A Prospective, Randomized, Open-label Clinical Trial to Assess the Safety of Simultaneous Vaccination with mRNA COVID-19 Vaccine and Other Vaccines in Young Children Aged 6 Months to <5 years.

Short Title: Safety of simultaneous mRNA COVID-19 with other childhood vaccines in young children

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.
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC or study sites.

TABLE OF CONTENTS

PROTOCOL SUMMARY

Title:	A Prospective, Randomized, Open-label Clinical Trial to Assess the Safety of Simultaneous Vaccination with mRNA COVID-19 Vaccine and Other Vaccines in Young Children Aged 6 Months to <5 years.
Phase:	Phase 4
Population:	Up to 600 children, aged 6 months to <5 years
Clinical Sites:	Four: Duke University (Lead); Cincinnati Children's Hospital (Contributing); Kaiser Permanente (Contributing); Columbia University (Contributing)
Study Duration:	24 months
Participant Duration:	Up to 105 days
Description of Study Procedures:	This is a prospective, randomized, open-label clinical trial to evaluate the safety of COVID-19 vaccination and other vaccines given simultaneously compared with sequential vaccination of mRNA COVID-19 vaccine and other vaccines at separate visits. Parent(s) or legal authorized representative(s) (LAR) will assess fever and other solicited systemic adverse events on the day of vaccination (Day 1) and the next 6 days (through Day 7) following Visit 1 and Visit 2 using either a web-based data collection system or a paper memory aid. Serious adverse events and adverse events of special interest will be captured during the entire study period. Parental/LAR perceptions about their child's vaccine schedule will be assessed on Day 7 following Visit 2.
Objectives:	**Primary Objective (PO):** To compare the proportion of children with fever after vaccination when mRNA COVID-19 vaccine is given simultaneously with other vaccines versus when mRNA COVID-19 vaccine and other vaccines are given at two separate visits. Children in the simultaneous vaccination group will receive routine non-COVID-19 childhood vaccinations and mRNA COVID-19 vaccination at Visit 1, followed by a health education visit without vaccination at Visit 2. Children in the sequential vaccination group will receive routine non-COVID-19 childhood vaccinations at Visit 1 followed by the mRNA COVID-19 vaccination and a health education visit at Visit 2. Fever will be assessed on the day (Day 1), and the day after each visit (Day 2).

	The primary hypothesis is that the proportion of children with fever in the simultaneous group will be noninferior (not higher) compared to the proportion of children with fever in the sequential group. **Secondary Objectives (SO):** SO 1: To compare the proportion of children with fever occurring 1-2 days after each visit (Visit 1 and Visit 2) in the simultaneous versus sequential group SO 2: To describe and compare the severity of fever, medical care utilization, and use of antipyretics for fever occurring 1-2 days after Visit 1 and Visit 2 (separately and combined) for the simultaneous and sequential group SO 3: To describe and compare the occurrence of solicited systemic reactogenicity events on days 1-7 after Visit 1 and Visit 2 in the simultaneous versus sequential group SO 4: To describe and compare the occurrence of serious adverse events in the simultaneous versus sequential group. **Exploratory Objectives (EO):** EO 1: To compare the height and duration of fever on days 1-2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group EO 2: To compare the proportions of children with fever 3-7 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group EO 3: To compare the severity of fever, duration of fever, and medical care utilization for fever occurring 3-7 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. EO 4: To describe and compare the occurrence of unsolicited adverse events and adverse events of special interest in the simultaneous versus sequential group.

	EO 5: To describe and compare the occurrence of fever after vaccination when COVID-19 vaccine is given simultaneously with other vaccines versus when COVID-19 vaccine and other vaccines are given at two separate visits, in a subset of participants receiving specific vaccine combinations EO 6: To describe and compare the perceptions among parents/ legally authorized representatives (LARs) of the simultaneous versus sequential schedule experience
Outcome Measures:	**Primary Outcome Measure (POM):** POM 1.1: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 1 and/or Visit 2 **Secondary Outcome Measures (SOM):** SOM 1.1: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 1 SOM 1.2: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 2 SOM 2.1: Number and percentage of children with moderate/severe fever (GRADE 2 and/or 3) on Day 1 and/or Day 2 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined SOM 2.2: Number and percentage of children with medical care utilization (telephone (advice) call, telehealth visit, medical office visit, emergency department visit, or hospital admission) for fever on Day 1 and/or Day 2 following Visit 1, Visit 2 and Visit 1 and Visit 2 combined SOM 2.3: Number and percentage of children with antipyretic use for fever on Day 1 and/or Day 2 following Visit 1, Visit 2 and Visit 1 and Visit 2 combined SOM 3.1: Number and percentage of children with solicited systemic reactogenicity events at different levels of severity (Grades 1, 2, 3, and all Grades) on days 1-7 following Visit 1 and Visit 2 SOM 4.1: Number and percentage of children with at least one serious adverse during the study period and a description of the event(s)

	Exploratory Outcome Measures (EOM): EOM 1.1: Average peak temperature of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined EOM 1.2: Total number of fever degree-days (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 per subject following Visit 1, Visit 2, and Visit 1 and Visit 2 combined EOM 2.1: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on at least one day on days 3-7 following Visit 1 EOM 2.2: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on at least one day on days 3-7 following Visit 2 EOM 2.3: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on at least one day on days 3-7 following Visit 1 and Visit 2 combined EOM 3.1: Number and percentage of children with moderate/severe fever (GRADE 2 and/or 3) on at least one day during days 3-7 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined EOM 3.2: Average number of consecutive days of fever (temperature ≥ 38.0°C or ≥ 100.4°F) per subject for fever starting on 3-7 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined. *Note: fever starting on day 3-6 could continue through day 7* EOM 3.3: Number and percentage of children with medical care utilization (telephone (advice) call, medical office visit, emergency department visit, or hospital admission) for fever on 3-7 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined) EOM 4.1: Number and percentage of children with at least one unsolicited adverse event in the 1-7 days after Visit 1 and Visit 2 and a description of these events EOM 4.2: Number and percentage of children with at least one adverse event of special interest during the study period and description of these events

	EOM 5.1: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 1 and/or Visit 2, in a subset of patients with specific vaccine combinations EOM 6.1 Number and percentage of parents or LARs reporting positive and negative perceptions about their vaccination schedule experience will be determined for each survey item
Estimated Time to Complete Enrollment:	Approximately 13 months for enrollment season

1 BACKGROUND

1.1 Background & Significance

Coronavirus disease 2019 (COVID-19), an acute illness caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first reported in the city of Wuhan, Hubei province, China in December 2019. (1) Within months of the first reported COVID-19 cases, SARS-CoV-2 virus circulated globally (including the United States), and the World Health Organization (WHO) declared the COVID-19 outbreak as a pandemic on March 11, 2020. (2). About three years later the WHO declared an ending to the COVID-19 pandemic emergency on May 5, 2023, but SARS-CoV-2 continues to circulate and cause morbidity and mortality worldwide. (3) As of July 2023, there have been 6.2 million hospitalizations and >1 million deaths associated with COVID-19 in the United States. (4) SARS-CoV-2 is a single stranded RNA virus that is transmitted through close contact from person-to-person primarily by respiratory droplets. Rapid transmission has been shown to occur in facilities with spread by asymptomatic, presymptomatic and symptomatic persons. (5, 6) The incubation period is thought to extend to 14 days (median time of 4-5 days) (7, 8) with variable clinical manifestations at illness onset. There is no clinical manifestation that reliably distinguishes COVID-19 from other acute viral respiratory diseases. (9-11) The majority of individuals with COVID-19 will recover spontaneously with supportive care but the clinical spectrum varies and ranges from no symptoms to clinical conditions characterized by complications such as pneumonia, respiratory failure, multiorgan failure, thromboembolic disease, myocarditis, multiorgan inflammatory syndrome in children, and death. (12-14) About 5% of adults will require intensive care. (15) Severe clinical outcomes are more commonly reported among older adults and those with underlying health conditions. (16, 17)

Fewer cases of COVID-19 have been observed in children than in adults, but the number of reported COVID-19 cases increased in the later part of the pandemic; as of June 2023, 17% of reported COVID-19 cases occurred in children aged <18 years. (18, 19) Complications can occur in children, including ICU admission, mechanical ventilation and death. (18) In fact, COVID-19 is now one of the top ten causes of death for children and youth younger than 19 years (20). Another complication of SARS-CoV-2 infection is Multisystem Inflammatory Syndrome in Children (MIS-C), which has been reported to occur in several thousand children in the United States. MIS-C is characterized by fever, laboratory evidence of inflammation, and multiorgan involvement. (21, 22)

The rapid development of safe and effective COVID-19 vaccines was a remarkable public health achievement to help control the COVID-19 pandemic. As of September 2023, COVID-19 vaccines are authorized or approved and recommended for U.S. children and adults aged 6 months and older. (23, 24)

Two mRNA COVID-19 vaccine products are currently authorized by FDA for use in infants and young children younger than 5 years- old: Pfizer-BioNTech and Moderna XBB.1.5 monovalent COVID-19 vaccines (these vaccine products are based on the Omicron XBB.1.5 variant of SARS-CoV-2). (24) The CDC recommendations as of September 2023 for COVID-19 vaccination in children aged 6 months to <5 years who have not been previously vaccinated for COVID-19 and are not moderately or severely immunocompromised are described below for each vaccine product. (24) For Pfizer-BioNTech vaccine, an initial 3-dose series is recommended. The first two doses are separated by 3–8 weeks and the third dose is administered at least 8 weeks after dose

2. For Moderna vaccine, an initial 2-dose series is recommended, with 4-8 weeks between dose 1 and dose 2.

Data to support the safety and immunogenicity of these mRNA COVID-19 vaccines in infants and young children were reviewed by the FDA prior to emergency use authorization. FDA considered safety data from original monovalent COVID-19 vaccines as relevant to the decision to authorize updated (2023–2024 Formula) mRNA COVID-19 vaccines and provides information to healthcare providers about these vaccines in Fact Sheets. (25, 26) The Pfizer-BioNTech vaccine safety data included 1,173 vaccine recipients and 595 placebo recipients aged 6 through 23 months as well as 1,824 vaccine recipients and 909 placebo recipients aged 2-4 years. (25) In the 6-23 month old cohort the most common solicited adverse reactions after dose 1 were irritability (51.2%), drowsiness (27.0%), decreased appetite (22.2%), and tenderness at the injection site (16.6%). Fever (≥38.0° C) occurred in approximately 7% of participants. In the 2-4-year-old cohort pain at the injection site (30.8%), fatigue (29.7%), and injection site redness (8.8%) were the most common solicited adverse reactions after dose 1. Fever ≥38.0C was reported in approximately 5% of vaccine recipients. (25)

The Moderna safety data included 1,761 children aged 6-23 months and 3,031 children aged 2-5 years. In the 6- 23 month cohort the most common solicited adverse reactions after dose 1 of mRNA-1273 were irritability/crying (67.6%), pain at the injection site (37.4%), sleepiness (37.1%) and loss of appetite (30.2%). Fever ≥38.0C was reported in 11.0% of recipients after dose 1 and 14.6% after dose 2. In the 2-5 year-old cohort, safety data were further stratified by age. In 24-36 month-old infants, fever was reported by 11.3% of recipients after dose 1, and 18.9% of recipients after dose 2. In children 37 months through 5 years, fever was reported by 7.7% of recipients after dose 1 and 16.0% of recipients after dose 2. (26)

Post-authorization vaccine safety data to date for pediatric vaccination are reassuring and COVID-19 vaccines have been added to the Child and Adolescent Immunization Schedule. (27-30) CDC recommends that COVID-19 vaccines may be administered during the same visit as other vaccines. (24) The FDA pediatric COVID-19 factsheets state that there "are no data to assess the concomitant administration" of the Pfizer-BioNTech or Moderna COVID-19 vaccines with other vaccines, but retrospective studies have been reassuring. (25, 26) A CDC retrospective cohort study assessed the safety of co-administration of influenza vaccine and mRNA COVID-19 monovalent booster in persons aged ≥12 years using v-safe, a smart-phone based system. (31) The study suggested a small increase in systemic reactions after simultaneous COVID-19 and influenza vaccination versus COVID-19 vaccination alone; reactions were usually mild. A Vaccine Safety Datalink (VSD) study assessed the safety of simultaneous vaccination with COVID-19 vaccine and other vaccines in persons aged ≥5 years. (32) The VSD study found that combined pre-specified health outcomes were not statistically different in persons receiving simultaneous COVID-19 and other vaccinations vs. persons receiving COVID-19 vaccine alone. (32) The Clinical Immunization Safety Assessment (CISA) Project is currently conducting a study to assess safety of simultaneous versus sequential administration of mRNA COVID-19 vaccine and influenza vaccine in adolescents and adults; a safety panel assessed no safety concerns after the first year of enrollment in the study. (33) It is important to better characterize the safety of simultaneous vaccination of mRNA COVID-19 vaccines and other vaccines in young children.

Fever is commonly reported in children following receipt of their routine immunizations. (34) The CDC vaccine information statements (VIS) designate fever as a side effect following numerous childhood vaccines including: Hepatitis B; diphtheria, tetanus, and acellular pertussis (DTaP); *Haemophilus influenza* type B (Hib); 13-valent conjugate pneumococcal (PCV13); inactivated influenza vaccine (IIV); measles, mumps, and rubella (MMR); varicella; and measles, mumps, rubella and varicella (MMRV) (https://www.cdc.gov/vaccines/hcp/vis/current-vis.html). (35) While the exact mechanisms and functions of fever are not completely understood, some have suggested fever has a beneficial role in response to infection. (36) However, in the context of immunization, fever is considered an adverse event that may lead to increased medical visits, and can contribute to reluctance to vaccinate. (37)

Fever is a clinically important outcome in young children, in part because young children are at risk for febrile seizure. (38) Understanding the risk for fever after vaccination may help provide anticipatory guidance to parents. A prior randomized clinical trial conducted by CISA by Walter et al. found that delaying quadrivalent inactivated influenza vaccine (IIV4) administration by 2 weeks in children receiving DTaP and PCV13 did not reduce fever occurrence after vaccination. (39) In brief, in the Walter study children were randomized 1:1 to a simultaneous or sequential schedule that included two study visits. Children in the sequential group received the non-influenza study vaccines at study Visit 1 and the influenza vaccine at Visit 2. Children in the simultaneous group received all vaccines at Visit 1 and a health education visit without vaccines at Visit 2. The risk period for fever was considered the day of each visit and the day after (Days 1-2), based on earlier studies. (39)

1.2 Summary & Rationale

Administering childhood vaccines is recommended by the CDC and the Advisory Committee on Immunization Practices (ACIP) and it allows children to be protected earlier from vaccine-preventable diseases and reduces the chance for missed vaccinations. As of May 3, 2023, only 13% of children aged 6 months – 4 years have initiated the COVID-19 vaccine series. As with other recommended vaccines, one strategy to increase COVID-19 vaccination rates is to incorporate it into routine clinical care when other vaccines are being administered. Clinical studies before authorization and post-authorization studies have not identified safety concerns when mRNA COVID-19 vaccines are used in young children in real world setting. (40, 41) However, the safety of simultaneous vaccination with mRNA COVID-19 vaccine and other childhood has not been prospectively studied.

The data available on the safety of simultaneous vaccination with mRNA COVID-19 vaccines and other childhood vaccines are limited in young children. We therefore propose to conduct a randomized clinical trial to assess fever following simultaneous vs. sequential mRNA COVID-19 vaccine in young children aged 6 months through <5 years. Clinics may administer COVID-19 vaccine as a stand-alone vaccine, and it is likely to be logistically feasible to separate visits between COVID-19 vaccine and other childhood vaccines; this could be done without a child becoming delayed on the recommended immunization schedule. The design used in the prior CISA study by Walter described above will be adapted for use in this study (39) with COVID-19 vaccine replacing influenza vaccine in the sequencing. Children in the sequential group in the proposed COVID-19 vaccine study will receive the non-COVID-19 vaccines at study Visit 1 and a mRNA COVID-19 vaccine at Visit 2. This COVID-19 vaccine study will provide evidence

that may help healthcare providers and parents or caregivers of young children make vaccination decisions. This information would also provide anticipatory guidance to parents about fever after simultaneous or sequential vaccination. The study team hypothesizes that the risk for fever in young children after a simultaneous schedule of COVID-19 vaccine with other childhood vaccines will not be higher than after sequential vaccination. Additional information about the occurrence of systemic reactogenicity and other health outcomes after simultaneous COVID-19 and other childhood vaccination would also be useful for providers and parents. We will also collect parental preferences about timing of COVID-19 vaccine around other recommended childhood vaccines.

2 STUDY OBJECTIVES

2.1 Primary Objective (PO):

PO 1

To compare the proportion of children with fever after vaccination when mRNA COVID-19 vaccine is given simultaneously with other vaccines versus when mRNA COVID-19 vaccine and other vaccines are given at two separate visits. Children in the simultaneous vaccination group will receive routine non-COVID-19 childhood vaccinations and mRNA COVID-19 vaccination at Visit 1, followed by a health education visit without vaccination at Visit 2. Children in the sequential vaccination group will receive routine non-COVID-19 childhood vaccinations at Visit 1 followed by the mRNA COVID-19 vaccination and a health education visit at Visit 2. Fever will be assessed on the day (Day 1), and the day after each visit (Day 2).

The primary hypothesis is that the proportion of children with fever in the simultaneous group will be noninferior (not higher) compared to the proportion of children with fever in the sequential group.

2.2 Secondary Objectives (SO):

SO 1: To compare the proportion of children with fever occurring 1-2 days after each visit (Visit 1 and Visit 2) in the simultaneous versus sequential group

SO 2: To describe and compare the severity of fever, medical care utilization, and use of antipyretics for fever occurring 1-2 days after Visit 1 and Visit 2 (separately and combined) for the simultaneous and sequential group

SO 3: To describe and compare the occurrence of solicited systemic reactogenicity events on day 1-7 after Visit 1 and Visit 2 in the simultaneous versus sequential group

SO 4: To describe and compare the occurrence of serious adverse events in the simultaneous versus sequential group

2.3 Exploratory Objectives (EO):

EO 1: To compare the height and duration of fever on days 1-2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group

EO 2: To compare the proportions of children with fever 3-7 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group

EO 3: To compare the severity of fever, duration of fever, and medical care utilization for fever occurring 3-7 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group.

EO 4: To describe and compare the occurrence of unsolicited adverse events and adverse events of special interest in the simultaneous versus sequential group.

EO 5: To describe and compare the occurrence of fever after vaccination when COVID-19 vaccine is given simultaneously with other vaccines versus when COVID-19 vaccine and other vaccines are given at two separate visits, in a subset of participants receiving specific vaccine combinations

EO 6: To describe and compare the perceptions among parents / legally authorized representatives (LARs) of the simultaneous versus sequential schedule experience

2.4 Study Outcome Measures as Related to Objectives

Primary Outcome Measure (POM):

POM 1.1: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 1 and/or Visit 2

Secondary Outcome Measures (SOM):

SOM 1.1: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 1

SOM 1.2: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 2

SOM 2.1: Number and percentage of children with moderate/severe fever (GRADE 2 and/or 3) on Day 1 and/or Day 2 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined

SOM 2.2: Number and percentage of children with medical care utilization (telephone (advice) call, telehealth visit, medical office visit, emergency department visit, or hospital

admission) for fever on Day 1 and/or Day 2 following Visit 1, Visit 2 and Visit 1 and Visit 2 combined

SOM 2.3: Number and percentage of children with antipyretic use for fever on Day 1 and/or day 2 following Visit 1, Visit 2 and Visit 1 and Visit 2 combined.

SOM 3.1: Number and percentage of children with solicited systemic reactogenicity events at different levels of severity (Grades 1, 2, 3, and all Grades) on days 1-7 following Visit 1 and Visit 2

SOM 4.1: Number and percentage of children with at least one serious adverse during the study period and a description of the event(s)

Exploratory Outcome Measures (EOM):

EOM 1.1: Average peak temperature of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined

EOM 1.2: Total number of fever degree-days (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 per subject following Visit 1, Visit 2, and Visit 1 and Visit 2 combined

EOM 2.1: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on at least one day on days 3-7 following Visit 1

EOM 2.2: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on at least one day on days 3-7 following Visit 2

EOM 2.3: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on at least one day on days 3-7 following Visit 1 and Visit 2 combined

EOM 3.1: Number and percentage of children with moderate/severe fever (GRADE 2 and/or 3) on at least one day during days 3-7 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined

EOM 3.2: Average number of consecutive days of fever (temperature ≥ 38.0°C or ≥ 100.4°F) per subject for fever starting on 3-7 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined. *Note: fever starting on day 3-6 could continue through day 7*

EOM 3.3: Number and percentage of children with medical care utilization (telephone (advice) call, medical office visit, emergency department visit, or hospital admission) for fever on 3-7 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined)

EOM 4.1: Number and percentage of children with at least one unsolicited adverse event in the 1-7 days after Visit 1 and Visit 2 and a description of these events.

EOM 4.2: Number and percentage of children with at least one adverse event of special interest during the study period and description of these events

EOM 5.1: Number and percentage of children with fever (temperature ≥ 38.0°C or ≥ 100.4°F) on Day 1 and/or Day 2 following Visit 1 and/or Visit 2, in a subset of patients with specific vaccine combinations

EOM 6.1 Number and percentage of parents or LARs reporting positive and negative perceptions about their vaccination schedule experience will be determined for each survey item

3 STUDY DESIGN

3.1 Main study design

This study is a prospective, randomized open-label clinical trial to assess fever, other reactogenicity events, and safety in young children after simultaneous versus sequential vaccination with mRNA COVID-19 vaccine and other routine childhood vaccines in 600 children aged 6 months to <5 years. Eligible children will be randomized to simultaneous or sequential administration in a 1:1 ratio (300 in each group). Children in the simultaneous vaccination group will receive mRNA COVID-19 vaccine and non-COVID-19 vaccine(s) at Visit 1, followed by an oral health education visit without vaccination at Visit 2, 1-3 weeks later. Children in the sequential vaccination group will receive non-COVID-19 vaccine(s) at Visit 1 followed by mRNA COVID-19 vaccine and oral health education at Visit 2, 1-3 weeks later. As part of the oral health education, all children will be provided with an age-appropriate toothbrush.

Fever and reactogenicity events will be assessed starting on the vaccination day (Day 1) and through to 6 days post-vaccination (Days 1- 7) after Visit 1 and Visit 2. The oral health education (Visit 2) will be the anchor (Day 1) for recording fever and reactogenicity data for the simultaneous group. Fever and systemic symptoms such as vomiting and diarrhea are common in this age group and may not be related to vaccination. The fever and reactogenicity data collected during the 7 days after Visit 2 in the simultaneous group should represent background rates of these events.

The primary comparison between groups will be the occurrence of fever on Day 1 and/or Day 2 (Days 1-2) following Visit 1 and/or Visit 2. Medical utilization for fever, reactogenicity, safety outcomes, and the perceptions among parents about their child's vaccination schedule in this study will be assessed as secondary and exploratory objectives.

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

Children who meet all of the following criteria will be eligible to participate in this interventional study:

1. Child 6 months through <5 years of age at time of enrollment.
2. Child is due to receive mRNA COVID-19 vaccine and at least one other routinely recommended non-live vaccine per CDC or ACIP recommendations.
3. Parental/LAR intention of child receiving mRNA COVID-19 vaccine and at least one recommended non-live vaccine.
4. The parent/LAR must be willing and capable of providing permission for their child to participate through the written informed consent process.
5. The parent/LAR must be available for follow-up and must at minimum have telephone access.
6. The parent/LAR must agree to sign a medical release for the child so that study personnel may obtain medical information about the child's health (if needed).
7. The parent/LAR must be willing to delay COVID-19 vaccination for their child for up to 3 weeks.
8. The parent/LAR must be able to read English or Spanish.

4.2 Subject Exclusion Criteria

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

1. History of any seizure (including febrile seizure) or first degree relative (biologic parent or biologic sibling including half-sibling) with a history of febrile seizure.
2. Contraindication to mRNA COVID-19 vaccine: A history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of the COVID-19 vaccine or a known diagnosed allergy to a component of COVID-19 vaccine.
3. A history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of a vaccine administered on the day of study enrollment.
4. For children receiving DTaP vaccine (alone or combination vaccine): Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP.
5. Received any other non-live vaccines within 14 days prior to enrollment or any other live vaccines within 28 days prior to enrollment.
6. Intention to receive non-COVID-19 non-live or live vaccines during the 4 weeks after Visit 1; vaccines may be administered after enrollment if deemed a personal or public health priority by the health care provider caring for this patient or the study team.
7. Received prior COVID-19 vaccine as part of a clinical trial.

8. Received any experimental/investigational agent (vaccine, drug, biologic, device, blood product, or medication) within 28 days prior to enrollment in this study or expects to receive an experimental/investigational agent during the study.
9. A moderate to severe acute illness and/or a reported temperature ≥ 100.4°F (≥38.0°C) within 48 hours prior to enrollment or a temperature (measured by temporal artery thermometer) ≥100.4°F (≥38.0°C) at the time of enrollment. (This may result in a temporary delay of vaccination).
10. Receipt of an antipyretic medication (acetaminophen or ibuprofen) within 72 hours prior to enrollment (this may result in a temporary delay of vaccination) or planned receipt of a prophylactic antipyretic medication on the day of and/or days following vaccination prior to any measured increase in temperature in anticipation of a fever (this exclusion does not apply if the Parent/LAR indicates they might administer antipyretics or analgesics after vaccination to reduce a fever or pain).
11. Immunosuppression as a result of an underlying illness or treatment, or use of anti-cancer chemotherapy or radiation therapy since birth.
12. Long term (at least 14 days of prednisone 2 mg/kg/day or equivalent other glucocorticoid) use of any parenteral steroids or high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) within the 6 months prior to enrollment (topical and nasal steroids are allowed).
13. Has an active case of COVID-19 infection.
14. History of multisystem inflammatory syndrome (MIS-C).
15. History of myocarditis or pericarditis.
16. Has any condition that would, in the opinion of the site investigator, place the participant at an unacceptable risk of injury or render the participant unable to meet the requirements of the protocol.
17. Any child or grandchild of a study investigator or study team member.

A modified list of Exclusion Criteria will be reviewed at Visit 2 to assess eligibility for receipt of COVID-19 vaccine at Visit 2. Subjects who meet any of the following exclusion criteria will not be eligible to receive COVID-19 vaccine in this study at Visit 2 but will continue participation in this study:

1. Received COVID-19 vaccine following Visit 1 in the study.
2. Contraindication to mRNA COVID-19 vaccine: A history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of the COVID-19 vaccine or a known diagnosed allergy to a component of COVID-19 vaccine.
3. A moderate to severe acute illness and/or a reported temperature ≥100.4°F (≥38.0°C) within 48 hours prior to vaccination or a temperature (measured by temporal artery thermometer) ≥100.4°F (≥38.0°C) at the time vaccination. (This may result in a temporary delay of vaccination).
4. Has an active case of COVID-19 infection.
5. History of multisystem inflammatory syndrome (MIS-C).
6. History of myocarditis or pericarditis.
7. Has any condition that would, in the opinion of the site investigator, place the participant at an unacceptable risk of injury.

Subjects who meet these modified exclusion criteria will continue to be followed for safety outcomes (SAEs and AESIs), but will not be included in the per protocol population. Study staff will facilitate administration of COVID-19 vaccine to participants who are ineligible to be vaccinated at Visit 2 but are able to be vaccinated in the future.

4.3 Recruitment

The 600 participants in this study will be healthy male or female children 6 months to <5 years of age with a Parent/LAR who expresses the intention for the child to receive an mRNA COVID-19 vaccine and at least one standard of care non-live vaccine, in accordance with CDC or ACIP recommendations. Approximately 160 participants will be enrolled at Duke, 170 will be enrolled at Cincinnati, 100 will be enrolled at Columbia, and 170 will be enrolled at KPNC.

Participants will be recruited from pediatric clinics and/or vaccination clinics affiliated with these sites. Medical records will be reviewed to identify, contact, and offer study enrollment to Parent/LAR of potentially eligible children. IRB-approved informational flyers/advertisements will be used to recruit children receiving vaccination through public COVID-19 vaccination sites or clinics (primary care, or other clinics administering vaccine). Potential participants will be screened for eligibility. The potential participant's Parent/LAR will provide consent for their child's 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 Parent/LAR 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
- Loss 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. Subjects who are withdrawn from the study prior to randomization or first vaccination visit will be replaced. Subjects who are withdrawn from the study after receiving vaccine will not be replaced. For subjects who received study vaccines, study data collected prior to withdrawal from 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 meeting the proposed eligibility criteria will be recruited. Written permission for the child to participate will be obtained from Parent(s)/LAR(s) prior to conducting any study procedures. The interval between Visit 1 and Visit 2 differs for children receiving non-live and live vaccines based on the risk interval for fever; the goal is to avoid identifying fever at Visit 2 that is caused by a vaccine received at Visit 1. Because fever

may occur in the first and second week after vaccination with live vaccines, children receiving live vaccines at Visit 1 should return for Visit 2 two to three weeks after Visit 1 (42). Children not receiving live vaccines at Visit 1 should return for Visit 2 one to two weeks later. **Tables 1a and 1b** describe the proposed schedule of study visits. Note that the table includes ability for parent(s)/LAR(s) to submit memory aid information electronically over the internet via REDCap or by using a paper memory aid (diary). For this study, use of REDCap for obtaining memory aid information is the preferred option.

Table 1a. Schedule of Events for Subjects Not Receiving Live Vaccines at Visit 1

Procedure	Visit 1	Visit 1a	Visit 2	Visit 2a	Visit 3
Type of contact	Clinic	Phone/Text /Email/Data Review	Clinic/ Telehealth	Phone/Text/E mail/Data Review	Phone/Da ta Review
Study Day	**1**	1-7 (+3)	8-15 (+7)		91 (+14)
Days Relative to Visit 2				1-7 (+3)	
Informed consent & Medical Release of Information	X				
Review Eligibility Criteria	X		X		
Data Collection (Demographic information and Medical History)	X				
COVID-19 Vaccination History	X				
Concomitant Medications and Vaccines	X	X	X	X	X
Temperature Measurement	X		X		
Randomization	X				
Non-COVID-19 Vaccines	X				
COVID-19 Vaccine[a]	(X)		(X)		
Provide thermometer and toothbrush[b]	X				
Memory aid training + supplies (training on temperature)	X		X		
Confirm next study visit	X	X	X	X	
Staff to review Memory aid form (REDCap or paper) [c]		X		X	
Obtain solicited adverse events		X		X	
Obtain unsolicited adverse events		X		X	
Obtain serious adverse event information and AESIs		X	X	X	X
Conduct Health education visit			X		
Obtain parents preferences for spacing of vaccinations				X	

a. mRNA COVID-19 Vaccine will be administered at Visit 1 in the simultaneous group, and at Visit 2 in the sequential group
b. Administer thermometer and toothbrush to all participants (simultaneous and sequential groups)
c. Memory aid (solicited systemic reactogenicity events) to be completed by LAR on Days 1-7 after vaccination.
d. LAR 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

Table 1b. Schedule of Events for Subjects Receiving Live Vaccines at Visit 1					
Procedure	Visit 1	Visit 1a	Visit 2	Visit 2a	Visit 3
Type of contact	Clinic	Phone/Text /Email/Data Review	Clinic/ Telehealth	Phone/Text/Email/ Data Review	Phone/Data Review
Study Day	1	1-7 (+3)	15-22 (+7)		91 (+14)
Days Relative to Visit 2				1-7 (+3)	
Informed consent & Medical Release of Information	X				
Review Eligibility Criteria	X		X		
Data Collection (Demographic information and Medical History)	X				
COVID-19 Vaccination History	X				
Concomitant Medications and Vaccines	X	X	X	X	X
Temperature Measurement	X		X		
Randomization	X				
Non-COVID-19 Vaccines	X				
COVID-19 Vaccine[a]	(X)		(X)		
Provide thermometer and toothbrush[b]	X				
Memory aid training + supplies (training on temperature)	X		X		
Confirm next study visit	X	X	X	X	
Staff to review Memory aid form (REDCap or paper) [c]		X		X	
Obtain solicited adverse events		X		X	
Obtain unsolicited adverse events		X		X	
Obtain serious adverse event information and AESIs		X	X	X	X
Conduct Health Education Visit			X		
Obtain parents preferences for spacing of vaccinations				X	

a. mRNA COVID-19 Vaccine will be administered at Visit 1 in the simultaneous group, and at Visit 2 in the sequential group
b. Administer thermometer and toothbrush to all participants (simultaneous and sequential groups)
c. Memory aid (solicited systemic reactogenicity events) to be completed by LAR on Days 1-7 after vaccination.
d. LAR 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

Visit 1, Study Day 1

- Obtain parental permission by written or electronic informed consent and a release of medical record information, based on site IRB requirements
- Obtain information on preferred method of contact for follow-up (telephone, email, or text reminder)
- Review and confirm study eligibility
- Obtain medical history
- Obtain demographic data & vaccine history
- Obtain concomitant medication use
- Obtain temperature using the temporal artery thermometer
- Randomize study participant to simultaneous or sequential vaccine administration
- Simultaneous group: Administer mRNA COVID-19 vaccine and concomitant non-COVID-19 vaccine(s) as per standard of care as needed for age according to ACIP

recommendations. COVID-19 vaccine may be administered as a research procedure at some sites (see section 5.8)
- Sequential group: Administer only non-COVID-19 vaccine(s) as per standard of care as needed for age according to ACIP recommendations
- Record vaccine administration in research database
- Observe for 15 minutes after vaccination
- Dispense the temporal artery thermometer and memory aid. Review instructions for use of thermometer and memory aid completion. Preference will be to complete the memory aid electronically, with paper as a back-up.
- Dispense toothbrush and educational handout
- Confirm date of next scheduled study visit

Visit 1a, Days 1-7 (+3) (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 automated electronic reminders to fill out the symptom diary
    - Study staff will review REDCap system to confirm data capture and assess for any AE, AESIs, or SAEs on Study Day 3 after vaccine
    - If any missing values or Grade 3 events occurred, the study staff will use phone contact to gather more information
- For participants using paper diary:
    - Study staff will call participants on Day 3 after vaccine as a reminder to fill out the symptom diary, and confirm fever history
    - Study staff will call participants on Study Day 8 to record symptom diary and remind participant of Visit 2 date and to bring symptom diary

Visit 2, (Clinic Visit for Sequential, Clinic or Telehealth Visit for Simultaneous)
    - **No Live Vaccines Administered** - Days 8-15 (+7) (see Table 1a)
    - **Live Vaccines Administered** - Days 15-22, (+7) (see Table 1b)
- For participants using memory aid, collect memory aid
- Record any, AESIs, SAEs, and concomitant medications and vaccinations since Visit 1.
- Temperature will be taken using the temporal artery thermometer. Temperature may be taken either by study staff or parent/LAR.
- Review modified list of Exclusion Criteria as outlined in Section 4.2 to assess eligibility for receipt of COVID-19 vaccine at Visit 2
- Administer COVID-19 vaccine as described in Section 5.5.2
- Observe for 15 minutes after vaccination
- Administer educational intervention
- Confirm preferred method of contact for follow-up (telephone, email, or text reminder)
- Review instructions for use of thermometer and memory aid completion

Visit 2a, Days 1 – 7 (+3) relative to Visit 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 automated electronic reminders to fill out the symptom diary
    - Study staff will review REDCap system to confirm data capture and assess for any AE, AESIs, or SAEs on Day 3 after vaccine
    - If any missing values or Grade 3 events occurred, the study staff will use phone contact to gather more information
    - Parent/LAR survey regarding preferences for spacing of vaccinations will be administered via REDCap 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, and confirm fever history
    - Study staff will call participants on Day 7 after vaccine
    - Record symptom diary
    - Administer parent/LAR survey regarding preferences for spacing of vaccinations
    - Confirm date of final study visit

Visit 3, Day 91 (+14) (Phone Visit)

- Study staff will contact study participants to record any SAEs, AESIs, concomitant medications, and any vaccines administered during the study period not already documented.
- Complete end of study form.

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. Parent(s)/LAR(s) will have the opportunity to take the consent form home and discuss the document with other family members or friends. We anticipate that the initial consent discussion, including presenting the information in the consent document and answering questions will take approximately 30 minutes. 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.

5.3 Demographic Information, Medical History, Immunization History

The participant's date of birth, age, and race/ethnicity will be recorded. The participant's medical history including: seizure disorder (including febrile seizure history and family history of febrile seizure in sibling or parent); significant medical conditions, such as asthma or recurrent wheezing and concomitant medications taken within 2 weeks prior to enrollment will be obtained by review of the electronic health record (EHR) and will be reviewed and confirmed by the parent/LAR at the time of enrollment. Concomitant medications, history of intercurrent hospitalizations, and AESIs will also be verified at Visit 2 and Visit 3.

Information on prior history of COVID-19 vaccine will be obtained at the time of study enrollment and again at Visit 2. The EHR and/or respective immunization registry will be reviewed for vaccination information. Research staff will document the vaccine, product brand, and date of administration of prior doses of COVID-19 vaccine received. If the information is not available in the EHR or immunization registry, a written record documenting prior receipt of these vaccines would be considered acceptable.

Any vaccines received by the child during the study period will be documented by the research staff in the research database. Documentation will include: product brand, lot number, site, and date/time of vaccine administered during study participation.

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

5.4 Temporal Artery Temperature Measurement and Fever Assessments

Participant temperatures will be taken using a digital temporal artery thermometer that will be provided to each parent/LAR during enrollment to use for the study and keep for use following the study. The initial temperature will be recorded in the clinic and study staff will demonstrate proper use of the thermometer to the parent/LAR. Temperatures will be collected during Visit 1 in both groups. Thereafter, parent(s)/LAR(s) in both groups will measure and record the participant's temperature at approximately the same time each day (preferably after 4:00 PM or right before participant goes to bed) beginning on Day 1 (day of vaccination) and will do so through Day 7 following Visits 1 and 2. In addition, parents will be instructed to take a temperature using the study-provided temporal artery thermometer if their child feels warm or feverish during Days 1-7 after Visit 1 and 2. If at any time a temperature ≥ 100.4°F (≥ 38°C) or ≤ 95°F (≤ 35°F) is recorded, a second measurement will be taken 10 - 20 minutes later. The highest temperature measurement of the day will be recorded on the paper memory aid or entered into REDCap. Any temperature measured after the bedtime memory aid entry has been completed, should be considered for the next day's memory aid entry. All temperatures will be measured using a study-supplied temporal artery thermometer.

For this study, temperatures will be documented using either the electronic memory aid through REDCap or the paper memory aid. The preferred method for documentation in this study is REDCap. For parents electing to use REDCap, missing or out of range temperature data will be verified with the parent(s)/LARS on Day 3 and missing data will be obtained on Day 8 as needed following Visits 1 and 2. For parents electing to use paper memory aids only, temperature data will be verified on Day 3 following Visits 1 and 2. Parents/LAR in the sequential group using the paper memory aid alone will submit the Visit 1 memory aid to study staff during Visit 2, and will mail the Visit 2

memory aid to the study team following the 7-day post-Visit 2 period. The study team will review the paper memory aid at the time of receipt. Parents/LAR in the simultaneous group using the paper memory aid alone will mail the Visit 1 and Visit 2 memory aids to the study team following each 7-day post-visit collection period.

For parent(s)/LAR(s) entering data into REDCap, if there are data discrepancies for temperatures entered directly into REDCap or obtained over the phone, the information provided by the parent in REDCap will be counted as the correct temperature information unless verified as otherwise by study staff.

For parent(s)/LAR(s) using only the paper memory aid, if there are data discrepancies for temperatures recorded on the memory aid or obtained over the phone, the information provided by the parent on the memory aid will be counted as the correct temperature information unless verified as otherwise by study staff.

5.5 Treatment Assignment Procedures

This is an open-label, prospective, randomized study for young children who are to receiving mRNA COVID-19 vaccine with other vaccines.

5.6 Randomization

Participants will be randomized (1:1) to receive either mRNA COVID-19 vaccine with other vaccines simultaneously or mRNA COVID-19 vaccine with other vaccines sequentially (non-COVID-19 vaccines, followed by COVID-19 vaccine at a separate visit) using a permuted block randomization scheme stratified by site and by age-groups; 6 – 23 months and 24 months - <5 years. The project statistician will generate permuted block randomization schemes which will be uploaded to REDCap. The randomization schedule will not be available to the study staff, so the next randomization allocation will not be known before randomization occurs. Following confirmation of study eligibility criteria during Visit 1, participant randomization will be through REDCap with treatment allocation recorded on the CRF.

In the event that REDCap is unavailable, manual randomization will occur through the use of envelopes. The project statistician will prepare 10 envelopes per age group and vaccine series per site (total of 60 per site) that will use the same randomization strategy as the primary scheme embedded in REDCap. When a team member is informed of the age group, he/she will pull the next envelope in order. In order to capture the allocation per subject, a separate form in REDCap will be used by the site personnel to add the assignment. A log will need to be kept at the site capturing these instances.

5.6.1 Blinding

This study will be open label. Study staff and participants/Parents/LAR will not be blinded to treatment arm assignments.

5.7 Educational Materials Reviewed with Parent(s)/LAR(s)

A brief educational intervention will be provided to all parent(s)/LAR(s). Parent(s)/LAR(s) will be provided educational materials regarding dental care for young children. A handout posted on the American Academy of Pediatric Dentistry website regarding caries prevention in young children will be given to parent(s)/LAR(s). See

Appendix C. Parent(s)/LAR(s) will also be provided with an age-appropriate toothbrush for their child.

5.8 Vaccine Supply, Storage, and Administration

mRNA COVID-19 vaccines authorized for emergency use or approved by FDA may be administered per standard of care by office staff or as a research procedure by study staff based on study site requirements. As of September 2023, the initial mRNA COVID-19 vaccine recommendations require two to three separate doses approximately three to eight weeks apart, depending on the vaccine manufacturer (24), young children previously vaccinated with mRNA COVID-19 vaccines and not immunocompromised are recommended to receive 1 to 2 doses.
Recommendations may be updated during the study. However, only one dose will be considered as part of the simultaneous or sequential schedule administered at Visits 1 or Visit 2. Dose, vaccine product (Pfizer BioNTech or Moderna), and site of vaccine administration for study vaccine will be recorded by research staff in the Case Report Form and within the REDCap database. COVID-19 vaccine will be administered to participants according to the EUA Fact Sheet or package insert indication if a vaccine is licensed by FDA during the study for providers administering vaccine. After administration, used study syringes will be disposed of according to site-specific standard operating procedure.

At Visit 1, the child's healthcare provider will determine which vaccines to recommend for the child, including COVID-19 vaccine. The vaccines should be licensed by FDA and recommended by CDC or ACIP for the child. All children in the study must be due for at least one non-live vaccine in addition to the COVID-19 vaccine at the time of enrollment, as part of the eligibility requirement. Children in this study will receive all non-COVID-19 vaccines recommended on the Visit 1 day.

Non-COVID-19 vaccines will be administered per routine care; administration of non-COVID-19 vaccines is not considered a research procedure. As noted above, administration of the mRNA COVID-19 vaccine in this study at Visit 1 or Visit 2 may be administered either as a standard of care practice (not a study procedure) or as a research study procedure.

At the time of enrollment, the study staff will document which non-COVID-19 vaccines will be administered in the study and whether or not the COVID-19 vaccine is administered as a study procedure.

For vaccines administered as a study procedure, guidance in the ACIP General Best Practices will be used.
General Best Practice Guidelines for Immunization
https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html

Non-COVID-19 vaccines will be administered only at Visit 1. Live vaccines may be administered to children in this study at Visit 1 if they are ordered by the healthcare provider. Unless necessary to protect the health of the child, additional vaccines should not be administered to children in this study until at least 7 days after Visit 2.

Emergency management supplies will be available for initial treatment of an allergic reaction if needed. Children will be observed in the respective clinic area by study staff for 15 minutes post-vaccination.
The vaccine brand, manufacturer, lot number, expiration date, site of administration, and date/time of administration will be recorded on the case report form (CRF). The study staff will enter study vaccine into the Immunization Registry and Medical

Record. Receipt and disposition of study supplied study vaccines will recorded on the study product accountability log. Following administration, used study syringes will be disposed of according to the respective clinic sites standard operating procedure.

Participants will receive the FDA factsheets for mRNA COVID-19 vaccines for recipients and caregivers and the CDC Vaccine Information Statements for the vaccines administered at Visit 1 and Visit 2. (25, 26, 35) For vaccines administered as study procedures, the study staff will administer the FDA fact sheet.

5.9 Solicited Systemic Adverse Events (Days 1-7 Following Visits 1 and 2)

Temperature and other solicited systemic adverse events will be assessed and documented by parent(s)/LAR(s) after Visit 1 and Visit 2. Beginning on the evening of Visit 1 and Visit 2 (Day 1), parent(s)/LAR(s) will measure and record their child's temporal artery temperature using the study-supplied thermometer as described in more detail in Section 5.4.

Parent(s)/LAR(s) will rate solicited systemic adverse events (other than fever) according to grading in **Tables 2a and 2b,** and document medical care utilization and antipyretic use according to **Table 3** beginning on the evening of Study Visits 1 and 2 (Day 1) and for the next 6 days following the study visits (i.e., through Day 7). At the time of the protocol development Pifzer-BioNTech was more widely used in study sites and reactogenicity events were largely defined based on the Pfizer trials; however, the solicited systemic events used in the Moderna trials in young children were similar. Fever and each systemic symptom should be assessed each day. For the day of vaccination, symptoms should be assessed from the time of vaccination until the time information is recorded. For each subsequent day through Day 7 symptoms should be assessed from the time information is recorded on the previous day until the time it is recorded on the subsequent day. Grading for the child solicited systemic symptoms will be recorded on the study-supplied paper memory aid.

Parent(s)/LAR(s) will be instructed to notify their child's primary care provider promptly in addition to study staff using the 24-hour contact number provided in the memory aid in the event of any severe (Grade 3) temperature elevation or solicited systemic adverse event. Parent(s)/LAR(s) who at any time report severe solicited adverse events or express any concern about symptoms/unsolicited events to the study team will be encouraged to follow up with their child's primary care provider. Study staff will assist with coordination of referral appointments as necessary.

Table 2a: Fever Assessment and Solicited Systemic Adverse Events (Age 6-23 Months)

	None	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Temporal Artery Temperature °C °F	<38.0 <100.4	≥38.0 - <38.4 ≥ 100.4 - < 101.1	≥38.4 - ≤38.9 ≥101.1- < 102.2	>38.9 ≥102.2
Fussiness or Irritability	None	Easily Consolable	Requiring increased attention	Unable to console

Table 2a: Fever Assessment and Solicited Systemic Adverse Events (Age 6-23 Months)				
	None	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Change in eating habits	None	Decreased interest in eating	Decreased oral intake	Refusal to eat
Drowsiness or Sleepiness	None	Increased or prolonged sleeping bouts	Slightly subdued, interfering with daily activity	Disabling, not interested in usual daily activity
Vomiting	None	One to two times in 24 hours	>2 times in 24 hours	Requires intravenous hydration
Diarrhea	None	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours

**Cut off values for fever referenced from Pfizer VRBPAC Briefing Document: https://www.fda.gov/media/159193/download*

Table 2b: Fever Assessment and Solicited Systemic Adverse Events (Ages 2 - < 5 years)				
	None	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Temporal Artery Temperature °C °F	<38.0 <100.4	≥38.0 - <38.4 ≥ 100.4 - < 101.2	≥38.4 - ≤ 38.9 ≥101.2- < 102.2	> 38.9 ≥102.2
Fatigue	None	Does not interfere with activity	Some interference with activity	Prevents daily activity
Headache	None	Does not interfere with activity	Some interference with activity	Prevents daily activity
Chills	None	Does not interfere with activity	Some interference with activity	Prevents daily activity
Vomiting	None	One to two times in 24 hours	>2 times in 24 hours	Requires intravenous hydration
Diarrhea	None	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours

Table 2b: Fever Assessment and Solicited Systemic Adverse Events (Ages 2 - < 5 years)				
	None	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
New or worsened muscle pain	None	Does not interfere with activity	Some interference with activity	Prevents daily activity
New or worsened joint pain	None	Does not interfere with activity	Some interference with activity	Prevents daily activity

**Cut off values for fever referenced from Pfizer VRBPAC Briefing Document: https://www.fda.gov/media/159193/download*

5.10 Medical Care Utilization, Antipyretic Use, and Febrile Seizures (Days 1-8 Following Visits 1 and 2)

Parent(s)/LAR(s) will record medical care utilization, use of antipyretic medications, and febrile seizure occurrence (**Table 3)** beginning on the evening of Visit 1 and Visit 2 (Day 1) and for the next 6 days following the study visits (through Day 7). For each subsequent day through Day 7, these factors should be assessed from the time the information is recorded on one day to the time information is recorded on the next day.

Table 3: Medical Care Utilization and Antipyretic Use		
Did you give your child fever or pain medicine? If yes, was it for fever? If yes, was it for pain? If yes, check type or types of medicine given □ Acetaminophen (e.g., Tylenol, paracetamol) □ Ibuprofen (e.g., Motrin, Advil) □ Other If Other, please indicate medication type: _____	Yes Yes Yes Yes Yes	No No No No No
Did your child receive medical attention? If yes, was it related to fever? If yes, check type or types of attention received □ Medical advice (Telephone call, email, or patient portal (e.g., EPIC MyChart) □ Video/Telehealth visit □ In person visit including urgent care visit □ Emergency department visit	Yes Yes	No No

Table 3: Medical Care Utilization and Antipyretic Use		
□ Hospital admission If yes, provide reason for medical attention _____		
Did your child have a seizure? If yes, was it related to fever?	Yes Yes	No No

5.11 Unsolicited SAEs, AEs, and AESIs

Unsolicited AEs will be assessed for 7 days following each vaccination visit. Serious adverse events (SAEs) and adverse events of special interest (AESI) will be accessed through 90 days following Visit 1 (study period). AESI includes the following:

- Myocarditis or pericarditis occurring during the study period
- Multisystem inflammatory syndrome in children (MIS-C) during the study period
- Febrile seizures during the study period

Parents/LARs will be encouraged to report and grade any significant unsolicited adverse events. Unsolicited adverse events, AESIs and SAEs will be graded as described in **Table 4**. Parents who report severe solicited adverse events or express any concern about symptoms/unsolicited events will be encouraged to follow up with their child's primary care provider. Study staff will assist with coordination of referral appointments as necessary. Parents will also be asked to report if their child had any seizures and if the seizures were febrile seizures. Medical records will be obtained and reviewed for any unscheduled medical appointment from enrollment through the 7 days following Visit 2.

COVID-19 vaccines are authorized for use by FDA and routinely recommended by CDC and ACIP. Other vaccines used in this study are approved by FDA and recommended by ACIP. Therefore, we do not anticipate having a significant issue with serious adverse events (SAEs). However, we will monitor study participants for SAEs during the protocol-defined surveillance period from enrollment through 90 days following Visit 1. An 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 during the period of protocol-defined surveillance (other than routine hospital admission for labor & delivery)
- 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.

Table 4: 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

5.12 Causality (relatedness) Assessment

Study site investigators will assess relatedness to vaccines received at Visit 1 or Visit 2 in the study or study procedures (related, possibly related, unlikely related, or not related) for unsolicited AEs, SAEs and AESIs. Relatedness determinations of these events will inform IRB reporting and safety monitoring. Solicited symptoms in **Tables 2a and 2b** will all be considered to be related to 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 Expert Safety Panel as described below (section 6.2.2) 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.

5.13 Reporting Adverse Events

SAEs will be reported to the CDC and participating IRBs according to institutional requirements.

The following 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 myocarditis
- Cases of pericarditis
- 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.

5.14 Parental Perceptions

At the telephone contact visit on Day 7 following Visit 2 we will survey parents about their preferences regarding receiving COVID-19 vaccine at the same time or separately from other routinely administered pediatric vaccines. In addition, we will collect information about the parent/LAR, such as their relationship to the child (mother, father, LAR). The questions are provided in **Table 5** below and are based on questions asked in a study of alternative vaccination schedule preferences among parents of young children. We will use a Likert scale (strongly agree, agree, disagree, strongly disagree) to assess parental response to the questions about preference for receiving COVID-19 vaccine at the same time or separately.

Table 5. Parental Preference Questions for Spacing of Vaccines	
Questions	
1.	What is your relationship to the child? a. Mother b. Father c. Legal Guardian
2.	How much do you agree with the following statement? "Recommended vaccines are safe for children" strongly disagree, disagree, agree, strongly agree
3.	Please tell us how much you liked the vaccination schedule your child was assigned during the study strongly disliked, disliked, liked, strongly liked
4.	What aspects of the study did you like? (check all that apply) a. My child did not have a fever b. My child did not have other side effects such as pain, fussiness, changes in sleep c. My child got protected from COVID-19 sooner d. My child had fewer injections at the same time e. The toothbrush and education materials I received for my child f. The temporal thermometer I received for my child. g. Other (please specify)
5.	Which option selected in Q4 did you like the most? a. My child did not have a fever b. My child did not have other side effects such as pain, fussiness, changes in sleep c. My child got protected from COVID-19 sooner d. My child had fewer injections at the same time e. The toothbrush and education materials I received for my child f. The temporal thermometer I received for my child. g. Other (as specified in Q4)
6.	What aspects of the study did you dislike? (check all that apply) a. Bringing child to doctor's office twice b. My child had a fever c. My child had other side effects such as pain, fussiness, changes in sleep d. My child did not get protected from COVID-19 soon enough e. My child received too many injections at the same time f. Other (please specify)
7.	Which option selected in Q6 did you dislike the most? a. Bringing child to doctor's office twice b. My child had a fever c. My child had other side effects such as pain, fussiness, changes in sleep d. My child did not get protected from COVID-19 soon enough e. My child received too many injections at the same time f. Other (as specified in Q6)
8.	How easy was it to use the thermometer in this study? very easy, easy, difficult, very difficult
9.	How easy was the method you chose to report your child's information (temperature and side effects) to the study team? very easy, easy, difficult, very difficult
10.	Please let us know if you have any other comments: Comments:

6 STATISTICAL CONSIDERATIONS

In collaboration with the Cincinnati, Columbia, and KPNC 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.

6.1 Sample Size and Power Estimation

, We assume that 14% of children will have fever (Temperature ≥ 38.0°C or ≥ 100.4°F) during days 1-2 after each vaccination visit when COVID-19 vaccine is given at a separate visit from the other recommended vaccines in the sequential group. (42, 43) The assumption for the simultaneous group is that 14% of children will have fever (Temperature ≥ 38.0°C or ≥ 100.4°F) during 1-2 days after the vaccination visit, when COVID-19 vaccine is given at the same visit with other recommended vaccines, or after the education only visit when vaccines are not administered. We have selected a clinically meaningful noninferiority margin of 10%. We plan to recruit a total of 600 children and assume a 5% drop out rate, leaving N=570 or N=285 per vaccination group. Statistical calculations show that with a one-side alpha level of 0.025, and 285 children in each group across all study sites, there is 93% power to be able to demonstrate that the proportion of children with fever (Temperature ≥ 38.0°C or ≥ 100.4°F) in the simultaneous group is noninferior to the sequential group.

6.2 Analysis Plan

6.2.1 Study Populations

There will be three study populations, the Intent-to-Treat (ITT), modified Intent-to-Treat (mITT) and Per Protocol populations. The ITT Population includes any participant that was enrolled and randomized into the study. The mITT Population includes any participant that was enrolled and randomized into the study and received at least one study vaccine at Visit 1.The Per Protocol Population is a subset of the mITT Population excluding those participants who are not eligible to receive COVID-19 vaccine at Visit 2 or who do not provide valid temperature data on Days 1 and 2 following Visit 1 and Visit 2 and those with major protocol violations as determined by the study investigators. Statistical analyses will be performed for both study populations, or the ITT Population only if no participants are excluded from the Per Protocol Population.

6.2.2 Primary Objective 1

To compare the proportion of children with fever after vaccination when mRNA COVID-19 vaccine is given simultaneously with other vaccines versus when mRNA COVID-19 vaccine and other vaccines are given at two separate visits. Children in the Simultaneous vaccination group will receive routine non-COVID-19 childhood vaccinations and mRNA COVID-19 vaccination at Visit 1, followed by a health education visit without vaccination at Visit 2. Children in the Sequential vaccination group will receive routine non-COVID-19 childhood vaccinations at Visit 1 followed by the mRNA

COVID-19 vaccination at Visit 2. Fever will be assessed on the day (Day 1), and the day after each visit (Day 2).

For the primary objective we will compare the proportions of children with fever on Day 1 or Day 2 following Visit 1 or Visit 2 between the simultaneous and the sequential vaccination groups.

- *Research hypothesis: The proportion of children in the Simultaneous group with fever on Day 1 or Day 2 will be noninferior (not higher – based on the noninferiority margin) to the proportion of children in the Sequential group with fever on Day 1 or Day 2.*

This objective will be assessed using a one-sided noninferiority test with the alpha level set at 0.025 (1-sided) and a noninferiority margin of 10%.

The null hypothesis assumes that Simultaneous group is inferior (i.e., Simultaneous group will have a higher proportion) to the Sequential group in regards to the proportion of children with fever on Day 1 or Day 2.

Ho: Simultaneous group - Sequential group ≥ 0.10 (10%)

The alternative hypothesis states that the Simultaneous group is noninferior to the Sequential group in regards to the proportion of children with fever on Day 1 or Day 2.

Ha: Simultaneous group - Sequential group < 0.10 (10%)

The upper bound of a stratified (by study site) Newcombe binomial confidence interval (Yan and Su 2010) with Cochran-Mantel-Haenszel (CMH) weighting of the difference will be used to make this assessment.

6.2.3 Secondary Objective 1

To compare the proportion of children with fever occurring 1-2 days after each visit (Visit 1 and Visit 2) in the simultaneous versus sequential groups.

For this secondary objective, we will present the proportions of children with any fever during the days 1-2 following vaccination for Visit 1 and for Visit 2.

6.2.4 Secondary Objective 2

To describe and compare the severity of fever, medical care utilization, and use of antipyretics for fever occurring 1-2 days after Visit 1 and Visit 2 (separately and combined) for the simultaneous and sequential group

We will present the proportions of children with moderate/severe fever (GRADE 2 and/or 3) on Day 1 and/or Day 2 following vaccination for Visit 1 and/or for Visit 2. We will further present the proportions of children with fever at these same cut points during the days 1-2 days following vaccination for Visit and for Visit 2 separately. Similarly, we will present the proportion of children with medical care utilization (any utilization, telephone contact, telehealth visit, clinic visit, urgent care visit, emergency department visit or hospitalization) on Day 1 and/or Day 2 after Visit 1 and/or Visit 2; we will also present these outcomes separately in days 1-2 after Visit 1 and Visit 2 separately. Lastly we will

describe the proportion of children with antipyretic use for (e.g., acetaminophen and ibuprofen) for fever on Day 1 and/or Day 2 following Visit 1 and/or Visit 2 (separately and combined).

Secondary Objectives 1 and 2 will be evaluated using a Mantel-Haenszal statistic in a stratified analysis by site at the alpha 0.05 level. No adjustments will be made to the alpha level for these evaluations.

6.2.5 Secondary Objective 3

To describe and compare the occurrence of solicited systemic reactogenicity events on days 1-7 after Visit 1 and Visit 2 in the simultaneous versus sequential group.

Tables (one for each visit 1 and 2) will be produced that summarize each solicited systemic reactogenicity event by classification (grades 1-3 as well as grades 2-3 combined), for each vaccination group. These tables will have the number and percentage for each classification by vaccination group and the 95% confidence interval of the difference between the vaccination groups for the percentage of grades 2 and 3 combined

6.2.6 Secondary Objective 4

To describe and compare the occurrence serious adverse events in the simultaneous versus sequential group.

A table will be produced that summarize participants experiencing at least one serious adverse event during the study period by group. This table will have the number and percentage for each outcome by study group and the confidence interval of the difference between the study groups. Listings with the clinical narratives will also be provided

6.2.7 Exploratory Objectives

Statistical analyses for exploratory outcomes will be described in the Statistical Analysis Plan.

6.2.8 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 an Expert Safety 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. The review will be initiated by March 2024.

6.3 Data Management

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. Duke will host the REDCap for this study. 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 KPNC, 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.

6.3.1 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. 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 Duke (lead) and contributing sites with secured password-protected computers.

6.4 Role of the CDC Investigators in the Project

This study is funded by a CDC contract with Duke University, Cincinnati, Columbia University, and KPNC as Task Orders in the CISA Project Contract. The Duke University PI (Michael J. Smith) will oversee the study in partnership with the Cincinnati PI (Elizabeth Schlaudecker), Columbia University PI (Melissa Stockwell), and KPNC PI (Nicola Klein). 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 public health priorities, and analyze the data and disseminate the results. CDC may receive access to coded data not containing any directly identifying information.

7 HUMAN SUBJECTS

7.1 Human Subjects Involvement, Characteristics, and Design

Duke, Cincinnati, Columbia, and KPNC investigators will be responsible for submitting the protocol, informed consent, memory aids, recruitment letters, flyers, and any written or verbally conveyed materials specific to this project to their institutional review boards. CDC staff will be responsible for submitting materials to the CDC for review and obtain reliance on Duke IRB.

To facilitate subject recruitment at the practices, we will request a waiver of consent and HIPAA authorization for ascertainment (identification, selection) and/or recruitment of potential subjects while recording identifiable private health information (PHI) prior to obtaining the subject'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. We will review only the minimum amount of information necessary to determine potential eligibility, e.g. to consent will be used to recruit and screen only. Use of PHI in this manner involves no more than minimal risk to subjects and no information will leave the study sites.

Continuing reviews will be submitted to the IRBs on an annual basis. Protocol deviations or concerns about study integrity will be reported promptly to the overseeing IRB in accordance with institutional requirements.

7.2 Sources of Material

Medical history, immunization history and concomitant medication history will be obtained from the medical record and from patient report. Demographic information will be obtained from the medical record and patient report. Subjects will record solicited adverse reactogenicity events and any medical intervention sought on the day of and 7 additional days following Visit 1 and Visit 2 on the memory aid. Memory aid information will be reported to the study team during a telephone call or in the web-based REDCap system. The research staff will assess temperature. Medical records will be reviewed to assess for the occurrence of AESI or serious adverse events during the entire study period.

7.3 Potential Study Biases/Limitations

Although we have proposed a sound and feasible clinical study design to achieve the proposed objectives, we recognize there are always potential pitfalls and limitations that must be addressed and mitigated, as follows:

- As per the task order request, we have designed a randomized, open-label trial of sequential vs. simultaneous administration of mRNA COVID-19 vaccine and other standard of care vaccinations as a pragmatic trial approach. The lack of blinding to the number and type of vaccines administered could introduce bias in participant data collection and reporting as well as research staff interpretation of solicited AEs, specifically fever.
- While all children are assessed in the clinic at Visit 1, the study assesses children in different settings for Visit 2 due to feasibility considerations for the families. Children in the sequential group have a clinic visit to receive the COVID-19 vaccine and a health education intervention. Children in the simultaneous group may have this visit in the clinic or at a telehealth visit.
- This study is being conducted at only 4 centers and may lack some generalizability. To address this issue, we will attempt to enroll a diverse patient population.
- While not as sensitive as rectal temperature measurement, measurement of temperature using a temporal artery thermometer is specific. Although we may slightly underestimate the actual rate of fever, it is likely that parents would recognize clinically important fever. Furthermore, temporal artery temperature measurements provide more acceptability for parents.
- It is possible that the composition of the COVID-19 vaccine product could change during the course of this study. While is it possible different COVID-19 formulations would have different safety profiles, this limitation is similar to that observed with influenza vaccine safety studies where strain changes happen most seasons.

7.4 Adequacy of Protection Against Risks

7.4.1 Protections against Risk

The vaccines used in this study are standard clinical practice and recommended by the CDC and ACIP. Parents/LARs will be provided with the CDC Vaccine Information Statements (VIS) for non-COVID-19 vaccines (35) and the FDA factsheets for COVID-19 vaccine and VIS if available. (25, 26) Non-COVID-19 vaccines are licensed by FDA and the mRNA COVID-19 vaccine used will be authorized for FDA for emergency use or licensed for use. Parents/LARs will be counseled on possible side effects following vaccination and followed closely during the 7 days post-vaccination (through study Day 7) for assessment of moderate to severe systemic reactogenicity. Subjects with a prior history of any severe allergic reaction following vaccine(s) administered in the study and those with a contraindication to mRNA COVID-19 vaccine will be excluded from study enrollment. The following is a contraindication to COVID-19 vaccine: History of a severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of the COVID-19 vaccine or History of a known diagnosed allergy to a component of the COVID-19 vaccine. Children with a history of MIS-C, a precaution to receipt of COVID-19 will also be excluded. Because myocarditis and pericarditis are considered rare risks for COVID-19 vaccine, children with a history of these conditions will also be excluded.

Emergency management supplies will be available for initial treatment of an allergic reaction if needed. Syncope after intramuscular vaccination is a known risk. Children will be observed in the respective clinic area by study staff for 15 minutes post-vaccination.

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.

7.5. ClinicalTrials.gov Requirements

The project is registered on ClinicalTrials.gov: NCT06038617

7.6 Human Subjects

In obtaining and documenting informed consent, the Investigator and study team will comply with the applicable regulatory requirements, Good Clinical Practices, and ethical principles. The parent or LAR must sign and date the written informed consent form prior to initiation of any study procedure.

7.6.1 Vulnerable Subjects Research

Vulnerable subjects

Children are a vulnerable research population and require additional protections when they are potential research subjects. This is a minimal risk study, involving the administration of routine childhood vaccinations in a manner that is consistent with ACIP recommendations. Because this study is no more than minimal risk, the permission of only one parent/LAR will be obtained.

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APPENDIX:

Appendix A: Memory Aids
Appendix B: Memory Aid Instructions
Appendix C: Educational Handout