A Prospective Observational Study to Evaluate the Safety of COVID-19 Vaccination in Children and Adolescents

Short Title: Safety of Pediatric COVID-19 Vaccination (Lead)

Centers for Disease Control and Prevention
Clinical Immunization Safety Assessment (CISA) Project

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STATEMENT OF COMPLIANCE

- This trial will be conducted in compliance with the protocol, the International Conference on Harmonization (ICH) Guideline E6-Good Clinical Practice (GCP), and the applicable guidelines and regulatory requirements from the United States (US) Code of Federal Regulations (CFR), 45 CFR Part 46.
- All study personnel with subject contact have completed Human Subjects Protection Training.

TABLE OF CONTENTS

PROTOCOL SUMMARY

Title:	A Prospective Observational Study to Evaluate the Safety of COVID-19 Vaccination in Children and Adolescents
Phase:	Phase 4
Population:	Up to 320 male or female children and adolescents ≥ 5 years to < 16 years
Clinical Sites:	Four: Duke University (Lead); Cincinnati Children's Hospital (Contributing); Kaiser Permanente (Contributing); Columbia University (Contributing)
Study Duration:	24 months
Participant Duration:	Approximately 7 months
Description of Study Procedures:	This is a prospective, observational study to evaluate the safety of COVID-19 vaccination in children and adolescents receiving vaccine as part of standard of care. Children and adolescents who have not received any previous COVID-19 vaccines will be enrolled with their first dose. Children and adolescents who have completed their primary vaccine series will enroll with their age-appropriate booster dose based on current FDA indications and CDC recommendations. Injection-site (local) and systemic reaction data and unsolicited adverse events will be assessed on vaccination day and daily during the 7 days following each COVID-19 vaccination dose using either identical web-based or paper memory aids, depending on study participant preference. At 3 sites, serum samples will be collected for optional assessment of antibody titers to COVID-19. Each participant who opts in will have baseline (within 3 days of vaccination) serologies obtained. Serum samples will also be collected for immunogenicity assessments at 28 (+7) days after dose 2 or a booster dose. All participants will be followed for 181 days after the last study dose 2 or a booster dose for serious adverse events (SAEs) and adverse events of special interest (AESI).
Objectives:	**Primary Objective (PO):** PO: To characterize the safety of authorized and recommended COVID-19 vaccines among children and adolescent participants

	Secondary Objective (SO): SO: To assess the safety of simultaneous administration of COVID-19 vaccine with other routinely recommended vaccines among children and adolescent participants **Exploratory Objectives (EO):** EO 1: To assess adolescent and parent perceptions of the COVID-19 vaccine recommendations and experience with receipt of the vaccine EO 2: To assess the safety of COVID-19 vaccine stratified by baseline COVID-19 serostatus (positive versus negative) in a subset of child and adolescent participants EO 3: To assess adverse events of special interest through 6 months after dose 2 of COVID-19 vaccine or a booster dose EO 4: To assess serious adverse events through 6 months after dose 2 of COVID-19 vaccine or a booster dose EO 5: To assess immune responses to SARS-CoV-2 antigens after COVID-19 vaccine
Outcome Measures:	**Primary Outcome Measures (POM):** POM 1: Proportion of participants with defined local or systemic reactogenicity events (stratified according to severity and in total) on days 1-7 after each dose of COVID-19 vaccine POM 2: Proportion of participants with at least one severe (Grade 3) solicited local or systemic reactogenicity event on days 1-7 after each dose of COVID-19 vaccine POM 3: Proportion of participants with at least one moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event on days 1-7 after each dose of COVID-19 vaccine POM 4: Proportion of participants with an unsolicited adverse event on days 1-7 after each dose of COVID-19 vaccine POM 5: Proportion of participants with an adverse event of special interest through 29 days after dose 2 of COVID-19 vaccine or a booster dose POM 6: Proportion of participants with at least one serious adverse event through 29 days after dose 2 of COVID-19 vaccine or a booster dose and a description of the events **Secondary Outcome Measure (SOM):**

	SOM 1: Assessment of primary outcome measures 1-6 in those receiving other routinely recommended vaccines with each dose of COVID-19 vaccine versus those receiving COVID-19 vaccine alone **Exploratory Outcome Measures (EOM):** EOM 1: Proportion of participants and legal guardians/parents with negative or positive perceptions of the vaccination experience based on participants responses to individual questions on the perceptions questionnaire EOM 2: Assessment of primary outcome measures 1-6 in those with positive baseline COVID-19 serostatus versus those with a negative baseline serostatus EOM 3: Proportion of participants with an adverse event of special interest through 6 months after dose 2 of COVID-19 vaccine or a booster dose EOM 4: Proportion of participants with a serious adverse event through 6 months after dose 2 of COVID-19 vaccine or a booster dose EOM 5a: The proportion of participants seropositive to SARS-CoV-2 variants tested prior to and following mRNA COVID-19 vaccine in a subset of children and adolescents. EOM 5b: The geometric mean ID_{50} and ID_{80} titers of neutralizing antibodies for each SARS-CoV-2 variant tested pre- and post-mRNA COVID-19 vaccine in a subset of children and adolescent participants.
Estimated Time to Complete Enrollment:	12 months

1 BACKGROUND

As of September 2022, there have been more than 95 million cases of COVID-19 leading to more than one million deaths in the United States (1). Although COVID-19 infection is generally milder in children than adults, it does cause significant pediatric morbidity and mortality. The American Academy of Pediatrics reports that 15 million children have been infected during the pandemic (2), leading to nearly 9000 cases of multisystem inflammatory syndrome in children (MIS-C) and 1500 deaths. From this perspective, safe and effective pediatric COVID-19 vaccines are needed to curb the pandemic.

In May 2021, the FDA issued an Emergency Use Authorization (EUA) for the Pfizer-BioNTech (Pfizer) mRNA COVID-19 vaccine in children aged 12-15. In the Phase III trial leading to the EUA, 2,260 adolescents 12-15 years old were randomized 1:1 to receive 2 doses of 30 ug of the BNT162b2 vaccine or placebo administered 3 weeks apart (3) . Pain at the injection site was the most common local reaction, occurring in 86% of vaccine recipients after dose 1, and was somewhat less common after dose 2 (79%). Fatigue (60%), headache (55%), and chills (28%) were the most common systemic events after dose 1. These were slightly more common after dose 2 (fatigue (66%), headache (65%), and chills (42%).

On October 29, 2021 the FDA issued an EUA for the Pfizer-BioNTech vaccine in children aged 5-11 years old, administered as 2 doses of 10 ug 3 weeks apart. The main safety study randomized children 2:1 to BNT162b2 (N=1518) vaccine or placebo (N=750); children were followed for at least 2 months after dose 2. In general, children had less severe systemic reactions than adolescents and young adults following the age-appropriate dose. The most common systemic reactogenicity events in children aged 5-11 years after were fatigue (33.6-39.4%) and headache (22.4-28%). In children aged 5-11 years fever was infrequent after dose 1 (2.5%) and dose 2 (6.5%). There were no serious adverse events in the pediatric study that were considered related to the BNT162b2 study vaccine. No cases of myocarditis or anaphylaxis occurred in the study (4).

In June 2022 the FDA issued an EUA for the Moderna mRNA-1273 vaccine in children and adolescents. In the published phase III adolescent clinical trial 2,732 adolescents 12-17 were randomized 2:1 to receive 2 doses of 100 ug of the mRNA-1273 vaccine or placebo, 4 weeks apart (5). . Pain was the most common local reaction, occurring in 94% of vaccine recipients after dose 1 and 93% after dose 2. The most common systemic reactions after dose 1 included fatigue (48%), headache (45%), myalgia and chills. Fatigue (68%) and headache (70%) were more common after dose 2.

Although these randomized controlled trials demonstrate the safety and immunogenicity of mRNA vaccines in children, there are several gaps in our current knowledge.

First, the initial clinical trials in adolescents excluded children with known history of COVID-19 infection. Baseline antibody testing was ascertained in both trials. Approximately 4% of participants in the Pfizer trial and 6% in the Moderna trial were seropositive at baseline, suggesting a prior history of asymptomatic infection. There were no significant differences in reactogenicity between children who were seropositive and those who were not. However, children with previous symptomatic infection may

have more robust reactogenicity, as has been seen in adults (6). The Pfizer 5-11 year-old trial did enroll children with prior COVID infections and found no significant differences in reactogenicity between children who did and did not have a prior history of infection (4).

Secondly, the published pediatric trials did not include a diverse population. COVID-19 infections, hospitalizations, and deaths disproportionately impact Black and Hispanic or Latinx populations (7). However, only 5% of participants in the Pfizer adolescent trial and 3% in the Moderna adolescent trial were Black. Similarly, only 12% of participants in each trial were of Hispanic or Latinx ethnicity. The Pfizer 5-11 year-old trial was slightly more diverse; 6.5% of participants were Black or African American and 21% were of Hispanic ethnicity (4).

Finally, there are sparse data regarding reactogenicity of COVID-19 vaccine when co-administered with other recommended vaccines. In all of the pediatric Phase III clinical trials to date, receipt of any vaccine within 7 days of enrollment was an exclusion criterion (8). The current CDC clinical considerations for COVID-19 vaccine do allow for receipt of COVID-19 vaccines on the same day as other vaccines. The guidance states that if multiple vaccines are administered at a single visit, each should be administered at a different injection site. (9). However, published data regarding the safety and reactogenicity of this approach are lacking.

In September 2022, the FDA amended the use of the Pfizer-BioNTech vaccine to authorize bivalent vaccine for individuals ≥ 12 year-old (10). However, there are no clinical data regarding the safety and immunogenicity of the BA.4 and BA.5 variant vaccines currently available in the United States.

Herein, we propose a prospective observational safety study of children receiving COVID-19 vaccine per standard of care, including booster doses. We hope to fill existing knowledge gaps concerning the safety of COVID-19 vaccines in the pediatric population by including children who were excluded from the trials, such as adolescents with a prior history of COVID-19 and those receiving concomitant vaccines. We also plan to make every effort to recruit a racially and ethnically diverse pediatric population.

2 STUDY OBJECTIVES

Primary Objective (PO):
To characterize the safety of authorized and recommended COVID-19 vaccines among children and adolescent participants

Secondary Objective (SO):
To assess the safety of simultaneous administration of COVID-19 vaccine with other routinely recommended vaccines among children and adolescent participants

Exploratory Objectives (EO):

EO 1: To assess adolescent and parent perceptions of the COVID-19 vaccine recommendations and experience with receipt of the vaccine

EO 2: To assess the safety of COVID-19 vaccine stratified by baseline COVID-19 serostatus (positive versus negative) in a subset of child and adolescent participants

EO 3: To assess adverse events of special interest through 6 months after dose 2 of COVID-19 vaccine or a booster dose

EO 4: To assess serious adverse events through 6 months after dose 2 of COVID-19 vaccine or a booster dose

EO 5: To assess immune responses to SARS-CoV-2 antigens after COVID-19 vaccine

Primary Outcome Measures (POM):

POM 1: Proportion of participants with defined local or systemic reactogenicity events (stratified according to severity and in total) on days 1-7 after each dose of COVID-19 vaccine

POM 2: Proportion of participants with at least one severe (Grade 3) solicited local or systemic reactogenicity event on days 1-7 after each dose of COVID-19 vaccine

POM 3: Proportion of participants with at least one moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event on days 1-7 after each dose of COVID-19 vaccine

POM 4: Proportion of participants with an unsolicited adverse event on days 1-7 after each dose of COVID-19 vaccine

POM 5: Proportion of participants with an adverse event of special interest through 29 days after dose 2 of COVID-19 vaccine or a booster dose

POM 6: Proportion of participants with at least one serious adverse event occurring through 29 days after dose 2 of COVID-19 vaccine or a booster dose and a description of the serious adverse events

Secondary Outcome Measure (SOM):

SOM: Assessment of primary outcome measures 1-6 in those receiving other routinely recommended vaccines simultaneously with each dose COVID-19 vaccine versus those receiving COVID-19 vaccine alone

Exploratory Outcome Measures (EOM):

EOM 1: Proportion of participants and legal guardians/parents with negative or positive perceptions of the vaccination experience based on participants responses to individual questions on the perceptions questionnaire

EOM 2: Assessment of primary outcome measures 1-6 in those with positive baseline COVID-19 serostatus versus those with a negative baseline serostatus

EOM 3: Proportion of participants with an adverse event of special interest through 6 months after dose 2 of COVID-19 vaccine or a booster dose

EOM 4: Proportion of participants with a serious adverse event through 6 months after dose 2 of COVID-19 vaccine or a booster dose

EOM 5a: The proportion of participants seropositive to SARS-CoV-2 variants tested prior to and following mRNA COVID-19 vaccine in a subset of children and adolescents

EOM 5b: The geometric mean ID_{50} and ID_{80} titers of neutralizing antibodies for each SARS-CoV-2 variant tested pre- and post-mRNA COVID-19 vaccine in a subset of child and adolescent participants.

3 STUDY DESIGN

3.1 Main study design

This study is a prospective, observational study to evaluate the safety of COVID-19 vaccine in 320 children and adolescents 5 - < 16 years-old receiving the vaccine per standard of care. Children and adolescents who have not received any previous COVID-19 vaccines will be enrolled with their first dose. Children and adolescents who have completed their primary vaccine series will enroll with their age-appropriate booster dose based on current FDA indications and CDC recommendations. With Day 1 serving as the day of vaccination, participants will be followed through Day 7 (total 7 days) after each dose of COVID-19 vaccine for symptoms of reactogenicity as described in **Section 5.1**. Participants will also be followed for 7 days after each vaccination for unsolicited adverse events, through day 181 for SAEs, and through day 181 for adverse events of special interest.

Demographic and medical history data will be collected and COVID-19 serostatus determined at baseline, and parent perceptions of COVID-19 vaccine will be assessed on Day 7 after each dose of vaccine. Participant perceptions will also be collected on Day 7 in adolescents aged ≥ 12 years.

3.2 Laboratory studies

3.2.1 Serologic studies

We will evaluate pre-serologic responses at three sites using an opt-in strategy. Prevaccination blood samples will be analyzed qualitatively for COVID-19 (SARS-CoV-2) antibody status (positive or negative) at Cincinnati Children's Hospital Medical Center in a CLIA-certified lab. Venous blood (approximately 5 mL of blood) will be collected from each participant in close proximity to the first vaccination (up to 3 days before or after vaccination). Venous blood will also be collected approximately 28 days after the second dose of vaccine received and stored for COVID-19 vaccine immunogenicity studies.

3.2.2 SARS-CoV-2 Antibody Assay

For children and adolescents at participating sites, optional blood draws will occur on Day 1 (before vaccination) and 28 (+7) days after dose 2 or a booster dose to be stored for serum COVID-19 neutralization assays. COVID-19 neutralizing antibody titers will be assessed for each variant tested. Participants will not receive individual COVID-19 antibody titer results; these are not routinely used in clinical practice.

3.2.3 Future studies

In addition to the specified analyses described thus far, there might be other tests or assays that have yet to be identified that might be important for interpreting our study findings or of relevance to pediatric health outcomes. Additional laboratory assays may test for antibodies against other bacteria or viruses, markers of inflammation, or used in research on the health of children and adolescents. Specimens banked for use in other studies will be linked to information (including identifying information) that participants provided to the study. Participants in the opt-in serology analyses must agree to potential future use of samples in order to be in the study. Because it is unknown if future testing will be of any utility, results of future testing will not be provided.

4 STUDY ENROLLMENT AND WITHDRAWAL

Subject Inclusion and Exclusion Criteria will be reviewed at Visit 1 to assess eligibility for study participation.

4.1 Subject Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in this observational study.

1. Children ≥ 5 years to < 16 years
2. Receiving first dose or a booster dose of a U.S. authorized or approved and recommended COVID-19 vaccine per standard of care.
3. Parent/legal authorized representative (LAR) willing to provide written informed consent per local IRB requirements
4. Participant willing to provide assent per local IRB requirements
5. Intention of being available for entire study period and complete all relevant study procedures, including follow-up phone calls
6. English or Spanish literate.

4.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in this study:

1. Current or planned participation in any clinical trial with an investigational product during the study period.*
   *Per protocol, co-enrollment in observational or behavioral intervention studies are permitted at any time. An investigational product may be permitted for therapy of an illness condition that occurs during the study period (e.g. COVID-19 illness)
2. Any condition, which, in the opinion of the investigators, may pose a health risk to the subject or interfere with the evaluation of the study objectives.
3. Anyone who is a relative of any research study personnel or is an employee supervised by study staff

4.3 Recruitment

The 320 participants in this study will be male or female children receiving COVID-19 vaccine per standard of care. Approximately 60 participants will be enrolled at Duke, 100 will be enrolled at Cincinnati, 70 will be enrolled at Columbia, and 90 will be enrolled at Kaiser Permanente.

Participants will be recruited from pediatric clinics and COVID-19 vaccination clinics affiliated with these sites. Medical records will be reviewed to identify, contact, and offer

study enrollment to potentially eligible children and adolescents. IRB-approved informational flyers/advertisements will be used to recruit children and adolescents receiving vaccination through public COVID-19 vaccination sites or clinics (primary care, or other clinic administering vaccine). Potential participants will be screened for eligibility and consented for study participation (if eligible) in-person (during routine care) or virtually (telephone or telehealth visit). Medical history, including vaccine history and COVID-19 disease history, will be obtained via participant and parent self-report with verification by chart review whenever feasible (including medical records, immunization registry records, and pharmacy records).

4.4 Reasons for and Handling of Withdrawals

The following may be reasons for study withdrawal:

- As deemed necessary by the principal investigator (PI).
- Parent(s)/LAR(s) withdrawal of permission for their child to participate.
- Subject withdrawal of assent (based on site IRB requirements)
- Lost to follow-up.
- Termination of the study by the sponsor.

A parent/LAR may withdraw permission for their child to participate at any time and for any reason, without penalty. Data collected prior to withdraw in the study will be included in the study.

4.5 Termination of Study

This study may be terminated for safety concerns of the principal investigators from the Lead or Contributing sites, CDC, or participating Institutional Review Boards (IRBs).

5 STUDY SCHEDULE, PROCEDURES, & EVALUATIONS

5.1 Schedule of Events

Children and adolescents meeting the proposed eligibility criteria (**Section 4.0**) will be recruited. Written informed consent will be obtained from study participants or their parent/guardian and assent from participants per local IRB requirements prior to conducting any study procedures. **Table 1** describes the schedule of study visits for children enrolling with their first COVID dose.

Table 1: Schedule of events: Primary Series (Dose 1 and 2)						
Procedure	Visit 1	Visit 1a	Visit 2	Visit 2a	Visit 3	Visit 4
Type of contact	Clinic	Phone/Text /Email/Data Review [a, b]	Phone/Data Review [c]	Phone/Text/Email/Data Review a, b	Clinic/ Phone [d]	Phone/Data Review
Time Relative to 1st COVID-19 Vaccine	**1 (-3)**	1-7 (+3)				
Time Relative to 2nd COVID-19 Vaccine			1 **(+3)**	1-7 (+3)	29 (+ 7)	181 (+/- 7)
Informed consent & Medical Release of Information	X					
Review Eligibility Criteria	X					
Data Collection (Demographic information and Medical History)	X					
COVID-19 Vaccination History	X					
COVID-19 Disease History	X	X	X	X	X	X
Concomitant Medications and Vaccines	X	X	X	X	X	X
Standard of Care COVID-19 Vaccine	X		X			
Memory aid training + supplies (training on temperature)	X		X			
Blood draw [e]	X [f]				X	
Staff to review Memory aid form (REDCap or paper)		X	X	X		
Obtain solicited adverse events		X	X	X		
Obtain unsolicited adverse events		X	X	X		
Obtain serious adverse event information and AESIs		X	X	X	X	X
Obtain parental and adolescent perceptions of COVID vaccine recommendations and receipt [g]		X		X		
Confirm date of next vaccine	X	X				
Confirm next study visit	X	X	X	X	X	

a. Memory aid (solicited local and systemic reactogenicity events) to be completed by LAR/participant on Days 1-7 after vaccination.
b. LAR/Participants completing paper diary only will be called 3 [+3] days after each dose of vaccine as a reminder and to prompt to bring paper diary to next visit
c. May be clinic visit if COVID vaccine is administered at research site
d. May be phone visit if not obtaining immunogenicity labs
e. Blood draws are optional and will be only performed at participating sites
f. Blood draw may be performed 3 days before or after vaccine
g. Adolescent perceptions of COVID-19 vaccine will be collected for adolescents (ages 12 - < 16 only)

Visit 1, Day of Vaccine or up to 3 Days Prior - Screening, Enrollment, and Vaccination (Clinic Visit)

- Obtain parental permission by written informed consent and a release of medical record information, based on site IRB requirements
- Obtain assent from child, based on site IRB requirements
- Review and confirm study eligibility
- Obtain information on preferred method of contact for follow-up (telephone or email, or text reminder reminder)
- Obtain demographic data & COVID-19 vaccine history
- Obtain history of vaccines within 2 weeks of enrollment
- Obtain medical history, including COVID-19 disease history
- Obtain concomitant medication and vaccine use
- For children at participating sites, obtain optional blood sample within 3 days before or after vaccination for serologic analysis
- Dispense thermometer, ruler (in order to standardize measurements) and memory aid. Review instructions for use of thermometer, ruler, and memory aid completion. Preference will be to complete the memory aid electronically, with paper as a back-

up.
- Confirm anticipated date of COVID vaccine, if not already occurred
- Confirm date of next scheduled study visit

Visit 1a, Days 1-7 after dose 1 (Phone Visit)
- Subjects/parent/LAR will complete their memory aid via paper or electronic entry at approximately the same time each day for days 1-7, study staff will review subject-entered data within the database or by phone contact
- For participants using REDCap web-based system:
    - Study staff will send daily reminders to fill out the symptom diary
    - Record clinical data related to COVID diagnoses
    - Study staff will review REDCap system to confirm data capture and assess for any AE, AESIs, or SAEs on day 3 and 7 after vaccine
    - If any missing values, reported hives, or Grade 3 events occurred, the study staff will use phone contact to gather more information
    - The first parental and adolescent (if applicable) survey will be administered on day 7 after vaccine
    - Study staff will verify date of next COVID-19 vaccine and remind subjects to complete memory aid with next dose
- For participants using paper diary:
    - Study staff will call participants on day 3 after vaccine as a reminder to fill out the symptom diary
    - The first parent and adolescent (if applicable) survey will be administered on day 7
    - Study staff will call participants on day 7 (+ 3 days)
        - Record symptom diary
        - Record COVID-19 diagnoses
        - Record first parental and adolescent (if applicable) survey
        - Verify date of next COVID-19 vaccine and remind subjects to complete memory aid with next dose

Visit 2, COVID-19 Vaccine Dose 2 (+ 3 Days) (Clinic or Phone Visit)
- Confirm receipt of second dose of COVID vaccine
- Record any AEs, AESIs, SAEs, and concomitant medications and vaccinations as described in **Section 5.5.**
- Record clinical data related to COVID-19 diagnoses
- Confirm preferred method of contact for follow-up (telephone, email, or text reminder)
- Review instructions for use of thermometer, ruler, and memory aid completion.

Visit 2a, Days 1 - 7 Days after dose 2 (Phone Visit)
- Subjects/parent/LAR will complete their memory aid via paper or electronic entry at approximately the same time each day for days 1-7, study staff will review subject-entered data within the database or by phone contact
- For participants using REDCap web-based system:
    - Study staff will send daily reminders to fill out the symptom diary
    - Record clinical data related to COVID diagnoses
    - Study staff will review REDCap system to confirm data capture and assess for any AE, AESIs, or SAEs on day 3 and 7 after vaccine

    - If any missing values, reported hives, or Grade 3 or greater events occurred, the study staff will use phone contact to gather more information
    - The second parental and adolescent (if applicable) survey will be administered on day 7 after vaccine
- For participants using paper diary:
    - Study staff will call participants on day 3 after vaccine as a reminder to fill out the symptom diary
    - The second parental and adolescent (if applicable) survey will be administered on day 7 after vaccine
    - Study staff will call participants on day 7 (+ 3 days) after vaccine
        - Record symptom diary
        - Record COVID-19 diagnoses
        - Record second parental and adolescent (if applicable) survey

Visit 3, 28 Days (window days 29-35) after COVID-19 Dose 2 (Clinic Visit or Phone Visit)

- Clinic visit for optional post-vaccination blood draw for immunogenicity studies
- If no blood draw, may be a phone visit
- Review concomitant medications and vaccinations.
- Solicit for the occurrence of any adverse events of special interest or serious adverse events.

Visit 4, 180 days (window Days 174 - 188) after Dose 2 (Phone Visit)

- Record any SAEs or adverse events of special interest as described in **Section 5.5**
- Obtain concomitant medication and vaccine use

Table 2 describes the schedule of study visits for children enrolling with their COVID-19 booster dose.

Table 2: Schedule of events: Booster Dose				
Procedure	Visit 1	Visit 1a	Visit 2	Visit 3
Type of contact	Clinic	Phone/Text /Email/Data Review [a, b]	Clinic/ Phone [c]	Phone/Data Review
Time Relative to COVID-19 Vaccine Booster	1 (-3)	1-7 (+3)	29 (+7)	181 (+/- 7)
Informed consent & Medical Release of Information	X			
Review Eligibility Criteria	X			
Data Collection (Demographic information and Medical History)	X			
COVID-19 Vaccination History	X			
COVID-19 Disease History	X	X	X	X
Concomitant Medications and Vaccines	X	X	X	X
Standard of Care COVID-19 Vaccine Booster	X			
Memory aid training + supplies (training on temperature)	X			
Blood draw[d]	X[e]		X	
Staff to review Memory aid form (REDCap or paper)		X		
Obtain solicited adverse events		X		
Obtain unsolicited adverse events		X		
Obtain serious adverse event information and AESIs		X	X	X
Obtain parental and adolescent perceptions of COVID vaccine recommendations and receipt [f]		X		
Confirm next study visit	X	X	X	

a. Memory aid (solicited local and systemic reactogenicity events) to be completed by LAR/participant on Days 1-7 after vaccination.
b. LAR/Participants completing paper diary only will be called 3 [+3] days after each dose of vaccine as a reminder and to prompt to bring paper diary to next visit
c. May be phone visit if not obtaining immunogenicity labs
d. Blood draws are optional and will be only performed at participating sites
e. Blood draw may be performed 3 days before or after vaccine
f. Adolescent perceptions of COVID-19 vaccine will be collected for adolescents (ages 12 - < 16 only)

Visit 1, Day of Vaccine or up to 3 Days Prior - Screening, Enrollment, and Vaccination (Clinic Visit)

- Obtain parental permission by written informed consent and a release of medical record information, based on site IRB requirements
- Obtain assent from child, based on site IRB requirements
- Review and confirm study eligibility
- Obtain information on preferred method of contact for follow-up (telephone or email, or text reminder reminder)
- Obtain demographic data & COVID-19 vaccine history
- Obtain history of vaccines within 2 weeks of enrollment
- Obtain medical history, including COVID-19 disease history
- Obtain concomitant medication and vaccine use
- For children at participating sites, obtain optional blood sample within 3 days before or after vaccination for serologic analysis
- Dispense thermometer, ruler (in order to standardize measurements) and memory aid. Review instructions for use of thermometer, ruler, and memory aid completion. Preference will be to complete the memory aid electronically, with paper as a back-up.
- Confirm date of next scheduled study visit

Visit 1a, Days 1-7 after dose 1 (Phone Visit)

- Subjects/parent/LAR will complete their memory aid via paper or electronic entry at approximately the same time each day for days 1-7, study staff will review subject-entered data within the database or by phone contact
- For participants using REDCap web-based system:
    - Study staff will send daily reminders to fill out the symptom diary
    - Record clinical data related to COVID diagnoses
    - Study staff will review REDCap system to confirm data capture and assess for any AE, AESIs, or SAEs on day 3 and 7 after vaccine
    - If any missing values, reported hives, or Grade 3 events occurred, the study staff will use phone contact to gather more information
    - The parental and adolescent (if applicable) survey will be administered on day 7 after vaccine
    - Study staff will verify date of next study visit
- For participants using paper diary:
    - Study staff will call participants on day 3 after vaccine as a reminder to fill out the symptom diary
    - The parent and adolescent survey (if applicable) will be administered on day 7
    - Study staff will call participants on day 7 (+ 3 days)
        - Record symptom diary
        - Record COVID-19 diagnoses
        - Record parental and adolescent survey (if applicable)

Visit 2, 28 Days (window days 29-35) after COVID-19 Booster (Clinic Visit or Phone Visit)

- Clinic visit for optional post-vaccination blood draw for immunogenicity studies
- If no blood draw, may be a phone visit
- Review concomitant medications and vaccinations.

- Solicit for the occurrence of any adverse events of special interest or serious adverse events.

Visit 3, 180 days (window Days 174 - 188) after COVID-19 Booster (Phone Visit)

- Record any SAEs or adverse events of special interest as described in **Section 5.5**
- Obtain concomitant medication and vaccine use

5.2 Parent/LAR Permission Process (Informed Consent)

The consent process will take place in research or clinic exam rooms behind closed doors to assure privacy of the prospective participant. Study staff will be available to answer all parent/LAR and participant questions before and after permission is obtained. Parent(s)/LAR(s) will be given as much time as needed to decide whether or not to allow their child to participate. We anticipate that the initial consent discussion, including presenting the information in the consent document and answering questions will take about 30 minutes. Parent(s)/LAR(s) will have the opportunity to take the consent form home and discuss the document with other family members or friends. During the consent process, it will be stressed that participation is voluntary and that parents/LARs can withdraw permission for their child to participate at any time. Permission will not be obtained from parent(s)/LAR(s) who do not read, who are blind, or who do not read/understand English or Spanish. Parent(s)/LAR(s) will be given a copy of the signed informed consent to take home with them. The original copy of the consent will be kept in the study records and a third copy will be included in the child's medical record per local requirements. Eligibility will be assessed. Depending on site IRB requirements, assent may also be obtained from the child.

5.3 Demographic Information, Medical History, Immunization History

The participant's age, race/ethnicity, and medical history will be obtained by parent/guardian report at the time of enrollment. The participant's medical history, concomitant medications and vaccines taken within 2 weeks of enrollment will be obtained by review of the electronic health record (EHR) and will be reviewed and confirmed by the parent/guardian at the time of enrollment.

Vaccines received during the study period will be documented by the clinic or research staff who administered the vaccines. Documentation will include: product brand, lot number, site and date/time of vaccine administered during study participation.

Throughout the study, the medical record will be reviewed to assess and record the occurrence of any serious adverse events or adverse events of special interest that occurred during the period of study enrollment.

5.3.1 Randomization

This is an observational study with no randomization.

5.4 Data Collection

Study staff will collect baseline participant data at study enrollment and reactogenicity data during follow-up phone calls visits. **Table 3** describes the proposed variable domains and measures with further details below.

Table 3. Proposed Data Collection	
Domain	**Candidate Variables**
Clinic Study Visits	
Socio-demographic characteristics of participant	Age (years), gender, race/ethnicity
Medical history of participant	Significant Medical Conditions
Concomitant medications	Over-the-counter and prescribed medications taken within 2 weeks of enrollment
Vaccine history	Collect vaccine history within 14 days prior to enrollment
Vaccine administration	Brand, lot number, site of vaccination, date/time of vaccination within 14 days prior to enrollment and during study enrollment.
Phone call and Clinic Visit Follow-up	
Solicited AEs	Local (Refer to **Table 4**) Systemic (Refer to **Table 5**)
COVID-19 Disease History	COVID-19 diagnoses
Adverse Events of Special Interest	Myocarditis, pericarditis, multisystem inflammatory syndrome in children (MIS-C), allergic type reactions (as described in Section 5.5)
Unsolicited AEs, SAEs and Clinically Significant Events	Responses to open-ended inquiry on health status changes since enrollment
Concomitant medications	Over-the-counter and prescribed medications initiated since vaccination
Concomitant vaccinations	Vaccines administered within14 days of enrollment and since COVID-19 vaccination
Adolescent perceptions (ages 12 to < 16 years old)	Adolescent perspectives about COVID vaccination
Parental perceptions	Parental perspectives about COVID vaccination

Vaccine Exposure Assessment
Information on prior history of COVID-19 vaccination will be obtained at the time of study enrollment, based on self-report, to ensure that participants are COVID-19 vaccine naive.

5.4.1 Vaccine Supply, Storage, and Administration

Vaccination is not a study procedure.

5.4.2 Biospecimen Collection & Handling

At 3 participating sites (excluding Columbia), blood specimens will be collected from children in the optional serologic analyses during study Visits 1 and 3 as detailed in **Table 1** for primary series as well as Visit 1 and Visit 2 for booster dose as detailed in **Table 2**. All blood samples will be collected into serum separator tubes, transported per site operational procedures and processed as follows:

- Gently mix the tube by inverting 5 times. Allow blood to clot at room temperature for at least 30 minutes.
- Centrifuge tube within 8 hours of collection at 1100 to 1300 RCF(g) for 10 minutes.
- Gently remove the vacutainer stopper avoiding serum contamination with red blood cells. Using a single-use pipette, transfer 0.5 mL aliquots of serum (top layer) into 1.0mL or 1.8 mL cryovials.

- Attach the study-specific barcode labels to the cryovial aliquots. Numbers should be placed lengthwise on the tube.
- Freeze the cryovials at -20°C in the temperature-monitored research center freezer for future shipment.

Serum aliquots will be stored at each of the participating site's accessioning units until immunogenicity assessments are performed.

5.5 Reactogenicity & Safety Assessment

Frequency and occurrence of local and systemic reactogenicity events will be assessed through post-vaccination Day 7 using a standard memory aid. At the time of study enrollment, participants will be given a thermometer and instructed on using the memory aid to document oral temperatures and post-injection symptoms. Beginning on the evening following the first COVID-19 vaccination, LARs/participants will record the participants oral temperature using the study-supplied thermometer, the occurrence of solicited and unsolicited AEs, and concomitant medication use for the next 7 days (Day 1 – 7). Similarly, following the second COVID-19 vaccination, LARs/participants will record the participant's oral temperature using the study-supplied thermometer, the occurrence of solicited and unsolicited AEs, and concomitant medication use for the next 7 days. Temperature will be recorded at roughly the same time each day. If a temperature > 100°F (37.8°C) is recorded, a second measurement will be taken. If more than one temperature is taken on the same day, the highest temperature should be recorded. Fever will be defined as a measured temperature ≥100.4°F (38°C). Participants will be queried during Visits 1a and 2a on solicited injection site adverse events, which will be classified as mild, moderate, or severe as described in **Table 4**. Participants will also be queried during Visits 1a and 2a on common post-injection systemic symptoms as described in **Table 5.**

Unsolicited adverse events (AEs) will be collected and reported for the 7 days following each vaccine. Any reports of new rash within 7 days after each dose will prompt a call from the study team to ascertain severity and the likelihood of an allergic reaction. Concomitant medication use, and concomitant vaccinations will be assessed through 29 days after dose 2 or a booster dose. Serious adverse events (SAEs), adverse events of special interest (AESIs) and unscheduled medical care for COVID-19 illness will be assessed at 29 days after dose 2 of COVID-19 vaccine or a booster dose and through the end of the study (181 days after dose 2).

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Participants (or their parents) will be encouraged to report any significant unsolicited adverse events in an open-ended question format, e.g. "How are you (or your child) doing? Are you (or your child) having any medical or clinical problems? If so, please tell me about them."

An adverse event of special interest (AESI) includes the following:

- Allergic type reactions (including anaphylaxis, hives, or facial and limb swelling occurring within 7 days of a vaccination visit)
- Myocarditis or pericarditis occurring during the study period
- Multisystem inflammatory syndrome in children (MIS-C) during the study period

A serious adverse event (SAE) is defined as an AE that meets one of the following conditions:

- Results in death during the period of protocol-defined surveillance
- Is life-threatening (defined as immediate risk of death at the time of the event)
- Requires inpatient hospitalization or prolonged hospitalization during the period of protocol-defined surveillance (other than routine hospital admission for an elective medical procedure or surgery)
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. 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.

Unsolicited adverse events, AESIs and SAEs will be graded as described in **Table 6**. Participants who report severe solicited adverse events or express any concern about symptoms/unsolicited events will be encouraged to follow up with their primary care provider. Study staff will assist with coordination of referral appointments as necessary. Parent/LAR will be asked to agree to the release of information to obtain and review medical records for any unscheduled medical appointments, including clinic visits and telehealth visits, through 29 days after the second dose. Frequency and occurrence of serious AEs (SAEs), AESIs and unscheduled medical care for COVID-19 illness will be assessed through 181 days after dose 2 or a booster dose.

Table 4: Injection-site Reactogenicity

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity
Tenderness	Does not interfere with activity	Interferes with activity	Prevents daily activity
Underarm or groin swelling on same side as vaccine	Does not interfere with activity	Interferes with activity	Prevents daily activity
Swelling	5-11 years: 5-20 mm	5-11 years: 21-70 mm	5-11 years: >70 mm
	12 years >: 20-50 mm	12 years >: 51 - 100 mm	12 years: >100 mm
Redness	5-11 years: 5-20 mm	5-11 years: 21-70 mm	5-11 years: >70 mm
	12 years >: 20-50 mm	12 years >: 51 - 100 mm	12 years: >100 mm

Table 5: Systemic Reactogenicity

Systemic	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C)	≥ 38.0 – 38.4 ≥ 100.4 - < 101.1° F	>38.4 – 38.9 ≥ 101.1 - < 102° F	> 38.9° C ≥ 102° F

Table 5: Systemic Reactogenicity			
Feverishness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Fatigue	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Muscle Pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Joint Pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Vomiting	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Diarrhea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Nausea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Facial or lip swelling	Does not interfere with activity	Some interference with activity	Prevents daily routine activity

Table 6: Grading for Unsolicited Adverse Events, AESIs and SAEs		
Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**
Does not interfere with activity	Some interference with activity	Prevents daily routine activity

In this study, COVID-19 vaccination is not a study procedure. COVID-19 vaccine administration will be given per standard of care to children and adolescents receiving vaccine under an EUA by the Food and Drug Administration. Published studies in children and adolescents found no vaccine-related serious adverse events in children or adolescents receiving BNT162b2 (3-5). Lymphadenopathy was identified as an adverse event occurring more frequently in BNT162b2 vs. placebo groups during clinical trials (11). Post-authorization vaccine safety data have identified two safety concerns that rarely can occur after vaccination: severe allergic reactions, including anaphylaxis, and myocarditis and pericarditis (11). Therefore, we do not anticipate any significant issue with serious adverse events (SAEs). Nevertheless, we will monitor study participants for SAEs during the protocol-defined surveillance period of 6 months after second dose or a booster dose. SAEs will be reported to the CDC and all participating IRBs according to institutional requirements.

Perceptions of COVID-19 vaccine

At Day 7 (+3) following each of the vaccination visits we will assess adolescent (ages 12 to < 16) and parent/LAR perceptions of the COVID-19 vaccine recommendations and experience with receipt of the vaccine. Questions are provided in **Tables 7 and 8** below. We will use a Likert scale (strongly agree, agree, neither, disagree, strongly disagree) to assess response to the questions about concerns regarding COVID-19 vaccine safety. As noted, adolescent and parent perceptions regarding vaccine receipt will be assessed at the reactogenicity assessment visits after each vaccine.

Table 7 Parental /LAR Perceptions of COVID-19 Vaccine Recommendations and Receipt
Vaccine Recommendation: What is your primary source of information about the COVID-19 vaccine (Choose one or more options): o Television o Internet o Radio o Social media o Family and friends o Your child's doctor or nurse o Another healthcare provider o Your child's school o Another source (please explain):
Vaccine Recommendation: COVID-19 vaccines have been adequately tested in adolescents and children
Vaccine Recommendation: COVID-19 vaccine should be required for school entry
Vaccine Receipt: Reactions at the vaccine site (pain, redness) were similar to other vaccines my child has received
Vaccine Receipt: Other reactions (fever, tiredness, muscle aches) were similar to other vaccines my child has received
Vaccine Receipt: I prefer that my child receives the COVID-19 vaccine on the same day as other vaccines

Table 8: Adolescent Perceptions (Ages 12 to < 16 years) of COVID-19 Vaccine Recommendations and Receipt
Vaccine Recommendation: What is your primary source of information about the COVID vaccine (Choose one or more option): ○ Television ○ Internet ○ Radio ○ Social media ○ Family and friends ○ Your doctor or nurse ○ Another healthcare provider ○ Your school ○ Another source (please explain):
Vaccine Recommendation: COVID-19 vaccines have been tested enough in adolescents
Vaccine Recommendation: COVID-19 vaccine should be needed to go to school
Vaccine Receipt: My reaction where I got the vaccine in the arm (pain, redness) were about the same to other vaccines I have received
Vaccine Receipt: Other reactions (fever, tiredness, muscle aches) were about the same to other vaccines I have received
Vaccine Receipt: I prefer to receive COVID-19 vaccine on the same day as other vaccines

Causality (relatedness) Assessment
Study site investigators will assess relatedness to COVID-19 vaccine or study procedures (related, possibly related, unlikely related, or not related) for SAEs and AESIs. Solicited symptoms in **Tables 4 and 5** will all be considered to be related to COVID-19 vaccine and causality assessment will not be done for these events. The study investigators will use their clinical judgement to make causality assessments and may consult the Safety Review Panel or CISA Project for assistance with causality determinations. The final causality assessment decision is the responsibility of the site PI where the subject was enrolled.

Reporting Adverse Events
SAEs and unanticipated problems will be reported to the CDC and all participating IRBs according to institutional requirements. Vaccination is not a study procedure.

Adverse events that occur in a recipient following COVID-19 vaccination should be reported to CDC's Vaccine Adverse Event Reporting System (VAERS). Vaccination providers are required by the Food and Drug Administration to report the following that occur after COVID-19 vaccination under Emergency Use Authorization:

- Vaccine administration errors
- Serious adverse events
- Cases of Multisystem Inflammatory Syndrome
- Cases of COVID-19 that result in hospitalization or death

Reporting is encouraged for any other clinically significant adverse event even if it is uncertain whether the vaccine caused the event. Information on how to submit a report to VAERS is available at https://vaers.hhs.gov or by calling 1-800-822-7967.

6 LABORATORY ANALYSES

Serum samples will be analyzed by the use of a qualitative enzyme-linked immunosorbent assay (ELISA) which measures IgG antibody to the SARS-CoV-2 Spike protein. Recombinant full length Spike protein is used to coat ELISA plates and serum samples that have an Optical Density (OD) value above the established cut off are considered positive for antibody. The assay was qualified for use in the Laboratory for Specialized Clinical Services at Cincinnati Children's Hospital Medical Center (CCHMC), a laboratory that is certified by the Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologist (CAP) under US FDA Emergency Use Authorization.

Qualitative serologic testing will be completed in periodic batches throughout the course of the study and will therefore not be available in real-time or for use in clinical decision-making. CCHMC will share participant results with submitting study sites as permitted by CDC. Study sites may share results with participants as permitted by FDA, CDC, and local site regulations.

6.1 COVID-19 Immunogenicity

The Duke NAb Laboratory for HIV and SARS-CoV-2 Vaccine Research and Development (Duke NAb Lab, PI: David Montefiori) will assess the magnitude, kinetics and duration of neutralizing antibody responses against SARS-CoV-2 by using a validated assay in an environment that operates in compliance with Good Clinical Laboratory Practices (GCLP).

Neutralization of SARS-CoV-2 Spike-pseudotyped viruses will be assessed in 293T/ACE2 cells as described in SOP "CFAR02-A0026 Measuring Neutralizing Antibodies Against SARS-CoV-2 Using Pseudotyped Virus and 293T/ACE2 Cells." This assay has been formally validated and is part of Drug Master File # 26862 with the US Federal Drug Administration. Assay validation was performed with human serum samples and monoclonal antibodies using the D614G form of the Wuhan-1 Spike, which is the dominant form of Spike protein in the global epidemic. This assay has also been validated using B.1.351(246R) and B.1.1.529 (BA1) and may be validated for other newly emerged variants as needed.

Neutralization is measured by using lentiviral particles pseudotyped with SARS-CoV-2 Spike and containing a firefly luciferase (Luc) reporter gene for quantitative measurements of infection by relative luminescence units (RLU). SARS-CoV-2 Spike-pseudotyped viruses are prepared and titrated for infectivity by using mutated forms of an expression plasmid encoding codon-optimized full-length Spike of the Wuhan-1 strain (VRC7480) provided by Drs. Barney Graham and Kizzmekia Corbett at the Vaccine Research Center, National Institutes of Health (USA). Mutations were introduced into VRC7480 by site-directed mutagenesis using the QuikChange Lightning Site-Directed Mutagenesis Kit from Agilent Technologies. All mutations were confirmed by full-length Spike gene sequencing. Pseudovirions are produced in HEK 293T/17 cells by transfection using Fugene 6 Transfection Reagent and a combination of Spike plasmid, lentiviral backbone plasmid (pCMV ΔR8.2) and firefly Luc reporter gene plasmid (pHR' CMV Luc) in a 1:17:17 ratio in Opti-MEM (Life Technologies). Pseudovirions are titrated

for infectious dose (TCID50) by making serial 3-fold or 5-fold dilutions in quadruplicate for a total of 11 dilutions in 96-well flat-bottom plates.

A pre-titrated dose of virus is incubated with 8 serial 5-fold dilutions of serum samples in duplicate in a total volume of 150 µl for 1 hr at 37°C in 96-well flat-bottom culture plates. Cells are detached using TrypLE Select Enzyme solution, suspended in growth medium (100,000 cells/ml) and immediately added to all wells (10,000 cells in 100 µL of growth medium per well). One set of 8 wells receives cells + virus (virus control) and another set of 8 wells receives cells only (background control). After 71-73 hrs of incubation, medium is removed by gentle aspiration and 30 µl of Promega 1X lysis buffer is added to all wells. After a 10 minute incubation at room temperature, 100 µl of Bright-Glo luciferase reagent is added to all wells. After 1-2 minutes, 110 µl of the cell lysate is transferred to a black/white plate. Luminescence is measured using a GloMax Navigator luminometer (Promega). Neutralization titers are the serum dilution at which RLUs are reduced by either 50% (ID50) or 80% (ID80) compared to virus control wells after subtraction of background RLUs. Serum samples are heat-inactivated for 30 minutes at 56°C prior to assay.

For assay internal quality controls (IQC), a qualified positive control is tested on each assay plate (plate control). Assay run controls may consist of COVID-19 convalescent serum samples or SARS-CoV-2 vaccine recipients with high, medium and low ID50 and ID80 titers against the test virus, plus a normal human serum negative control. Levey-Jennings plots will be generated during testing and checked for violations of standards that are based on the Westgard Rules. Violations of the Westgard Rules are investigated in real-time.

7 STATISTICAL CONSIDERATIONS

In collaboration with the Cincinnati, Columbia, and Kaiser teams, the research team at Duke will oversee the statistical analysis. Data will reside on a secure Duke server maintained by Duke Health Technology Solutions (DHTS). For the study, a database will be developed and a data set for the study without personal identifiers will be made available to the CDC upon request. Duke statisticians will develop a comprehensive Statistical Analysis Plan. The summary points of the analysis plan are presented below.

7.1 Sample Size and Power Estimation

Because this is an observational study with no randomization of subjects into treatment groups, there will be no formal statistical power or sample size calculation

7.2 Analysis Plan

7.2.1 Analysis Populations

There will be one study population named the Study Cohort. The Study Cohort includes any participant that was enrolled and received at least one dose of a COVID-19 vaccine.

7.2.2 Primary Objective

Primary Objective – To characterize the safety of authorized and recommended COVID-19 vaccines among children and adolescent participants

1) Tables will be produced that summarize each solicited local and systemic reactogenicity event by maximum classification (none, mild, moderate, and severe), as well as by moderate or severe through days 1-7 following COVID-19 vaccination for dose 1 and dose 2 or a booster dose. These tables will have the number and percentage for each classification and will be broken down by each site and across all sites. In addition, the number and percentage of participants with at least one moderate-to-severe local or systemic reactogenicity event will be described, as well as the proportion of participants with at least one severe local or systemic reactogenicity event. (POM 1, POM 2 and POM 3)

2) Tables will be produced that summarize each unsolicited adverse event by maximum classification (none, mild, moderate, and severe), as well as by moderate or severe through days 1-7 following COVID-19 vaccination for dose 1 and dose 2 or a booster dose. These tables will have the number and percentage for each classification and will be broken down by each site and across all sites (POM4).

3) Tables will be produced that summarize participants experiencing at least one serious adverse event or one AESI through the 29 days after dose 2 or a booster dose. This table will have the number and percentage for each outcome. Listings with the clinical narratives will also be provided. (POM5 and POM6)

7.2.3 Secondary Objective

Secondary Objective - To assess the safety of simultaneous administration of COVID-19 vaccine with other routinely recommended vaccines among children and adolescent participants.

1) Tables will be produced that summarize each solicited local and systemic reactogenicity event by maximum classification (none, mild, moderate, and severe), as well as by moderate or severe through days 1-7 following COVID-19 vaccination for dose 1 and dose 2 or a booster dose. These tables will have the number and percentage for each classification and will be broken down by concomitant childhood vaccine status (yes/no) by each site and across all sites. (SOM 1, SOM 2 and SOM 3)

2) Tables will be produced that summarize each unsolicited adverse event by maximum classification (none, mild, moderate, and severe), as well as by moderate or severe through days 1-7 following COVID-19 vaccination for dose 1 and dose 2 or a booster dose. These tables will have the number and percentage for each classification and will be broken down by concomitant childhood vaccine status (yes/no) by each site and across all sites. (SOM 4)

3) Tables will be produced that summarize participants experiencing at least one serious adverse event or one AESI through the 29 days after dose 2 or a booster dose. This table will have the number and percentage for each outcome and will be broken down by concomitant childhood vaccine status (yes/no). (SOM5 and SOM6)

The proportions by concomitant vaccine status (yes/no) for secondary outcomes 1 to 6 will be descriptively assessed using an exact Mantel-Haenszal statistic calculated using the Proc Logistic command in SAS at the two-sided alpha 0.05 level. Further details will

be described in the statistical analysis plan. The analysis for exploratory objectives will be described in the statistical analysis plan.

7.2.4 Exploratory Objective

Exploratory Objective- To assess immune responses to SARS-CoV-2 antigens after COVID-19 vaccine.

The analysis for exploratory objectives will be detailed in the comprehensive Statistical Analysis Plan. .

7.2.5 Safety Monitoring Plan

An interim safety data review of all SAEs will be performed with the goal of identifying unexpected safety concerns of clinical importance. The interim safety data review will be performed by a panel with relevant expertise who are not investigators on the study. The safety review panel will assess the clinical narratives of SAEs and AESIs for all participants who were vaccinated. Additional data reviews will be generated if the CDC and study investigators determine they are needed. There are no statistical analyses planned for this safety data review.

7.3 Data Management Plan

The novel Vanderbilt-designed resource developed specifically for online collection of research information, the Research Electronic Data Capture (REDCap) platform (https://projectredcap.org/), will be used to design study forms, including the reaction forms, and short customized questionnaires to collect information from study subjects. REDCap provides: 1) a streamlined process for rapidly building a database; 2) an intuitive interface for collecting data, with data validation and audit trail; 3) automated export procedures for seamless data downloads to common statistical packages; 4) branching logic, file uploading, and calculated fields; and 5) a quick and easy protocol set-up. This system will be used by Duke for data management. All electronic linkages will fulfill regulations for protection of human subjects and requirements to minimize the risk of breach of confidentiality.

All study-related documents containing protected health information, (e.g., enrollment logs, case report forms, memory aids, and perception surveys) completed by study participants, will be maintained in secure research offices at Duke, Cincinnati, Columbia and Kaiser, which are accessible to research staff only.

The study team will utilize a secure, encrypted, file transfer method for sharing study documents and data with the CDC. No personal identifiers will be included in any shared documents or datasets.

7.3.1 Research Electronic Data Capture (REDCap)

REDCap (http://project-redcap.org/) assists with the collection and management of data for diverse clinical and translational research studies. REDCap was designed around the concept of giving research teams an easy method to specify project needs and rapidly develop secure, web-based applications for collection, management and sharing of research data. REDCap accomplishes these key functions through use of a single study

metadata table referenced by presentation-level operational modules. Based on this abstracted programming model, databases are developed in an efficient manner with little resource investment beyond the creation of a single data dictionary. The concept of metadata-driven application development is well established, and the critical factor for successful data collection lies in creating a simple workflow methodology allowing research teams to autonomously develop study-related metadata in an efficient manner. Both products include secure institutional data hosting and include full audit-trails in compliance with Health Insurance Portability and Accountability Act (HIPAA) security requirements. The REDCap Consortium is comprised of 647 active institutions. The REDCap currently supports 68,000 projects with over 89,000 users spanning numerous research focus areas across the consortium. The current project will use this software application for the design of electronic forms to collect information from study participants, to link the baseline data, sample collection date, and laboratory results in an automated database family, to perform data cleaning and data quality assurance efficiently, and to design an analytical dataset for the analysis of the project data.

Data will be entered into the REDCap database by members of the study team from Duke, Cincinnati, Columbia, and Kaiser, using the paper case report forms utilized to record data collected as part of study procedures. Study investigators will be responsible for assuring that all paper records are securely stored according to the requirements of their IRBs. The study investigators will be responsible for assuring the accuracy of the data entered from the paper forms into REDCap.

In order to perform data cleaning and data quality assurance efficiently, numerous built-in filters and checks for consistency of the data including range and limit checks, branching logic and pull down menus to limit choices for categorical variables to a pre-specified list will be implemented and performed automatically to minimize data entry error. The data will be randomly sampled and checked against source records on a regular basis. The data and related analytical datasets will also be stored at the lead and contributing sites with secured password-protected computers.

7.3.2 Role of the CDC Investigators in the Project

This study is funded by a CDC contract with Duke University, Cincinnati Children's Hospital, Columbia University, and Kaiser Permanente as Task Orders in the CISA Project Contract. The Duke University PI (will oversee the study in partnership with the Cincinnati Children's Hospital PI, the Columbia University PI and the Kaiser Permanente PI). CDC staff will collaborate with all sites to develop the protocol, conduct the study, ensure the study is aligned with US Department of Health and Human Services (CDC) public health priorities, and analyze the data and disseminate the results. CDC may receive access to coded data not containing any directly identifying information.

8 HUMAN SUBJECTS

8.1 Human Participants Involvement, Characteristics, and Design

Duke, Cincinnati, Columbia, and Kaiser investigators will be responsible for submitting the protocol, informed consent, memory aids, recruitment materials and any written or verbally conveyed materials specific to this project to their institutional review boards. The CDC, as the funding agency, supports an exception to the sIRB mandate for the participating sites under the provision at 114(b)(2)(ii). CDC staff will be responsible for submitting materials to the CDC for review and obtain reliance on Duke IRB.

To facilitate participant recruitment at the practices, we will request a waiver of consent and HIPAA authorization as per institutional requirements for ascertainment (identification, selection) and/or recruitment of potential participants while recording identifiable private health information (PHI) prior to obtaining the participant's consent. This information will be obtained from review of the electronic scheduling and medical record systems in the clinics in order to determine eligibility for study enrollment. The PHI collected prior to consent will be used to recruit and screen only. Use of PHI in this manner involves no more than minimal risk to participants and no information will leave the study sites. Informed consent will be sought in accordance with 45 CFR 46.116, prior to enrollment.

Continuing reviews will be submitted to the IRBs in accordance with the new Common Rule. Protocol deviations or concerns about study integrity will be reported promptly to the overseeing IRB in accordance with institutional requirements.

8.2 Sources of Material
Medical history and immunization history will be obtained from the medical record and from parent and patient report. Demographic information will be obtained from the medical record and parent/LAR and patient report. Participants will record solicited adverse reactogenicity events and any medical intervention sought on the day of and 7 days following both vaccinations on the memory aid. Memory aid captured information will be reported to the study team during a telephone call or in the web-based REDCap system. Information about SAEs and AESIs will be obtained through medical record review and visits.

8.3 Potential Risks and Benefits
Risks of blood drawing include pain, swelling, bleeding, or bruising at the site where the blood sample is collected. Subjects may also experience dizziness or fainting.

8.4 Adequacy of Protection
Every effort possible will be made to keep information about participants confidential. Computerized participant information will be kept in password protected files on secured servers. Paper case report forms will be kept in locked files belonging to the study personnel. Any publications resulting from this work will not contain any identifiable participant information.

8.4.1 ClinicalTrials.gov Requirements
This observational study is not required to be registered on ClinicalTrials.gov by regulation. However, as requested by CDC, the study is registered on ClinicalTrials.gov (NCT NCT05157191). It is the responsibility of the lead site for creating, maintaining, and uploading pertinent information regarding the study to ClinicalTrials.gov.

9.0 HUMAN SUBJECTS

9.1.1 Vulnerable Subjects
This study proposes to include children and adolescents.

9.1.2 Vulnerable Subjects Research

Children are a vulnerable research population and require additional protections when they are potential research subjects. Because this study is minimal risk with the potential for benefit, the permission of only one parent/LAR will be obtained. Assent from participants 5 through <16 years of age will be obtained in a manner consistent with local IRB regulations.

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