine type, other than J&J, will represent what is commonly done in pragmatic study designs. The study team will track the prior vaccination manufacturer to see if there may be interactions between different combinations of vaccines. From a clinical perspective there is no concern with a heterologous vaccination approach, as there have been a number of studies which demonstrate that such an approach is clinically appropriate. This has led to the CDC issuing guidance supporting "mix-and-match" vaccine strategy.

### 5.5.4 Follow-up Surveys

Brief surveys will be administered over the course of the study for three purposes. First, surveys will allow participants to update information on their occupation and work responsibilities, health status, potential exposures to COVID-19 at work, home, and in the community, and their use of PPE in these settings. Second, surveys will allow participants to report if they were unable to report a qualifying illness and/or submit illness specimens for any reason, and to provide an estimate of when this missed illness event occurred so that their surveillance record can be updated accordingly. Third, surveys will assess participants KAP regarding COVID-19 vaccines, intention to be vaccinated, and then after vaccination, to recall their overall health status on the days following vaccination.

- Post-Vaccination Survey (Appendix W. Post-Vaccination Survey), for participants who choose to receive a COVID-19 2023-2024 updated vaccine, will be administered 24 hours ±1 day, 48 hours ±1 day, and 6 days ±1 day after receiving the vaccine in order to monitor events for 168 hours following vaccination.
- Follow-up Survey 1 (Appendix O. Mid-Study Survey) will allow participants to report any adverse events following immunization (AEFI), and update chronic medical conditions, KAP responses, occupational, exposures, PPE use, and employer-mandated COVID-19 vaccination requirements. This survey will also give participants an opportunity to report their influenza vaccination status for the season. Participants also can report any illnesses missed during surveillance. All

participants will be asked supplemental questions to collect information about receipt of COVID-19 vaccines outside of the study during the study period.

- Follow-up Survey 2 (Appendix O. End-of-Study Survey) will provide a final opportunity to allow participants to report any AEFI, and update chronic medical conditions, KAP responses, occupational, exposures, PPE use, and employer-mandated COVID-19 vaccination requirements. This survey will also give participants an opportunity to report their influenza vaccination status for the season. Participants also can report any illnesses missed during surveillance. All participants will be asked supplemental questions to collect information about receipt of COVID-19 vaccines outside of the study during the study period.
    - If participants indicate they want to withdraw from the study before completing the follow-up period, they will be invited to complete the End-of-Study Survey before withdrawal. Specific efforts will be made to collect survey responses from participants who did not complete the full follow-up period. The protocol status of all participants will be tracked in the database platform to record early termination, loss to follow-up, participant-directed withdrawal, and protocol completion. Utah study staff will complete the Participant Withdrawal Form (Appendix R5) for each participant who chooses to withdraw from the study.
- Long COVID Survey (Appendix P) will provide participants an opportunity to report Long COVID symptoms that last longer than 1 month. The survey will be distributed to participants with a first positive COVID-19 rapid test within the study (cases) and also participants who report their first COVID-like illness (CLI) symptoms during the study but did not test positive on the rapid test (controls). The survey will ask participants to identify which symptoms lasted more than 1 month, duration of these symptoms, and how these symptoms impact function and mental health. The Long COVID Survey will be distributed at the same time as the Mid-Study and End-of-Study Surveys.

**Table 3. Survey Instruments and Timing**

| Instrument | Appendix | Title | Purpose | Timing |
|---|---|---|---|---|
| Post-Vaccination Survey | W | Post-Vaccination Survey | To monitor for adverse events by answering questions about reactions to the vaccine for participants who choose to receive the COVID-19 2023-2024 updated vaccine | Day 1, Day 2, and Day 7 post-vaccination |
| Follow-up Survey 1 | O | Mid-Study Survey | Self-reported documentation AEFI; update chronic medical conditions, KAP responses, occupational, exposures, PPE use, and employer-mandated COVID-19 vaccination requirements; report any illnesses missed during surveillance.<br>They will be asked supplemental questions to collect information about receipt of COVID- | December 2023/January 2024 |

| | | | | |
|---|---|---|---|---|
| | | | 19 vaccines outsides of the study during the study period. | |
| Follow-up Survey 2 | O | End-of-Study Survey | Same as Mid-Study survey | April/May 2024 |
| Long COVID Survey | P | Long COVID Survey | The intended recipients are participants who had an illness that lasted longer than 4 weeks. The survey asks about symptoms that lasted at least 4 weeks, how long each symptom lasted, and how bothersome the symptoms were. The survey also asks questions about mental health of the participant. | Distributed to all cases and controls at the same time as the Mid-Study and End-of-Study surveys. |

## 5.6 Specimen Collection

### 5.6.1 Respiratory Mucosal Samples

Respiratory mucosal specimens will be self-collected and tested according to rapid antigen test FDA and manufacturer guidelines.

During this study, a standard respiratory specimen is defined as a participant-collected anterior nasal swab using a rapid antigen test. Participants will take a digital photo of their test result and upload the file to database platform.

- Participants will be asked to self-collect a respiratory specimen each week regardless of symptoms throughout the study surveillance period. For weekly and illness testing, participants will use FDA-approved COVID-19 Rapid Antigen Self-Test. Ideally, the sample will be collected no later than 24 hours from the weekly text notification or illness onset. Participants will receive detailed written and/or visual instructions for self-collection of a respiratory specimen (Appendix V3 Test Instructions Video Script and Appendix V4 Test and Upload Instructions). At the vaccination visit, participants will be given a "self-collection kit" that includes written and/or visual instructions, and all prepared supplies for routine, weekly specimen collection and for acute illness specimen collection. Study staff will track the use of kits and ship replacements to participants as needed.
- The study will provide all participants with the OSANG Healthcare (OHC) COVID-19 Antigen Self Test. The OHC COVID-19 Antigen Self Test is the sole test for the study. The OHC Self Test is authorized for non-prescription of home use with self-collected anterior nasal swab samples from individuals 14 years or older.[37]

### 5.6.2 SARS-CoV-2 Rapid Antigen Test Results

State or local health department regulations may require reporting of incident cases of SARS-CoV-2 infection. The Investigator will be responsible for contacting state or local SARS-CoV-2 surveillance coordinators to ensure study procedures comply with all reporting requirements.

Participants will be informed that:

- Results are not meant to replace recommended clinical and/or occupational molecular tests;
- False positive and false negative results are possible;
- Receiving a negative diagnostic result should not alter their preventive behaviors, given that results are specific to the date and time they are collected, and current assays may not be sensitive to all infections;
- Results will not be shared with the participants' medical providers.
- Participants should consult their personal medical provider if they have questions, concerns, or any medical needs related to their illness;
- They should follow their employer's guidelines for reporting illnesses and returning to work.

# 6. Statistical Considerations

This randomized, three arm, active comparator trial will compare the clinical efficacy of NVX 2023-2024 updated vaccine (Arm 1) with a single dose of the mRNA 2023-2024 updated strain (Arm 2) as well as non-boosted comparison group (Arm 3). The study hypotheses are 1) to compare vaccine efficacy (VE) between participants who receive either the NVX (Arm 1) or mRNA 2023-2024 updated strain (Arm 2) with the non-boosted participants who are recommended to be boosted based on CDC, state or organizational guidelines but decline the 2023-2024 updated vaccine and 2) to determine the relative vaccine efficacy (relative VE) of the Pfizer mRNA 2023-2024 updated vaccine and the NVX 2023-2024 updated vaccine in preventing SARS-CoV-2 infection to confirm non-inferiority for NVX. Detailed plans for statistical analysis are provided in Appendix S1. Statistical Analysis Plan (SAP) and Appendix S2. Post-Vaccination SAP. These plans have been updated to reflect revised power calculations based on more accurate estimations of assumed rates of infection throughout the study period. As a result of these revised power calculations, the surveillance period has been expanded from 20 to 24 weeks to ensure sufficient data capture within the study.

## 6.1 Sample size & Power Considerations

### 6.1.1 Sample Size for Primary Objectives

Power and sample size are examined for both primary objectives to 1) compare VE between vaccinated arms (both NVX and mRNA) and the non-vaccinated comparison arm with a 2-sided alpha=0.05 superiority test and 2) determine non-inferiority of NVX 2023-2024 formula vaccine variant compared to a single dose of Pfizer mRNA 2023-2024 updated vaccine with a 1-sided alpha=0.05 confidence interval. The rate of CLI-associated SARS-CoV-2 infection, confirmed by COVID-19 rapid antigen test (RAT) in those not vaccinated with the 2023-2024 formulation is expected to be 60 per 100,000 person-days. We expect those choosing not to vaccinate in Fall 2023 to Spring 2024 to be a mix of unvaccinated and fully vaccinated but not boosted individuals, but to be conservative we will assume this group is solely comprised of fully vaccinated individuals. Using publicly available data on the historic case rates in Utah for COVID-19 from the week of November 20, 2022 to the week of July 30, 2023,[39] the average rate of cases in those fully vaccinated in Fall 2022-Spring 2023 is 39.64 per 100,000 person-days for those fully

vaccinated. From a survey conducted in spring of 2022, it has previously been reported that of those testing for COVID-19 44.2% report testing at a lab or clinic and 25.7% reported testing at a drive-thru clinic[40]. Therefore, using at-home test kits to identify cases, we expect rates to be 43.1% higher (1/(0.257+0.442)) than what is shown on Utah's dashboard. This under-reporting adjustment to Utah's observed rates from last fall leads to a conservative estimate for the rate of CLI-associated SARS-CoV-2 infection, confirmed by COVID-19 rapid antigen test (RAT), in those not vaccinated with the 2023-2024 formulation to be 60 per 100,000 person-days. Using the same logic applied to the reports for those with a bivalent booster last fall, after adjusting for under-reporting, we estimate the infection rate to be 48 per 100,000 person-days in those vaccinated in Fall 2023 to Spring 2024.

For the superiority test of the first primary objective, on which the sample size is based, the null hypothesis that vaccine efficacy, or VE, of the 2023-2024 formula compared to no vaccination in Fall 2023-Spring 2024 is 0 is tested against the alternative that the VE is not equal to 0. That is, $H_0$: VE = 0 is tested against $H_a$: VE ≠ 0. VE is calculated as 1- hazard ratio, HR, comparing those receiving the 2023-2024 formulation (either NVX or Pfizer) to those choosing not to be vaccinated in Fall 23 to Spring 24, times 100 or 100*(1-HR). HR will be estimated using Cox proportional hazards models with $\alpha$=0.05. Table 4 provides the required sample size to yield 80% power to detect VE of 40%, 50%, and 60% or higher, assuming an attrition rate of 15% or less. We plan that the NVX and Pfizer arms will each have twice as many participants as the arm of those choosing no Fall 2023 to Spring 2024 vaccination, a ratio of 4:1. Calculations were made in PASS using the Multi-Arm Tests for Treatment and Control Survival Curves using Cox's Proportional Hazards Model[41]. In 24 weeks of follow-up, the rate of 60 cases per 100,000 person-days equates to an event probability of 10.08%. This probability corresponds to a hazard rate of 0.10625. With a total of 1500 participants enrolled (1200 with 2023-2024 formulation and 300 without Fall 2023 to Spring 2024 vaccination), we have 80% power to detect a VE of 56.25% or more, even if we see 15% attrition. With 1500 enrolled and an observed VE of 50%, we anticipate there will be approximately 85 RAT confirmed symptomatic COVID-19 cases in total (30 in the not vaccinated arm and 55 in the vaccinated arm) with no attrition, and 72 with 15% attrition.

**Table 4. Relationship between Vaccine Efficacy and Sample Size, assuming a 4:1 ratio vaccinated with 2023-2024 formulation to not vaccinated in Fall 2023-Spring 2024 and 15% rate of attrition.**

| **Lowest Detectable VE comparing between non-vaccinated and vaccinated (NVX and Pfizer combined) arms** | **Sample size for 80% power** |
|---|---|
| 40% | 3,183 |
| 50% | 1,954 |
| 56.25% | 1,500 |
| 60% | 1,289 |

For the non-inferiority test in the second primary objective, the null hypothesis that the NVX vaccine of 2023-2024 formulation is inferior to the Pfizer vaccine of the 2023-2024 formulation is tested against the alternative that NVX is non-inferior. That is, $H_0$: rVE < 0 + $\delta$ is tested against $H_a$: rVE ≥ 0 + $\delta$, where $\delta$ is the "interval of equivalence", the range in which the effectiveness of the two vaccines would be considered clinically equivalent. Relative VE, or rVE, is calculated as 1- hazard ratio, HR, comparing

those receiving the NVX 2023-2024 formulation to those receiving the Pfizer 2023-2024 formulation, times 100, or 100*(1-HR). We believe an interval of -50% would be clinically acceptable. For example, if Pfizer reduces the hazard of infection by half, reducing the hazard by 25% (VE of 25%) would correspond to an rVE of -50%. Similarly, if Pfizer shows 80% VE compared to the non-vaccinated, a NVX VE of 70% would correspond to an rVE of -50%. For the power calculations for the second primary objective, the significance level is $\alpha$=0.05.

Table 5 gives the power for testing the non-inferiority hypothesis with a sample of 600 enrolled patients per arm with an equivalence interval of -50%, with observed rVE ranging from -20 to 20 and observed rates of CLI-associated SARS-CoV-2 infection, confirmed by COVID-19 rapid antigen test (RAT) in the Pfizer arm ranging from 50 to 90 per 100,000 person-days. Additionally, an attrition rate of 15% from 600 is assumed. The power decreases as the observed case-rate in the Pfizer arm decreases or as the observed rVE decreases. Calculations were made in PASS 2023 using Non-Inferiority Tests for Vaccine Efficacy using the Hazard Ratio (Cox's Proportional Hazards Model). If we assume an infection rate of 60 per 100,000 person-days in the Pfizer vaccinated arm we have 81.12% power to determine non-inferioirty of NVX for observed rVEs of 10 or greater.

**Table 5. Power assuming 600 at enrollment for each group (NVX and Pfizer) accounting for 15% attrition for non-inferiority of NVX vs. Pfizer 2023-2024 formulations and a non-inferiority limit of -50 rVE.**

| Assumed rate of COVID-19 infection in 100,000 person days for Pfizer 2023-2024 formulation arm | Possible Observed Relative VE | | | | | | |
|---|---|---|---|---|---|---|---|
| | 20 | 10 | 5 | 0 | -5 | -10 | -20 |
| **50** | 86.88 | 74.60 | 67.13 | 59.16 | 51.02 | 43.03 | 28.63 |
| **60** | 91.71 | 81.12 | 74.00 | 65.94 | 57.33 | 48.57 | 32.20 |
| **70** | 94.84 | 86.12 | 79.58 | 71.75 | 62.97 | 53.70 | 35.66 |
| **80** | 96.84 | 89.88 | 84.08 | 76.70 | 67.98 | 58.41 | 38.98 |
| **90** | 98.08 | 92.68 | 87.66 | 80.86 | 72.41 | 62.72 | 42.16 |

With a planned sample size of 600 per arm and 15% attrition, if the observed rate of infection in the Pfizer 2023-2024 formulation arm differs from 60 per 100,000 person-days, 600 participants in each arm assures 80% power to claim non-inferiority for observed rVE greater than 10, sometimes less than 10, as outlined in the table above. The grey cells in the table indicate which scenarios will have 80% power with 600 participants.

## 6.2 Statistical Analysis

The modified intent-to-treat (mITT) population will be the primary population for efficacy analyses and participants are analyzed according to their randomized treatment. All participants who are randomized, received a study vaccine, and participated in study surveillance by responding to at least one surveillance contact during the SARS-CoV-2 circulation period (active surveillance ) will be included in the mITT population for the primary objectives. For participants who were identified as not receiving a 2023-2024 updated vaccine (comparison group) they will be analyzed in that group under the mITT population, even if they subsequently do get a 2023-2024 updated vaccine from elsewhere during the study period.

Additionally, a per protocol analysis will also be performed. The per protocol population will include participants who met eligibility criteria, received study vaccine per protocol, participated in study surveillance by responding to at least one surveillance contact during the SARS-CoV-2 circulation period (active surveillance), and did not receive another SARS-CoV-2 vaccine outside of the study during the study period. If participants were in the non-vaccinated comparison group but subsequently received a 2023-2024 updated vaccine, they will be censored at that point.

### 1.2.1 Descriptive Analysis

Location, age group, sex, self-reported race and ethnicity, occupation, preexisting medical conditions, SARS-CoV-2 vaccine history during prior seasons (as feasible), and frequency of mask-use while in close proximity of others during the SARS-CoV-2 circulation period will be summarized overall and by vaccine group. All demographics and baseline characteristics will use the mITT population.

### 6.1.2 VE Primary Objective

The primary analysis for VE will be a superiority test comparing vaccine efficacy (VE) between participants who receive either the NVX 2023-2024 updated vaccine (Arm 1) or Pfizer mRNA 2023-2024 updated vaccine(Arm 2) with the non-vaccinated participants who are recommended to be vaccinated based on CDC, state or organizational guidelines but decline the 2023-2024 updated vaccine. Cox proportional hazards models will use the Andersen and Gill counting method[42] with participants able to contribute time at risk for each day of follow-up. Cox proportional hazard models will have randomized vaccine group versus the non-randomized arm as the main effect. For both primary objectives age, prior COVID-19 vaccination in the past 4 years and week will be adjusted for (time-varying covariate). Prior COVID-19 vaccination will be categorized (Never vaccinated, 1 prior vaccine (2 course vaccination), 2 prior vaccines (initial vaccination and 1 additional vaccine dose), 3 prior vaccines and ≥4 prior vaccines), if there are less than 30 people in a category, then we will collapse down (e.g. ≥3 instead of 3 and ≥4) until we have stable estimates. Other baseline characteristics will be included as covariates if there are significant imbalances between vaccine groups and kept in the model if they adjust the hazard ratio by ≥5. If an analysis has <10 events, an unadjusted model only will be calculated.

If models for a single month do not meet the proportional hazard assumption, the Andersen and Gill counting method will be used to allow for weekly circulation as a covariate. If a model still does not meet the assumption the proportional hazards assumption after the inclusion of weekly circulation as a covariate, the Prentice, Williams, and Peterson total time model[43] will be used with season as a strata

and circulation as a covariate, allowing for circulation to vary. Participants who do not experience an SARS-CoV-2 case prior to the discontinuation of the study will be right censored at their last response to weekly surveillance contacts.

### 6.1.3 Relative VE Primary Objective

The primary analysis for relative VE efficacy against SARS-CoV-2 illness for NVX (2023-2024 formula) vaccinated participants versus Pfizer mRNA (2023-2024 formula) vaccinated participants will be calculated using time at risk with the following null and alternative hypotheses for the objective comparing NVX vs mRNA:

$H_0$: rVE < -50 and $H_a$: rVE$\geq$ -50

Here rVE is estimated with the same analytic approach described for the VE, however the Cox proportional hazard models will have NVX vaccinated arm versus the mRNA vaccinated arm as the main effect. The primary objective will be achieved if the lower limit of the one-sided confidence interval of rVE estimate exceeds -50 between NVX and mRNA vaccine groups, adjusting for potential confounders or differences in baseline groups.

### 6.1.4 Secondary Objectives

Incidence of SARS-CoV-2 will be calculated using Poisson regression with vaccine group as a main effect, and study month as covariates and log person weeks as an offset. Person weeks is defined as the time at risk (in days) divided by seven and rounded up. If assumptions for Poisson regression do not hold, zero-inflated Poisson and Negative Binomial models will be considered instead.

Proportional hazard or logistic regression analyses will be used to assess hazard ratio or relative risk and associated 95% confidence intervals for secondary endpoints such as individual, occupational, and environmental predictors of SARS-CoV-2 infection and of asymptomatic infection versus symptomatic COVID-19 illness. The choice to use PH or logistic model will depend on the specific secondary outcome being identified. If PH models are used, time-varying covariates will be used as available. Multivariable models will be adjusted for potential confounders.

## 7. Data Entry and Management

Westat will host and maintain a permission-based research data platform and study database for this trial. University of Utah study staff will have access to the database. Tracking databases with participant identifying information and contact information will be kept securely according to the standard operating procedures with respect to cybersecurity, privacy, participant confidentiality, and compliance with applicable HIPAA regulations. Any study-related papers with personal identifiers will be stored in a locked cabinet or other secure, limited-access area in the research offices of University of Utah.

All survey data will be entered directly into the study database through the use of online surveys, the text messaging interface, and/or the mobile application. Study site staff will enter response data directly

into the database if surveys are administered by telephone or in person interviews. The questions in the approved forms will appear on the research data platform rather than in paper form.

All study related documents and samples will contain a unique identifier per person. The online, mobile application, text message, and data entry screens will provide some Quality Assurance and Quality Control (QA/QC) thorough the use of logic and range checks and automated skip patterns. Additional quality checks of the data will be performed on a weekly basis including checks for out-of-range values and missing data.

Rapid antigen test results will be entered directly into the study database by the participant or study staff.

Upon execution of an appropriate data use agreement (DUA), data extracted from the state registry will be loaded into the database following the specifications of the study codebook and data dictionary (to be developed and submitted as an amendment to the IRB prior to implementation).

### 7.1 Data Sharing

Westat, Inc. will deliver Full Data Sets to University of Utah. Westat, Inc. will deliver Limited Data Sets (de-identified) to Novavax, Inc. This is a two-part data delivery component:

1. Westat will regularly clean and share identifiable data sets with UT.
2. Westat will only share a final, de-identified data set with Novavax.

## 8. Protection of Human Subjects

### 8.1 IRB Review

Prior to study implementation, the protocol, informed consent form, participant education and recruitment materials, data collection instruments and other documents associated with the protocol shall be approved by the University of Utah IRB as the IRB of record responsible for overseeing study activities. All protocol amendments must be approved by the IRB prior to implementation. The Investigator/Sponsor or designee (i.e. co-investigator or study coordinator) will be responsible for submitting documents for initial approval, continuing review, amendments, and all unanticipated problems involving risk to human participants or others according to IRB policy. The records of IRB approvals will be maintained in in the regulatory record/file and University of Utah's Electronic Research Integrity & Compliance Administration system (ERICA), as applicable.

An IRB authorization agreement using the Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform (SMART) IRB platform will be established for Westat to rely on UT for oversight of study activities involving human subjects and any associated identifiable data. University of Utah will obtain additional approval from the appropriate independent ethics committees or IRBs as required by their institution.

### 8.2 IRB Reporting Requirements

An incident refers to an unanticipated problem that occurs during the research study. Incidents may or may not involve a risk of harm to study participants. For the BEEHIVE study, examples of incidents include protocol deviations, i.e., anytime established study protocols are not followed; confidentiality breaches; participant complaints; events involving participants' safety and health; and problems related to study procedures such as the consent, enrollment, study vaccine, or test kit administration. Within 24 hours of learning about an incident, study staff will complete the BEEHIVE Incident Report Form (Appendix R1) in the study portal and notify the designated BEEHIVE study coordinator that an incident report form has been completed for a specific participant ID. For all protocol deviations, adverse events, serious adverse events, and participant withdrawals noted in the Incident Report Form, study staff will also be prompted to complete the University of Utah Protocol Deviation Log (Appendix R4), Adverse Event Log (Appendix R2) or Serious Adverse Event Log (Appendix R3). The BEEHIVE study coordinator will review the information received for all incidents and complete all required submissions to the University of Utah IRB.

## 8.3 Vaccine Products

Two COVID-19 vaccine products will be used in this trial: NVX vaccine (Novavax COVID-19 Vaccine, Adjuvanted, 2023-2024 formula (monovalent, Omicron XBB.1.5 containing)) or mRNA vaccine (Pfizer-BioNTech COVID-19 Vaccine, 2023-2024 formula (monovalent, Omicron XBB.1.5 containing)). Novavax, Inc. will provide the research team with the NVX vaccines for the trial. University of Utah will purchase the Pfizer mRNA vaccines when it is commercially available in Fall 2023.

Information on the individual vaccine products and details on storage and monitoring will be included in the Appendices once the vaccine products are available. Both vaccines have received approval or authorization prior to use in this trial. The Pfizer vaccine has received approval from the FDA for use in persons aged ≥ 12 years in the United States as of September 12, 2023 (Appendix V2. Pfizer COVID-19 Vaccine Fact Sheet). The Novavax vaccine has received Emergency Use Authorization (EUA) from the FDA for use in persons aged ≥ 12 years in the United States as of October 3, 2023 (Appendix V1. Novavax COVID-19 Vaccine Fact Sheet).

The study vaccines will only be administered to participants under the care of the Investigator/Sponsor. The study vaccines will be stored in a locked temperature monitored medication refrigerator at the University of Utah Clinical & Translational Science Institute (CTSI). The study vaccines will be under temperature monitoring continuously. If there is a temperature excursion, the affected study vaccines will be quarantined and status of quarantine will be documented per local policy. We will follow manufacturer storage guidance to determine if the vaccine is still appropriate to be used. If it is not appropriate for use, the affected vaccines will be destroyed or returned to the manufacturer. At the end of the study, unused vaccines will be destroyed per local policy.

## 8.4 Confidentiality

Each participant will be given a unique study ID which will be used on all study materials. Multiple forms of contact information, including telephone, email, mailing address and information from close contacts (e.g., spouse or other family members) likely to know how to reach the participant should the study lose

contact will be collected, but will only be accessible by study staff.

Only descriptive information included in the contact lists (non-identifiable demographic information and occupation) will be recorded for potential participants who cannot be contacted, are ineligible, or are eligible but refused participation, in order to examine potential participation or selection biases. Stated reasons for refusal will also be recorded.

Participation rates will be monitored by sex, age group, and vaccine status. If participation rates are significantly lower among a specific subgroup, efforts during the final phases of recruitment will focus on expanding recruitment for these under-represented groups.

All study data, test results, reports, study data collection, study procedure, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All study data will be stored separately from study records that contain names or other personal identifiers (such as locator forms and informed consent forms). All databases must be secured with password protected access systems. Westat will deliver a final, identifiable dataset to the University of Utah via a secure, encrypted file sharing program.

Forms, lists, logbooks, appointment books, and any other listings that link Study IDs to other identifying information must be stored in a separate, locked file in an area with access limited to study staff. If participant names and corresponding Study IDs are entered into a computer database, this database must be password protected and must be maintained in a directory separate from any study specific data.

## 8.5 Benefits

This study may benefit participants directly by allowing them to receive a vaccine that prevents or minimizes the effects of severe SARS-CoV-2 infection. Completing the at-home rapid antigen tests for SARS-CoV-2 virus infections may also indirectly benefit participants by aiding them in making decisions to prevent secondary exposure to others. The study may also provide indirect benefits to participants by improving the understanding of whether one of the study vaccines offers greater protection than the other and by how much in comparison. Knowledge learned from the results of this study may impact vaccine policy and practices that could ultimately benefit the adult population broadly.

## 8.6 Remuneration

In appreciation of their time and effort involved in this study, participants will receive compensation in the form of Amazon gift cards. The actual amount received will depend on the number of study activities they complete up to a maximum of $550 per participant. Participants will receive a gift card even if their responses to certain surveys (i.e. enrollment survey) may disqualify them from participating in the study. Table 6 provides a list of study activities and the associated Amazon gift card amount.

**Table 6. Study activities and Amazon gift card amount**

| Study Activity | Amazon Gift Card Amount |
|---|---|
| **Enrollment Survey**<br>• Answering questions about yourself, your work, health, and COVID-19 and flu vaccine history | $30 |
| **Enrollment Visit**<br>• Attending a visit in person at the University of Utah Health<br>• Receiving a supply of COVID-19 test kits<br>• Learning how to complete the study surveys in the study portal<br>• Receiving a COVID-19 booster if you choose to get one | $50 |
| **Post-Vaccination Surveys** (if applicable)<br>• Answering questions about any reactions on Day 1, Day 2, and Day 7 post-vaccination, if you choose to get a booster | $12 per survey on Day 1 and Day 2, $20 for completing a survey on Day 7 (Total amount up to $44) |
| **Weekly and Illness Surveys and COVID-19 Test Photo Submission beginning after the enrollment visit for 24 weeks**<br>• Answering questions about how you feel<br>• Uploading a photo of your test results to the study portal | $14 per survey with photo submission (Total amount up to $336 for 24 weeks) |
| **Mid-Study Survey and End-of-Study Survey**<br>• Answering questions about your work, health, thoughts about COVID-19, and COVID-19 and flu vaccinations received | $30 each (Total amount up to $60) |
| **Long COVID Surveys** (if applicable)<br>Answering questions at mid-study and end-of-study about COVID-19 symptoms if you tested positive for COVID-19 or had symptoms without testing positive | $15 each (Total amount up to $30) |
| **TOTAL AMOUNT** | **Up to $550 Total** |

## 8.7 Risks

All COVID-19 2023-2024 updated vaccines used in this study will have received EUA by the FDA for U.S. adults aged 18 years and older to prevent COVID-19. The risks to participants receiving the 2023-2024 updated vaccines include potential discomforts associated with intramuscular injection of the vaccine and possible vaccine reactions. Some recipients may develop reactions at the site of vaccination, such as redness, swelling at the injection site, swelling of the lymph nodes, pain, or tenderness. There is also a slight risk of infection, which study staff will minimize by swabbing the site with alcohol and using sterile equipment.

Occasionally, adult recipients of COVID-19 vaccines may develop reactions such as fever, body aches, headache, malaise, myalgia, and/or nausea. If present, these symptoms usually occur soon after vaccination and may last up to 1-2 days post-vaccination. Analgesics, such as ibuprofen or acetaminophen, and rest will generally relieve or moderate these symptoms. While severe reactions are

rare, possible acute and potentially life-threatening allergic reactions may include: shortness of breath; wheezing; hives or rash; hoarseness; difficulty swallowing; swollen face/tongue/pharynx, tachycardia; paresthesia (tingling or crawling feeling); hypoesthesia (decreased feeling or sensitivity); dizziness and/or weakness. Finally, myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside of the heart) have occurred in some people who received the Novavax or mRNA COVID-19 vaccines. Symptoms of myocarditis and pericarditis include chest pain, shortness of breath, or feelings of having a fast-beating, fluttering, or pounding heart, with symptoms most commonly reported as beginning within 10 days after vaccination. These side effects were seen more often in male adolescents and young adults after the second dose of the vaccine. However, they were also seen in women and older adults after the first dose. The chance of having this occur is very low. In the rare case participants experience myocarditis or pericarditis symptoms, they will be advised to seek immediate medical attention and notify the study staff. Additionally, by participating in this study there is a risk of loss of confidentiality given the involvement of participant's identifiable data. This is risk is mitigated through the provisions described in section 8.8.

### 8.8 Provisions for Protecting Privacy/Confidentiality

Study investigators and institutions are committed to protecting personal health information through the maintenance of privacy and security of each subject's personal information in this study. To protect confidentiality, we will use a study assigned number instead of personal information on study forms and we will store data in locked files and/or secured computers. In accordance with 21 CFR 312.62 (c), adequate case histories will be kept at the site 2 years following the end of trial and FDA is notified. Identifiable information will be destroyed after that required timeframe. If information from this study is presented publicly or published in a medical journal, individuals will not be identified by name or by any other personally identifiable information. The researchers in this study will be looking at personal health information but will not disclose personally identifying information about individual participants to others.

### 8.9 Protocol Completion or Termination

Participant changes in status, such as termination or protocol completion, will be recorded and tracked in the database platform. In the case the participant reports that they no longer reside in the Greater Salt Lake area, they will no longer be eligible to participate in the study and will be withdrawn. In the case the participant reports an unexpected personal event, e.g. family emergency, out of town for an extended period of time, the participant will be paused or withdrawn at PI and/or Steering Committee discretion.

## 9. Regulatory Requirements

### 9.1 Timeframe for Safety Assessments

The timing and frequency of all safety assessments are listed in Table 7.

**Table 7. Timing and Frequency of all Safety Assessments**

| **Study Period:** | **Screening Period** | **Clinic visit** | **Hours/Days after study vaccination** | | | **Months after study vaccination** | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study Day:** | **-30 to 0** | **0[a]** | **24 hours** | **48 hours** | **6** | **28 days** | **3** | **6** | **EOS[b]** |
| **Study visit:** | **Screening** | **1** | **-** | **-** | **-** | | **-** | **-** | **-** |
| **Randomization** | | X | | | | | | | |
| **Study vaccination[c]** | | X | | | | | | | |
| **Post-vaccination survey[d] (all vaccinated participants)** | | X | X | X | X | | | | |
| **Monitoring for COVID-19[e]** | | | COVID-19 surveillance will commence from Day 0 to up approximately 24 weeks after study vaccination[e] | | | | | | |
| **Unsolicited AEs that are study-related** | | X | X | X | X | X | X | X | X |
| **All unsolicited AEs[f]** | | X | X | X | X | X | | | |
| **SAEs/AESIs[g]** | X | X | X | X | X | X | X | X | X |

[a] The Screening visit and Day 0 visit may be combined if feasible.
[b] End of the study
[c] Study vaccination on Day 0 will consist of study vaccine only.
[d] Solicited AEs (e.g., local and general systemic reactogenicity symptoms) will be captured in all participants on 24 hours, 48 hours, and 6 days after receipt of study vaccine. On study vaccination day, participants will remain in clinic for at least 15 minutes to be monitored for acute reactions and solicited AEs. Severe reactions will be noted as AEs on day of study vaccination.
[e] Participants will monitor for COVID-19 symptoms weekly during the surveillance period. Participants will self-collect rapid antigen tests on a weekly basis to monitor for COVID-19 during the surveillance period. Illnesses that occur more than 28 days after administration of the study vaccine will not be reported as AEs unless a study investigator determines that the illness is related to the study vaccine.
[f] All unsolicited AEs may be reported to the study team from the time of study vaccination completion to the participant's last study-related procedure. Unsolicited reports that occur more than 28 days after administration of the study vaccine will not be reported as AEs unless a study investigator determines that the illness is related to the study vaccine.
[g] SAEs/AESIs may be reported to the study team from the time of study vaccination completion to the participant's last study-related procedure, which is approximately 24 weeks after study vaccination.

Safety assessments will include monitoring and recording of solicited (local and systemic reactogenicity events) and unsolicited AEs, SAEs, and AESIs. UT is responsible for overseeing all IND submissions, which includes the capturing and reporting of these AEs, SAEs, and AESIs.

After study vaccination, participants will remain under observation at the clinic for at least 15 minutes for the presence of any acute reactions and solicited AEs. Solicited AEs, collected through the Post-

Vaccination Survey (Appendix W), will be recorded 24 hours, 48 hours, and 6 days after study vaccination in all participants.

All solicited AEs captured within 7 days of vaccination will be recorded on the University of Utah Adverse Event (AE) Log (Appendix R2).

All unsolicited AEs captured within 28 days of vaccination will be recorded on the University of Utah Adverse Event (AE) Log (Appendix R2).Medical events that begin prior to study vaccination will be recorded as medical history on the Enrollment Survey (Appendix F) and not the University of Utah AE Log.

All unsolicited AEs of any severity may be reported to the study team from the time of study vaccination completion to the participant's last study-related procedure. Unsolicited reports that occur more than 28 days after administration of the study vaccine will not be reported as AEs unless a study investigator determines that the illness is related to the study vaccine.

All SAEs may be reported to the study team from the signing of informed consent until completion of the participant's last study-related procedure. Study staff will record all SAEs on the University of Utah Serious Adverse Event (SAE) Log (Appendix R3).

All AEs will be followed until resolution or withdrawal from the study. All AEs, SAEs, and AESIs will be followed until resolution, until the end of the study, until clinically stable or considered chronic, or withdrawal from the study. In the case of persistent non-response from a participant reporting an AE, SAE, or AESI, staff will make at least three attempts to contact the participant via differing methods (text message, phone call, email) over 30 days. At which point, the event will be reported with all available information and administratively closed.

All vaccine administration errors, AEs, SAEs, AESIs, cases of multisystem inflammatory syndrome, and hospitalized or fatal cases of COVID-19 following vaccination with the authorized-vaccines must be reported following local regulatory reporting guidance for safety events that occur in participants who receive authorized-vaccines within the study.

Investigators are not obligated to actively solicit information on AEs, SAEs, or AESIs after the participant has concluded study participation. At any time after the participant has concluded study participation or after the end of the study, if the Investigator learns of an SAE that could reasonably be considered related to study vaccine, they must promptly notify the vaccine manufacturer(s).

## 9.2 Adverse Events (AE)

AEs will be assessed during the study as described in Table 7 and should be followed until they are resolved, stable, or judged by the Investigator/Sponsor to be not clinically significant. AEs will be captured after the study vaccine is administered on Day 0. AEs will not be captured for those who are

not administered a study vaccine unless they are considered by the Investigator/Sponsor to be related to study procedures.

All participants will be assessed for unsolicited AEs from the time of study vaccination until Day 28 after the initial set of vaccinations; SAEs will be assessed from the time of informed consent is signed until completion of the participant's last study-related procedure; all Medically Attended AEs (MAAEs) will be reported from the time of the study vaccination until Day 35; MAAEs related to study vaccination and AESIs will be reported from the time of first study vaccination until completion of the participant's last study-related procedure.

The Investigator/Sponsor is responsible for ensuring that all AEs and SAEs are recorded in the University of Utah AE Log (Appendix R2) or SAE Log (Appendix R3). If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

Please note that the expansion of sections 9.2 and 9.3 is the result of expanding on the capture, documentation, and reporting of adverse events and serious adverse events to reflect what is requested by the FDA due to the IND requirements – all activities outlined here are mandated by the FDA and will be completed by UT staff.

**AE Definitions**

AEs may arise from symptoms or other complaints reported to the Investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator is responsible for reporting all solicited AEs that are observed or reported during the first 7 days, and unsolicited AEs that are reported during the first 28 days after administration of the study vaccine, regardless of their relationship to study vaccination or their clinical significance. After 28 days, only AEs which investigators deem to be related to the study vaccine will be reported. Any event that occurs during the duration of the study, which the investigators deem to be an SAE, will be recorded regardless of whether the investigators determine that it is related to the study vaccine.

Adverse Event means any untoward medical occurrence in a patient or clinical trial subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether considered related to the investigational product or not. This includes other safety information such as:

- Overdose, abuse, or misuse of the product;
- An adverse event occurring from the withdrawal of the product;
- Lack of product effect/efficacy;
- Accidental exposure;
- Medication error (i.e., administration of expired product)
- Suspected transmission of infectious agents;
- An unexpected therapeutic or clinical benefit;

- Off label use.
- Items that are reported as medical history will not be captured as AEs, unless their frequency, nature, severity, etc. is greater than what was normally encountered by the participant prior to participation in the study and/or receipt of the vaccine.

The Investigator will pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE.

**Serious Adverse Events (SAE)**

An SAE means any untoward medical occurrence that, at any dose,

- results in death;
- is life-threatening (an event is considered "life-threatening" if, in the view of the Investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction (SAR) that, had it occurred in a more severe form, might have caused death);
- requires inpatient hospitalization or prolongation of an existing hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Adverse Events of Special Interest (AESI)**

Myocarditis and pericarditis are our AEs of special interest. All AESIs may be reported to the study team from the time of study vaccination to the participant's last study-related procedure. AESIs will be captured through participant report only.

**Myocarditis and Pericarditis**

Due to the risk of myocarditis and pericarditis with the COVID-19 vaccines, participants reporting signs and symptoms of acute chest pain, shortness of breath, palpitation, or other signs or symptoms of myocarditis and pericarditis within 4 – 6 weeks after vaccination will be referred to a cardiologist for evaluation and management. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings.

At the study visit, vaccinated participants will receive an informational sheet (Appendix V5. Myocarditis and Pericarditis Information Sheet) describing the signs and symptoms of myocarditis and pericarditis

and guidance on seeking medical care and contacting study personnel. Participants reporting signs and symptoms of myocarditis or pericarditis may notify the study staff at any time via any and all methods of communication (i.e. email or phone call or text message).

In the event a participant report signs and symptoms or diagnoses of myocarditis and pericarditis, the Investigator will refer to the CDC case definitions for myocarditis, pericarditis, and myopericarditis (https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm) when making the determination.

In terms of reporting, cases of myocarditis or pericarditis occurring in temporal association with vaccination will be considered a potentially related, unexpected, and serious reaction (SUSAR) and will require expedited reporting to the FDA.

**Local and General Systemic Reactogenicity Symptoms**

Solicited AEs (e.g., local and general systemic reactogenicity symptoms) will be captured in all participants after the study vaccination (Table 7) through the Post-Vaccination Survey (Appendix W).

During the 7 days after study vaccination, potential COVID-19 symptoms that overlap with solicited systemic events should be assessed by the Investigator. The participant will be asked to complete the Acute Illness Survey (Appendix H) and self-collect a specimen using the rapid antigen test for COVID-19 and submit results per study procedures. The results of the rapid antigen test and reported symptoms will be recorded in the Acute Illness Survey (Appendix H). Following the 7-day assessment period, only unsolicited AEs will be reported. After 28 days from the administration of the study vaccine, only events that the investigators deem to be related to the study vaccine will be reported as AEs.

Investigator will review the reactogenicity data daily as part of the ongoing safety review.

**Pregnancy**

Pregnancy is not considered an AE unless the Investigator/Sponsor considers that an investigational vaccine may have interfered with the effectiveness of a contraceptive medication. Pregnancy will not be reported for participants who do not receive a study vaccine. Participants may report pregnancy that occurs during study participation using Mid-study and End-of-study surveys (Appendix O). To ensure participant safety, each pregnancy must be reported to vaccine manufacturer(s) within 24 hours of learning of its occurrence. Pregnancy must be followed using the Pregnancy Assessment Form (Appendix Z) to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of both mother and child, even if the participant was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Abnormal pregnancy outcomes are considered SAEs. Spontaneous miscarriages, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital abnormalities must be reported as an SAE.

Any pregnancy in a vaccinated participant brought to the investigator/Sponsor's attention before the study is completed must be reported to the vaccine manufacturer(s).

Any pregnancy in a vaccinated participant brought to the investigator/Sponsor's attention after the participant has completed the study but occurring while the participant was in the study must be promptly reported to the vaccine manufacturer(s).

**Overdose or Misuse**

A drug overdose is defined as the accidental or intentional use of a drug or medicine or an administration error in an amount that is higher than normally used. Every overdose must be reported to the vaccine manufacturers within 24 hours of awareness if the overdose was associated with an SAE. Other overdoses and those associated with a non-serious AEs must be recorded on the University of Utah AE Log. Only overdoses associated with a clinical SAE need to be reported as an SAE and recorded in the University of Utah SAE Log. The quantity and duration of the excess dose must be recorded in the Incident Report Form, University of Utah AE Log, and/or University of Utah SAE Logs (as applicable).

Overdose in this study is specifically defined as any dose greater than the intended protocol dose. In case of overdose, it is recommended that the participant be monitored for any signs and symptoms of Adverse Reactions and/or referred for appropriate treatment to be administered immediately. Note that administration of the "wrong" vaccine is a protocol deviation, but not, in the absence of associated AE, an SAE.

**Medication Error**

A medication error may result from the administration or consumption of the study vaccine by the wrong participant, or at the wrong time, or at the wrong dosage strength. Medication errors include:

- Administration of expired study vaccine
- Administration of incorrect study vaccine
- Administration of incorrect dosage
- Administration of study vaccine that has undergone temperature excursion from specific storage range, unless it is determined by the Investigator/Sponsor that the study vaccine under question is acceptable for use per vaccine manufacturer guidelines.

Medication errors are to be captured in the Incident Report Form, University of Utah AE Log, and/or University of Utah SAE Logs (as applicable).

Medication errors should be reported to vaccine manufacturer(s) within 24 hours on a CIOMS I Form when associated with an SAE.

## 9.3 Documenting an Adverse Event, SAE, AESI

All AEs reported or observed during the study will be recorded on the University of Utah AE Log (Appendix R2). Information to be collected includes type of event, date of onset, date of resolution or ongoing, Investigator-specified assessment of intensity and relationship to study vaccine and/or study procedure, determination of whether the event was expected or not, concomitant medications or

treatments, seriousness, treatment for event, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease must also be reported, if they occur within 28 days of administration of the study vaccine. All AEs will be followed until they are resolved, stable, or judged by the Investigator/Sponsor to be not clinically significant, or until participant non-response with regards to questions about the AE has exceeded three failed contact attempts and 30 days of follow-up.

Any events that do not meet the criteria for reporting listed above prior to Jun 24, 2024 will not be reported, with the exception of SAEs and AESIs.

All concomitant medications or treatments will be collected during enrollment on the University of Utah Concomitant Medication Log (Appendix R6).

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study and the participant reports it to the study, it should be recorded as an AE.

In the situation an AE results in a death, life-threatening, requires hospitalization or extends existing hospitalization, persistent or significant disability, congenital/birth defect, and/or recognized by the Investigator as medically important event or reaction, it would be considered a SAE. The SAE will be recorded on the University of Utah SAE Log (Appendix R3). Information to be collected includes whether the report is initial or a follow up, subject information, event type, serious criteria (death, life threatening, etc.), resolution date, causality, severity, event outcome, alternative causality if assessed as not related to study drug, vaccine product information (in situations where the meets criteria for unblinding or at Investigator/Sponsor discretion), narrative of the course of events, health history, and concomitant medications. If an AE is assessed as an SAE, and subsequently determined not to be an SAE, an AE Addendum report justifying the determination may be filed by the investigator, supplementary to the AE log (appendix R2.).

**Assessment of Intensity**

The Investigator will assess the intensity for each AE and SAE reported during the study. The severity (or intensity) of an AE refers to the extent to which it affects the participant's daily activities and will be classified as mild, moderate, or severe using the following criteria:

- Mild (grade 1): These events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate (grade 2): These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.
- Severe (grade 3): These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening (grade 4): Life-threatening consequences; urgent intervention indicated.

- Death (grade 5)

If the severity of an AE changes, the most intense severity should be reported. We record and will keep records of all previous intensities reported. An AE characterized as intermittent does not require documentation of the onset and duration of each episode.

**Assessment of Causality**

The investigator/Sponsor's assessment of an AE's relationship to study vaccine is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The Investigator/Sponsor will assess causality (i.e., whether there is a reasonable possibility that the study vaccine caused the event) for all AEs and SAEs (solicited reactions are to be considered as being related to study vaccination). The Investigator will use clinical judgement to determine the relationship. The Investigator/Sponsor will consult the vaccine manufacturer Fact Sheet in their assessment. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The relationship will be classified as follows:

- **Not related:** There is not a reasonable possibility of relationship to study vaccine. The AE does not follow a reasonable temporal sequence from administration of study vaccine or can be reasonably explained by the participant's clinical state or other factors (e.g., disease under study, concurrent diseases, other risk factors, and concomitant medications).
- **Related:** There is a reasonable possibility of relationship to study vaccine. The AE follows a reasonable temporal sequence from administration of study vaccine and cannot be reasonably explained by the participant's clinical state or other factors (e.g., disease under study, concurrent diseases, other risk factors, and concomitant medications), represents a known reaction to study vaccine or other vaccines in its class, is consistent with the and/or known pharmacological properties of the study vaccine. The Investigator/Sponsor will determine if the AE is "probably not related," "possibly related," or "definitely related" to study vaccine.

For each AE or SAE, the Investigator must document in the source records that they reviewed the AE or SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator/Sponsor has minimal information to include in the initial report to the regulatory authority(ies) and the vaccine manufacturer(s). However, it is very important that the Investigator/Sponsor always make an assessment of causality for every event before the initial transmission of SAE data to regulatory authority(ies) and the vaccine manufacturer(s).

The Investigator/Sponsor may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

**Follow-up of AEs and SAEs**

All AEs must be reported in detail on the appropriate page of the University of Utah AE Log and followed until they are resolved, stable, or judged by the Investigator/Sponsor to be not clinically significant, or until participant non-response with regards to questions about the AE has exceeded three failed contact attempts and 30 days of follow-up.

The Investigator is responsible for performing or arranging the conduct of supplemental evaluations, as medically indicated, to elucidate the nature and/or causality of the AE or SAE as fully as possible.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator/Sponsor will notify the vaccine manufacturer(s).

New or updated information will be recorded in the originally submitted documents.

The Investigator/Sponsor will submit any significant SAE follow-up information to the regulatory agency(ies) and vaccine manufacturer(s) within 15 calendar days of receipt of the information.

## 9.4 Reporting an Adverse Event, SAE, AESI

University of Utah, the Investigator/Sponsor, will be responsible for notification of AE, SAE, and AESI, to the IRB according to the IRB's policy and guidelines.

University of Utah, the Investigator/Sponsor, will be responsible for notification of SAE, AESI, and other qualifying events that are considered to be unexpected and related to the study vaccine as expedited (e.g. 7- or 15-day) reports to relevant regulatory authorities and vaccine manufacturers (Novavax and Pfizer-BioNTech). In addition, Investigator/Sponsor will report SAE, AESI, and other qualifying events that are considered to be unexpected and related to the study vaccine to the IRB.

The CIOMS I Form will be used to report SAE, AESI, and Suspected Unexpected Serious Adverse Reaction to relevant regulatory authorities and vaccine manufacturers (Novavax and Pfizer-BioNTech) as applicable. For events determined as Suspected Unexpected Serious Adverse Reaction (SUSAR), the Investigator/Sponsor will be responsible for preparing and reporting on the IND safety report to the FDA with the local IND office. The IND safety report and corresponding approvals/acknowledgements documents will be maintained and kept on file with the regulatory record.

The table below summarizes the requirements for recording safety events and for reporting to IRB(s), vaccine manufacturer(s) and submitting an IND safety report to regulatory authority(ies):

**Table 8. Recording and Reporting Safety Events**

| Safety Event | Recorded on the University of Utah AE or SAE/AESI log | Reported to IRB[a] | Reported on the CIOMS I Form | Reported on the IND safety report to regulatory authority(ies) |
|---|---|---|---|---|
| **SAE**[b] **AESI**‡ | UU SAE/AESI log | Yes* | Yes | No |
| **SUSAR**[c] ‡ | UU SAE/AESI log | Yes* | Yes | Yes |
| **Suspected Adverse Reaction (SAR)**[d, e] | UU AE log | Yes* | No | No |
| **Non-serious AE**[e] | UU AE log | Yes* | No | No |
| **Medication errors** | Protocol deviation, unless qualifies as an AE | Yes (regardless of whether associated with an AE) | Only if associated with an SAE | Only if meets IND safety report criteria |

[a] All adverse events that are reported through the University of Utah AE log are submitted to the University of Utah IRB

[b] An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator/Sponsor, it results in the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

‡ Cases of myocarditis or pericarditis occurring in temporal association with vaccination will be considered a potentially related, unexpected, and serious reaction (SUSAR) and will require expedited reporting.

[c] Suspected Unexpected Serious Adverse Reaction; an adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if any investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

[d] Suspected Adverse Reaction: any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

*Recorded in the AE section of the Incident Report Form

[e]Non-serious AEs and SARs will only be reported immediately if they meet the reporting criteria for AEs: (1) The AE is unexpected. (2) The AE is related to the trial (3) The AE suggests an increase in risk or

potential harm than was previously understood or known when the IRB reviewed/approved the trial. Otherwise, non-serious AEs and SARs will be submitted yearly as part of the Continuing Review.

Source: Guidance for Industry and Investigators Safety Reporting Requirement for INDs and BA/BE Studies. U.S. Department of Health and Human Services, Food and Drug Administration. December 2012.

## 9.5 Protocol and Information Amendments

Protocol amendments which significantly affect the safety of subjects and information amendments which fall under 21 CFR 312.31 will be submitted to the FDA, all participating clinical investigators, and the IRB. Information amendments include new toxicology, chemistry, or other technical information or a report regarding the discontinuation of a clinical investigation. The Sponsor-Investigator will be responsible for preparing and submitting these amendments to the FDA in collaboration with the local IND office. The Sponsor-Investigator or designated staff will be responsible for submitting the amendments to the University of Utah IRB, the IRB of record. The Sponsor-Investigator or designated clinical research coordinator will be responsible for submitting the amendments to University of Utah IRB. Amendments will be submitted as necessary but not more than every 30 days. The amendment documents submitted to the FDA will be maintained and kept on file with the regulatory record. Changes will not be implemented until approved by the University of Utah IRB.

## 9.6 Reports

**Annual Reports and Final Reports**

The Sponsor-Investigator will ensure that annual reports will be submitted to the FDA within 60 days of the anniversary date that the IND went into effect. The Sponsor-Investigator will be responsible for preparing and submitting these reports. The reports will follow the requirements outlined in 21 CFR 312.33. These annual and final report documents will be maintained and kept on file with the regulatory record.

**IND Withdrawal**

If the Investigator/Sponsor withdraws the IND, they will be responsible to notify the FDA and the University of Utah IRB. The Investigator/Sponsor will provide the appropriate documentation to the FDA. The Investigator/Sponsor will directly notify the IRB of this withdrawal. The study participants will be notified in the event the IND is withdrawn within 24 hours of the withdrawal date. In the notification, participants will be given information on how to contact the Investigator/Sponsor to report any adverse events or pregnancy events after the IND withdrawal date.

If the Investigator/Sponsor withdraws the IND, the Investigator/Sponsor or designee (i.e., co-investigator, study coordinator) will promptly report this to the IRB.

**Clinical Holds**

In the event the study is placed on a clinical hold by the FDA, the study will not administer the study vaccines, surveillance will be paused, and no new participants will be recruited to the study. The study participants will be notified of the clinical hold by the FDA within 24 hours of the clinical hold date. In the notification, participants who have received the study vaccine will be given information on how to contact the Investigator/Sponsor to report any adverse events or pregnancy events after the clinical hold date.

If the FDA places the study on a clinical hold, the Investigator/Sponsor or designee (i.e. co-investigator, study coordinator) will promptly report this to the University of Utah IRB.

**Study Termination by the FDA**

In the event that the study is terminated by the FDA, the Investigator/Sponsor will stop administering the study vaccines, stop all surveillance activities (i.e. IT team turns off database platform), and stop recruitment activities. The disposition of all unused study vaccines will be conducted under University of Utah Pharmacy SOPs. The study participants will be notified of the study termination by the FDA within 24 hours of the termination date. In the notification, participants who have received the study vaccine will be given information on how to contact the Investigator/Sponsor to report any adverse events or pregnancy events after the termination date.

If the study is terminated by the FDA, the Investigator/Sponsor or designee (i.e. co-investigator, study coordinator) will promptly report this to the University of Utah IRB.

## 9.7 Investigators and Monitors

All participating clinical investigators are qualified by training and experience as appropriate experts to investigate the study vaccines. Investigator and co-investigator will submit their curriculum vitae (CV) to the FDA and the CVs will be kept on file with the regulatory file. The Investigator will submit their CV to the University of Utah IRB.

The study vaccines will only be shipped to the Investigator/Sponsor and tracked by the Investigator/Sponsor or designee (i.e. co-investigator, study coordinator).

The Clinical Research Support Office (CRSO), a core within the Utah Clinical & Translational Science Institute (CTSI), supports investigators and research teams across the University of Utah campus in conducting clinical research. The Clinical Research Support Office Quality Assurance Group (CRSO QA) provides independent monitoring support and quality assurance guidance for investigators and study teams to ensure that studies are conducted in compliance with IRB-approved protocols, Good Clinical Practice (GCP) guidelines, and applicable Federal, State, and University policies and procedures. All University of Utah Sponsor-Investigators (SI) holding an Investigational New Drug (IND) or Investigational Device Exemption (IDE) receive the following services:

- Pre-IND/IDE Audit: The Pre-IND/IDE Audit is conducted following IRB submission but prior to IRB review. The audit will ensure that the IND/IDE application is completed and documented properly.
- First-Enrollment Review: Following enrollment of the first participant, the CRSO QA team will perform a complete review of the regulatory record and a risk-based review of the first participant's record. Pharmacy records will also be reviewed, if applicable. The baseline scope and frequency of the monitoring services listed above for an individual trial will be determined with a CRSO QA trial risk assessment prior to initial review. The trial risk factors used to determine baseline monitoring scope and frequency may include, and are not limited to: the phase of the trial, trial complexity, enrollment goals, multi-site trial, and/or investigator and trial team experience.
- Routine Monitoring: An ongoing monitoring schedule will be established following the first-enrollment review. The monitoring scope and frequency is dynamic throughout the life of the trial. The frequency and/or scope may increase or decrease throughout the trial based on performance of the investigative team, in accordance with the CRSO QA Oversight Plan.

The study can be ended before the planned end date as a result of study termination by the FDA, observed efficacy of the treatment (benefit), evidence of adverse effects (harm), or likelihood of failing to reject the null hypothesis (futility).

## 9.8 Recordkeeping and Record Retention

The Investigator/Sponsor or their designee will maintain records of receipt, shipment, administration or disposition of the study vaccines.

Participant case histories (i.e. signed and dated consent forms, medical history, vaccination history, study vaccine administration, surveillance data, etc.) will be electronically captured the M3 database system. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

The records of the drugs disposition and case histories will be kept for 2 years after a marketing application is approved for the study vaccines. If an application is not approved for the study vaccines, records will be kept until 2 years after shipment and delivery of the study vaccines is discontinued and FDA has been so notified. Electronic records will be stored in a secure, HIPAA-compliant system and paper records will be stored in a locked cabinet or a similarly secure space in the secure, restricted-access research offices.

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## 11. Appendices

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