

A Prospective, Randomized, Open-label Clinical Trial to Assess Fever Following Simultaneous versus Sequential Administration of 13-valent Conjugate Pneumococcal Vaccine, Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccine and Inactivated Influenza Vaccine in Young Children

Short Title: Fever after Simultaneous versus Sequential Vaccination 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.

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PROTOCOL SUMMARY

Title:	A Prospective, Randomized, Open-label Clinical Trial to Assess Fever Following Simultaneous versus Sequential Administration of 13-valent Conjugate Pneumococcal Vaccine, Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccine and Inactivated Influenza Vaccine in Young Children
Phase:	Phase 4
Population:	Up to 280 children, 12-16 months of age, who will receive 13-valent conjugate pneumococcal vaccine (PCV13), Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccine (DTaP), and inactivated influenza vaccine (IIV) during the 2017-2018 influenza season
Clinical Sites:	Two: Duke University (Lead); Kaiser Permanente (Contributing)
Study Duration:	8 months during the 2017-2018 influenza season
Participant Duration:	Up to 37 days
Description of Study Procedures:	<p>This is a prospective, randomized, open-label clinical trial. Young children will be randomized (1:1) to receive either simultaneous administration of PCV13, DTaP, and IIV vaccines (Visit 1) followed by a health education visit without vaccination ~ 2 weeks later (Visit 2), or sequential administration of PCV13 and DTaP (Visit 1) followed by IIV and health education ~ 2 weeks later (Visit 2).</p> <p>Parents or a legal authorized representative (LAR) will assess fever and other solicited systemic adverse events on the day of, the next 7 days (through Day 8) following Visit 1 and Visit 2 using either a web-based data collection system or a paper diary card. Febrile seizure and serious adverse events will be captured during the entire study period. Parental/LAR perceptions about their child's vaccine schedule will be assessed on the 8th day following Visit 2.</p>
Objectives:	<p>Primary Objective (PO):</p> <p>PO 1: To compare the proportions of children with fever following simultaneous versus sequential vaccination with PCV13, DTaP, and IIV during 2 visits. Children in the <u>sequential vaccination group</u> will receive PCV13 and DTaP at Visit 1 followed by IIV and health education at Visit 2. Children in the <u>simultaneous vaccination group</u> will receive PCV13, DTaP, and IIV at Visit 1, followed by a health education visit without vaccination at Visit 2. Fever will be assessed on the visit day of, and the day after (days 1-2) each visit.</p>

	<p><i>The primary hypothesis is that the proportion of children with fever will be higher in children after the simultaneous vs. the sequential schedule.</i></p> <p>Secondary Objectives (SO): SO 1: To compare the proportions of children with fever on day 1 and/or day 2 after Visit 1 and Visit 2 separately, in the simultaneous versus sequential vaccination group. SO 2: To compare the clinical importance of fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever.</p> <p>Exploratory Objectives (EO): EO 1: To compare the height and duration of fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group EO 2: To compare the use of antipyretics for fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. EO 3: To describe and compare the level of severity of fever following Visit 1 and Visit 2 (separately) in the simultaneous versus sequential group EO 4: To compare the proportions of children with fever 3-8 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. EO 5: To compare the clinical importance of fever occurring 3-8 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever. EO 6: To describe and compare the occurrence of solicited systemic adverse events on day 1-8 after Visit 1 and Visit 2 in the simultaneous versus sequential group. EO 7: To describe and compare the occurrence of febrile seizure and/or serious adverse events during the period of enrollment (i.e. from Visit 1 through 8 days after Visit 2) in the simultaneous versus sequential group. EO 8: To describe and compare the perceptions among parents/ legally authorized representatives (LARs) of the simultaneous versus sequential schedule experience.</p>
<p>Outcome Measures:</p>	<p>Primary Outcome Measure (POM): POM 1.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1 and/or Visit 2</p> <p>Secondary Outcome Measures (SOM): SOM 1.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1. SOM 1.2: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 2</p>

	<p>SOM 2.1: Proportions 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</p> <p>SOM 2.2: Average number of consecutive days of fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) per subject for fever starting on day 1 or 2 following Visit 1, Visit 2 and Visit 1 and Visit 2 combined.</p> <p><i>Note: fever starting on day 1 or 2 could continue through day 8.</i></p> <p>SOM 2.3: Proportion of children with medical care utilization (telephone call, 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.</p> <p>Exploratory Outcome Measures (EOM):</p> <p>EOM 1.1: Average peak temperature of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined.</p> <p>EOM 1.2: Total number of fever degree-days (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 per subject following Visit 1, Visit 2, and Visit 1 and Visit 2 combined.</p> <p>EOM 2.1: Proportion 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.</p> <p>EOM 3.1: Proportions of children with fever at different levels of severity (Grades 1, 2, and 3) on day 1 and/or day 2 following Visit 1 and Visit 2</p> <p>EOM 3.2: Proportions of children with fever at different levels of severity (Grades 1, 2, and 3) on days 3-8 following Visit 1 and Visit 2</p> <p>EOM 3.3: The proportion of children with fever at different levels of severity (Grades 1, 2,3 and all Grade) on days 1-8 following Visit 1 and Visit 2</p> <p>EOM 4.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on at least one day on day 3-8 following Visit 1.</p> <p>EOM 4.2: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on at least one day on day 3-8 following Visit 2.</p> <p>EOM 4.3: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on at least one day on day 3-8 following Visit 1 and Visit 2 combined.</p> <p>EOM 5.1: Proportions of children with moderate/severe fever (GRADE 2 and/or 3) on at least one day during days 3-8 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined</p> <p>EOM 5.2: Average number of consecutive days of fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) per subject for fever starting on 3-8 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined.</p> <p><i>Note: fever starting on day 3-8 could continue through day 8.</i></p> <p>EOM 5.3 Proportion of children with medical care utilization (telephone call, medical office visit, emergency department visit, or hospital admission) for fever on 3-8 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined).</p>
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	<p>EOM 6.1: The proportion of children with solicited systemic adverse events (excluding fever) at different levels of severity (Grades 1, 2, 3, and all Grades) on day 1-8 following Visit 1 and Visit 2</p> <p>EOM 7.1: The proportion of children with febrile seizure and/or serious adverse events during the period of enrollment (i.e. from Visit 1 through 8 days after Visit 2).</p> <p>EOM 8.1: Proportion of parents reporting positive and negative perceptions about their vaccination schedule experience will be determined for each survey item.</p>
Estimated Time to Complete Enrollment:	Approximately 7 months for enrollment season

1 BACKGROUND

1.1 Background

Fever is commonly observed in children following receipt of their routine immunizations.¹ 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 influenzae* 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>). While the exact mechanisms and functions of fever are not completely understood, some have suggested fever has a beneficial role in response to infection². However, in the context of immunization, fever is considered an adverse event that leads to increased medical visits, and can contribute to reluctance to vaccinate³.

In most cases, the fever following childhood vaccination is mild and resolves within a few days; however, in a small proportion of cases, fever can be clinically severe. For young children, fever following immunizations can also trigger the occurrence of a febrile seizure (FS) which is the most common neurological event in childhood⁴. As also noted in the VIS, FS occur as a potential side effect following several different vaccines including MMR, varicella, and MMRV vaccines. In addition, the VIS for IIV notes that young children receiving IIV along with PCV13 or DTaP may be more likely to have a FS. Likewise, the VIS for PCV13 notes that children receiving IIV at the same time as PCV13 may be more likely to have a FS. The DTaP VIS discusses fever in children with a history of seizure, but FS are not specifically mentioned as a potential complication.

While a potential complication of fever following pediatric vaccinations, FS can also occur in the setting of other fever triggering illnesses in young children. Typically, FS are most commonly observed in children between 6 months and 3 years of age with the peak occurrence at 18 months of age.⁵ Approximately, 2-5% of children experience at least one FS before the age of 5 years⁶. Besides a prior FS, a family history of FS is also a risk factor for FS occurrence⁷. For children experiencing a FS, the recurrence rate is generally believed to be 30% but may approach 50% in the youngest children. Although generally considered a benign condition, the occurrence of a FS can be quite frightening and anxiety provoking in parents of these children.

The current statements regarding risks for FS following IIV and PCV13 vaccines, as noted above, were included in the VIS following clinical and study observations made during the 2010-2011 influenza season. In 2010 an increased risk of FS was noted among southern hemisphere children within 24 hours of receiving CSL influenza vaccine.⁸ With a heightened awareness after the southern hemisphere experience, during the 2010-2011 influenza season, the Vaccine Adverse Event Reporting System (VAERS) detected a signal for an increased occurrence of FS among children younger than 2 years of age who had received IIV.⁹ As Fluzone was the only US licensed vaccine for children of this age, the increased occurrence was specific to this IIV product. A study by the Vaccine Safety Datalink (VSD) to assess FS after the 2010-2011 influenza vaccine noted an elevated risk of FS on the day of and day following (days 1-2) the first dose of trivalent influenza vaccine (IIV3).¹⁰ The risk was elevated for both IIV3 and PCV13 and was highest when IIV3 was co-administered with PCV13. Among children 6 to 59 months of age in this VSD study, 16 month-olds had the highest risk for FS. The VSD continued with additional studies to further explore this

association. A subsequent analysis by VSD for the 2013-2014 and 2014-2015 seasons noted an increased FS risk on the day of and day following the first dose of IIV3 during the 2014–2015 season in children aged 6–23 months.¹¹ An analysis including both seasons noted that the relative risk of FS was significantly elevated for IIV3 and IIV4 with concomitant PCV13 vaccination and not for IIV3 or IIV4 alone. Finally, the VSD did a study of children 6 through 23 months of age during the periods from 2006 to 2011. The concomitant administration of IIV3 + PCV and IIV3 + DTaP-containing vaccines had higher risks of FS than when the vaccines were given independently. The concomitant administration of PCV + DTaP + IIV-containing vaccines had the highest relative risk. These increased risks with concomitant vaccination were observed in all influenza seasons studied.¹² A separate study conducted by the Post-Licensure Rapid Immunization Safety Monitoring Program (PRISM) was unable to confirm the VSD findings and did not detect an increased risk of FS for 2010–2011 IIV3 or PCV13, when adjusting for concomitant vaccines.¹³ It is unclear why the VSD and PRISM studies did not find comparable results.

As an elevated risk of FS has been noted, particularly with concomitant administration of PCV13 and IIV, one would expect to observe higher rates of fever when PCV13 is administered with IIV compared to when they are administered separately. An observational study conducted by Clinical Immunization Safety Assessment (CISA) investigators in 2011-2012, a season during which the vaccine was unchanged from 2010-2011 when higher rates of FS were detected, noted that on day of and day following vaccination, children aged 6-23 months, receiving IIV3 and PCV13 simultaneously had higher rates of fever than those receiving IIV3 or PCV13 without the other product.¹⁴ Temperatures were measured using a temporal artery thermometer. The proportion of children with fever $\geq 38^{\circ}\text{C}$ in the 1-2 days after vaccination was 7.5% in those receiving IIV3 alone, 9.5 % in those receiving PCV13 alone and 37.6%, in those receiving both vaccines. This effect was greater following the first dose of IIV3 when compared to the second dose. These data lend support to findings of the VSD investigations suggesting a higher rate of FS occurring after concomitant administration of PCV13 and IIV. In addition, in an early 2003 study of IIV in children 6 through 23 months of age, we noted the percentage of children with axillary temperatures $> 37.8^{\circ}\text{C}$ within 3 days of IIV was 7% when IIV3 was given concomitantly with pneumococcal conjugate vaccine, 4% when given with any diphtheria-tetanus toxoid-acellular pertussis combination vaccine, and 5% when given alone.¹⁵

1.2 Summary & Rationale

Fever after vaccination is relatively common and may serve as a proxy for febrile seizure risk. Given the uncertainties about the association of simultaneously administered PCV13, DTaP, and IIV in young children and risk for febrile seizure, a prospective randomized clinical study could provide much-needed data on risks of increased fever and hence the potential for the development of FS. Although one potential strategy for preventing FS is the use of antipyretic medications around the time of vaccination, the use of antipyretics to prevent FS in the setting of fever has not been shown to be an effective strategy.¹⁶ Furthermore, an antipyretic strategy to prevent FS following vaccination has yet to be proven to work and has the potential for blunting of vaccine immune responses particularly for PCV and DTaP vaccines.¹⁷ An alternate strategy is administering vaccines sequentially rather than concomitantly when their concomitant use has been shown to result in more fever and resulting FS. Furthermore, clinics frequently administer influenza vaccine as a stand-alone vaccine; among children who

received IIV in the VSD 2010-11 study, 54% of children received it alone.¹⁰ It is likely to be logistically feasible to separate visits between influenza vaccine and other non-influenza childhood vaccines; this could be done without a child becoming delayed on the recommended immunization schedule. Parents and providers would benefit from knowing if separating the IIV vaccine from other recommended vaccines actually reduces fever and hence the overall risk for febrile seizure after vaccination or if it just spreads the risk over two time points.

We therefore propose to conduct a study to assess fever following simultaneous vs. sequential PCV13, DTaP and IIV administration in children of an age of peak FS risk. This study will provide evidence that may help healthcare providers who care for children at high risk for FS make vaccination decisions. The current study will not include children at high risk of FS, as anecdotally it has been noted that some of these children per recommendations from their provider may already be receiving PCV13/DTaP and IIV sequentially. Although the study will not include these at risk children, the findings will provide indirect evidence on whether spacing IIV and other childhood vaccines over two visits might potentially be useful as a strategy to prevent fever and febrile seizures after inactivated vaccines in children at high risk for febrile seizure. This study could help quantify the number of additional fevers, if any, which occur after simultaneous vs sequential vaccination. This information would also provide anticipatory guidance to parents about fever after simultaneous vaccination.

2 STUDY OBJECTIVES

Primary Objective (PO):

PO 1: To compare the proportions of children with fever following simultaneous versus sequential vaccination with PCV13, DTaP, and IIV during two visits. Children in the sequential vaccination group will receive PCV13 and DTaP at Visit 1 followed by IIV and health education at Visit 2. Children in the simultaneous vaccination group will receive PCV13, DTaP, and IIV at Visit 1, followed by a health education visit without vaccination at Visit 2. Fever will be assessed on the visit day of, and the day after (days 1-2) each visit.

The primary hypothesis is that the proportion of children with fever will be higher in children after the simultaneous vs. the sequential schedule.

Secondary Objectives (SO):

SO 1: To compare the proportions of children with fever on day 1 and/or day 2 after Visit 1 and Visit 2 separately, in the simultaneous versus sequential vaccination group.

SO 2: To compare the clinical importance of fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever.

Exploratory Objectives (EO):

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

EO 2: To compare the use of antipyretics for fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group.

EO 3: To describe and compare the level of severity of fever following Visit 1 and Visit 2 (separately) in the simultaneous versus sequential group

EO 4: To compare the proportions of children with fever 3-8 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group.

EO 5: To compare the clinical importance of fever occurring 3-8 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever.

EO 6: To describe and compare the occurrence of solicited systemic adverse events on day 1-8 after Visit 1 and Visit 2 in the simultaneous versus sequential group.

EO 7: To describe and compare the occurrence of febrile seizure and/or serious adverse events during the period of enrollment (i.e. from Visit 1 through 8 days after Visit 2) in the simultaneous versus sequential group.

EO 8: To describe and compare the perceptions among parents/ legally authorized representatives (LARs) of the simultaneous versus sequential schedule experience.

2.1 Study Outcome Measures as Related to Objectives**Primary Outcome Measure (POM):**

POM 1.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1 and/or Visit 2.

Secondary Outcome Measures (SOM):

SOM 1.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1.

SOM 1.2: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 2

SOM 2.1: Proportions 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: Average number of consecutive days of fever (temperature $\geq 38.0^{\circ}$ C or $\geq 100.4^{\circ}$ F) per subject for fever starting on day 1 or 2 following Visit 1, Visit 2 and Visit 1 and Visit 2 combined.

Note: fever starting on day 1 or 2 could continue through day 8.

SOM 2.3: Proportion of children with medical care utilization (telephone call, 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.

Exploratory Outcome Measures (EOM):

EOM 1.1: Average peak temperature of children with fever (temperature $\geq 38.0^{\circ}$ C or $\geq 100.4^{\circ}$ 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 $\geq 38.0^{\circ}$ C or $\geq 100.4^{\circ}$ 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: Proportion 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.

EOM 3.1: Proportions of children with fever at different levels of severity (Grades 1, 2, and 3) on day 1 and/or day 2 following Visit 1 and Visit 2

EOM 3.2: Proportions of children with fever at different levels of severity (Grades 1, 2, and 3) on days 3-8 following Visit 1 and Visit 2

EOM 3.3: The proportion of children with fever at different levels of severity (Grades 1, 2,3 and all Grade) on days 1-8 following Visit 1 and Visit 2

EOM 4.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}$ C or $\geq 100.4^{\circ}$ F) on at least one day on day 3-8 following Visit 1.

EOM 4.2: Proportion of children with fever (temperature $\geq 38.0^{\circ}$ C or $\geq 100.4^{\circ}$ F) on at least one day on day 3-8 following Visit 2.

EOM 4.3: Proportion of children with fever (temperature $\geq 38.0^{\circ}$ C or $\geq 100.4^{\circ}$ F) on at least one day on day 3-8 following Visit 1 and Visit 2 combined.

EOM 5.1: Proportions of children with moderate/severe fever (GRADE 2 and/or 3) on at least one day during days 3-8 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined

EOM 5.2: Average number of consecutive days of fever (temperature $\geq 38.0^{\circ}$ C or $\geq 100.4^{\circ}$ F) per subject for fever starting on 3-8 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined.

Note: fever starting on day 3-8 could continue through day 8.

EOM 5.3 Proportion of children with medical care utilization (telephone call, medical office visit, emergency department visit, or hospital admission) for fever on 3-8 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined).

EOM 6.1: The proportion of children with solicited systemic adverse events (excluding fever) at different levels of severity (Grades 1, 2, 3, and all Grades) on day 1-8 following Visit 1 and Visit 2

EOM 7.1: The proportion of children with febrile seizure and/or serious adverse events during the period of enrollment (i.e. from Visit 1 through 8 days after Visit 2).

EOM 8.1: Proportion of parents 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 that will be conducted during the 2017-2018 influenza season. Results from the 2017-2018 influenza season will help guide whether this study will be repeated during the 2018-2019 influenza season under a new protocol. During the 2017-2018 season, approximately 280 children will be enrolled at Duke University Medical Center and Kaiser Permanente Northern California. Eligible children will be randomized to receive simultaneous or sequentially administered US-licensed PCV13, US-licensed DTaP vaccine, and US-licensed inactivated influenza vaccine (IIV). Children in the simultaneous group will receive PCV13, DTaP, and IIV vaccines at Visit 1, and then return for a health education visit without vaccination about 2 weeks later (Visit 2). Children in the sequential group will receive both PCV13 and DTaP without IIV at Visit 1, and then will receive IIV and health education about 2 weeks later (Visit 2). Parents will record the occurrence of fever, solicited adverse events, medical care utilization, and receipt of antipyretics over 8 days following Visit 1 and Visit 2. In addition, febrile seizures and serious adverse events will be recorded for the entire study period (from enrollment through 8 days following the Visit 2) will be assessed through parental report and chart review.

Young children aged 12-16 months will be enrolled over a period of approximately 7 months. Children will be followed for up to 37 days following enrollment. The first 10 children enrolled at Duke University Medical Center will be enrolled in a study pilot to quickly assess study feasibility benchmarks and make protocol adjustments if necessary. Data from pilot participants will also contribute to the analysis of primary, secondary and exploratory outcomes.

4 STUDY ENROLLMENT AND WITHDRAWAL

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

4.1 Subject Inclusion Criteria

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

1. 12 through 16 months of age (i.e. from the 1-year birthday until the day before 17 months of age) at the time of vaccination
2. Stable health as determined by investigator's clinical examination and assessment of child's medical history
3. Has received all immunizations recommended by Advisory Committee for Immunization Practices (ACIP) during the first year of life with the exception of rotavirus and influenza vaccines.*

**Immunizations recommended during the first year of life include: 3 doses of DTaP, 3 doses of PCV13, 2- 3 doses of inactivated polio virus vaccine, 3 doses of Hepatitis B vaccine, and 2 or 3 doses of Hib vaccine such that the primary Hib series is complete depending upon the brand used.*

(<https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html>).

4. The parent(s)/ legally authorized representative(s) LAR(s) intend for the child to receive DTaP and PCV13 in addition to this season's IIV
5. The parent(s)/LAR(s) must be willing and capable of providing permission for their child to participate through the written informed consent process
6. The parent(s)/LAR(s) must be able to comply with the requirements of the protocol (e.g., completion of the memory aid (either electronic or paper diary), return for follow-up visits, respects intervals between the visits and have telephone access.
7. The parent(s)/LAR(s) must be English speaking
8. The parent(s)/LAR(s) 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)

4.2 Subject Exclusion Criteria

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

1. History of any seizure (including febrile seizure) in the child or a febrile seizure in a first degree relative*
**First degree relatives include biological parents or siblings*
2. Has already completed influenza vaccination during the current season per ACIP recommendations*
**Children needing two doses of influenza vaccine per ACIP recommendations and who are receiving a second dose of influenza vaccine may be enrolled; however, an attempt will be made to preferentially enroll children needing two doses at the time of receipt of their first dose of influenza vaccine*
3. Receipt of more than 3 previous doses of DTaP
4. Received the 3rd dose of DTaP within 6 months of Visit 1
5. Receipt of more than 3 previous doses of PCV13
6. Received the 3rd dose of PCV13 within 8 weeks of Visit 1
7. History of a severe allergic reaction (e.g. anaphylaxis) to a previous dose of any influenza, diphtheria toxoid-, tetanus toxoid-, or pertussis-containing vaccine, or pneumococcal vaccine.
8. History of a severe allergic reaction (e.g., anaphylaxis) to any component (including egg protein) of any of the three vaccines used in this study; or a latex allergy.

9. History of Guillain-Barré syndrome within 6 weeks following a prior dose of influenza, DTaP, or tetanus toxoid containing vaccine
10. History of a progressive neurologic disorder
11. History of encephalopathy within 7 days of a previous pertussis-containing vaccine
12. History of collapse within 3 days after a prior dose of DTaP
13. Received any other licensed vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Visit 1*
**Concomitant vaccine administration of vaccines on ACIP recommended immunization schedule for children and adolescents aged 18 years and younger are allowed to be administered on the first vaccination day in this study but at no other time in this study period unless deemed a personal or public health priority by the health care provider caring for this patient or the study team.*
14. Received an experimental/investigational agent (vaccine, drug, biologic, device, blood product, or medication) within 28 days prior to Visit 1, or expects to receive an experimental/investigational agent during the study period (up to 8 days after visit 2)
15. A moderate to severe acute illness within 72 hours of Visit 1*
**All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection without fever.*
16. A reported temperature greater than or equal to 100.4°F (38.0°C) within 72 hours prior enrollment or a temperature (measured by temporal artery thermometer) greater than or equal to 100.4°F (38.0°C) at the time of enrollment*
**This may result in a temporary delay of vaccination*
17. Receipt of an antipyretic medication (acetaminophen or ibuprofen) within 24 hours prior to enrollment*
**This may result in a temporary delay of vaccination*
18. Parent(s)/LAR is planning to administer a prophylactic antipyretic or medication on the day of, and/or within 7 days following Visit 1 or Visit 2*
**This exclusion does not apply if the caretaker indicates he/she might administer antipyretics or analgesics after vaccination to reduce fever or pain*
19. Long term (at least 14 consecutive days) oral corticosteroids (prednisone 2 mg/kg/day or equivalent other glucocorticoid), any parenteral steroids, high-dose inhaled steroids (>800 mcg/day of beclomethasone dipropionate or equivalent) or other immune-modifying drugs or immunosuppressants within the preceding 6 months prior to Visit 1*
**Topical and nasal steroids are allowed*
20. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and or their provider's routine physical examination*
**No laboratory testing required*
21. Has an active neoplastic disease, a history of any hematologic malignancy, current bleeding disorder, or taking anticoagulants.
22. Unable to receive an intramuscular injection in the thigh*
** For example – a broken bone or cast for treatment of broken bone in a lower extremity, congenital anomaly in lower extremity precluding administration in the affected extremity or if deemed inappropriate by the study investigator*

23. Any condition deemed by the investigator to place the child at increased risk as a result of their participation in the study
24. 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 continued study participation.

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

1. Has already completed influenza vaccination during the current season per ACIP recommendations
2. History of a severe allergic reaction (e.g. anaphylaxis) to a previous dose of any influenza vaccine.
3. History of a severe allergic reaction (e.g., anaphylaxis) to any component (including egg protein) of the influenza vaccine used in this study.
4. History of Guillain-Barré syndrome within 6 weeks following a prior dose of any influenza vaccine
5. Received an experimental/investigational agent (vaccine, drug, biologic, device, blood product, or medication) after randomization or expects to receive an experimental/investigational agent during the remaining study period (up to 8 days after visit 2)
6. A moderate to severe acute illness within 24 hours of Visit 2*
** This may result in a temporary delay of Visit 2 and/or vaccination.
All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection without fever.*
7. A reported temperature greater than or equal to 100.4°F (38.0°C) within 24 hours prior to Visit 2 or a temperature (measured by temporal artery thermometer) greater than or equal to 100.4°F (38.0°C) at the time of Visit 2*
**This may result in a temporary delay of Visit 2 and/or vaccination*
8. Receipt of an antipyretic medication (acetaminophen or ibuprofen) within 24 hours prior to Visit 2*
**This may result in a temporary delay of Visit 2 and/or vaccination*
9. Parent(s)/LAR is planning to administer a prophylactic antipyretic or medication on the day of, and/or within 7 days following Visit 2*
**This exclusion does not apply if the caretaker indicates he/she might administer antipyretics or analgesics after Visit 2 to reduce fever or pain*
10. Unable to receive an intramuscular injection in the thigh*
** For example – a broken bone or cast for treatment of broken bone in a lower extremity, congenital anomaly in lower extremity precluding administration in the affected extremity or if deemed inappropriate by the study investigator*
11. Any condition deemed by the investigator to place the child at increased risk as a result of their participation in the study

4.3 Recruitment

The 280 participants in this study will be healthy male or female children 12 through 16 months of age. Children will be recruited from designated study sites affiliated with the Duke University Health System (Duke Children's Primary Care Roxboro Street, Duke Children's Primary Care Southpoint, Duke Children's Primary Care Brier Creek,

Durham Pediatrics, and Regional Pediatrics) or from designated Northern California Kaiser Permanente pediatric clinics. Children will primarily be recruited at the time of well child visits. About 160 children will be enrolled at the Duke University Health System Clinics and 120 children will be enrolled at the Northern California Kaiser Permanent pediatric clinics.

4.4 Reasons for and Handling of Withdrawals

The following may be reasons for study withdrawal:

- As deemed necessary by the principal investigator (PI).
- Meets criteria for exclusion at Visit 2
- Parent(s)/LAR(s) withdrawal of permission for their child to participate.
- Loss to follow-up.
- No longer a member of the Kaiser Foundation Health Plan (KFHP) – only includes children enrolled at the Northern California Kaiser Permanent pediatric clinics.
- 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, data collected prior to withdraw in the study will be included in the study.

4.5 Termination of Study

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

5 STUDY SCHEDULE, PROCEDURES, & EVALUATIONS

5.1 Schedule of Events

Children 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. **Table 1** describes 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 by (REDCap) or using a paper memory aid (diary). For this study, use of (REDCap) for obtaining memory aid information is the preferred option.

Table 1. Proposed Study Visit Schedule						
Procedure	Visit 1 Day 1	Visit 1A Day 3 (+3)	Visit 1B Day 9 (+3)	Visit 2 Day 15 (+7)	Visit 2A Day 3 (+3) Post Visit 2	Visit 2B Day 9 (+6) Post Visit 2
Type of contact by group (REDCap/Paper Form)	Clinic REDCap - All Paper – All	Phone/Email REDCap-PRN Paper – All	Phone/Email REDCap-PRN Paper – No	Clinic REDCap-All Paper – All	Phone/Email REDCap-PRN Paper – All	Phone/Email REDCap-PRN Paper – PRN
Written Parent/LAR Permission & Medical Release of Information	X					
Review Eligibility Criteria	X			X		

Table 1. Proposed Study Visit Schedule						
Procedure	Visit1 Day 1	Visit 1A Day 3 (+3)	Visit 1B Day 9 (+3)	Visit 2 Day 15 (+7)	Visit 2A Day 3 (+3) Post Visit 2	Visit 2B Day 9 (+6) Post Visit 2
Data Collection (Demographic information and Medical History)	X					
Influenza, DTaP, and PCV13 Vaccination History	X					
Temperature measurement (temporal artery)	X			X		
Randomization	X					
Vaccination with study vaccine(s)	X			X ¹		
Provide Educational Materials				X		
Concomitant Vaccination with non-study vaccines	X					
Dispense Memory aid (Paper ²) & Thermometer	X			X ³		
Complete Memory aid form (REDCap or Paper) for fever, solicited systemic adverse events, medical care utilization, antipyretic use	X	X	X	X	X	X
Review REDCap and paper memory aid entries for completeness and out of range values for fever data		X			X	
Review REDCap entries for completeness fever, solicited systemic adverse events, medical care utilization, antipyretic use			X			X
Review Paper Memory aid for completeness fever, solicited systemic adverse events, medical service utilization, antipyretic use				X		X
Obtain concomitant medication use	X			X		
Obtain serious adverse event information and febrile seizure information		X	X	X	X	X
Obtain parent(s)/LAR(s) perceptions about vaccination and/or the vaccination schedules						X

¹Indicates vaccination of subjects in sequential group only. ²All subjects receive paper memory aid ³New thermometer dispensed only for those who have misplaced it or if not working properly

Visit 1, Study Day 1 Clinic Visit

- Obtain parent(s)/LAR(s) permission by written informed consent and a release of

medical record information

- Review and confirm study eligibility (Section 4.1 and 4.2)
- Obtain information on parent(s)/LAR(s) preferred method for submitting memory aid information – either direct entry by the parent(s)/LAR(s) into REDCap using the memory aid as a tool or directly submitting information recorded on the paper memory aid. Parents will be encouraged to submit information recorded on the memory aid into REDCap.
- Obtain information on parent(s)/LAR(s) preferred method of contact by the study team to assist with obtaining follow-up information (e-mail or telephone)
- Obtain medical history
- Obtain demographic data & month/ day /year of prior influenza, DTaP and PCV13 vaccines
- Obtain concomitant medication use within 2 weeks of enrollment
- Obtain temperature using the temporal artery thermometer to be dispensed to parent(s)/LAR(s) for use at home. Use temperature measurement as an opportunity to instruct the parent(s)/LAR(s) on use of temporal artery thermometer.
- Dispense temporal artery thermometer to all parent(s)/LAR(s). Parent(s)/LAR(s) will get to keep the temporal artery thermometer dispensed.
- Randomize study participant to simultaneous or sequential vaccine administration
- Ensure participants receive corresponding Vaccine Information Sheets (VIS) during visit.
- Administer assigned study products – Trained, licensed research staff will administer PCV13, DTaP, and IIV or PCV13 and DTaP
- Administer other concomitant vaccines as needed for age according to ACIP recommendations (either research or clinic staff). This is per usual clinical practice and is not considered a study procedure
- Observe child in the clinic for at least 15 minutes after vaccination
- Dispense paper memory aid to all parent(s)/LAR(s) to record temperatures, solicited adverse events, medical care utilization and antipyretic use.
- Review use of REDCap for those preferring submitting memory aid information by internet and collect email address
- Confirm date of next scheduled telephone and clinic study visit appointments.
 - Parent(s)/LAR(s) electing to use REDCap will only be called/contacted on Study Day 3 following Visit 1 if missing fever information or if out of range fever values and will only be called/contacted on Study Day 9 following Visit 1 if missing information
 - All parent(s)/LAR(s) electing to use the paper memory aid only will be called/contacted on Study Day 3 following Visit 1.
 - All children will return for a visit on Visit 2 on Day 15. Remind parents using paper memory aid only to return memory aid at Visit 2.

Visit 1A, Study Day 3 (window Days 3-6) Memory Aid Check - Phone Call/E-mail Follow-up

- *REDCap Follow-Up for Memory Aid Information*
 - Review of REDCap information submitted for fever only on Day 1 and Day 2 for completeness and out of range values for fever.
 - If missing fever information or out of range fever values, contact parent(s)/LAR(s) to review the memory aid data for Day 1 and Day 2 and obtain any missing fever information or clarify any out of range fever values.
 - Instruct parent to enter any missing days of data in REDCap

- Record missing information regarding fever on paper case report form (CRF)
- If missing days of information for solicited adverse events, medical care utilization, antipyretic use, occurrence of febrile seizure or occurrence of a serious event remind parent to complete information in REDCap,
- *Paper Memory Aid Completion*
 - Contact parent(s)/LAR(s) to review and obtain Day 1 and Day 2 memory aid information for fever only (completeness and out of range values)
 - Record information regarding fever on paper CRF
 - Remind parent(s)/LAR(S) to bring the paper memory aid to Visit 2
 - Confirm date of next scheduled clinic visit appointments.

Visit 1B, Study Day 9 (window Days 9-12) Memory Aid Check – Phone Call/E-mail Follow-up

- *REDCap Follow-Up for Memory Aid Information*
 - Review of electronically submitted memory aid information (fever, solicited adverse events, medical care utilization, antipyretic use, occurrence of febrile seizure, or occurrence of a serious adverse event) for Days 1-8 for completeness
 - If missing information, contact parent(s)/LAR(s) to review the memory aid data for Days 1-8 and obtain any missing information
 - Instruct parent to enter missing days of data into REDCap
 - Record missing information on a paper CRF
- *Paper Memory Aid Completion*
 - No scheduled follow-up for this visit

Visit 2, Study Day 15 (window Days 15 – 22) Clinic Visit

- *Paper Memory Aid Completion for Visit 1*
 - Collect paper memory aid.
 - Review of paper memory aid information (fever, solicited adverse events, medical care utilization, antipyretic use, occurrence of febrile seizure, or occurrence of a serious adverse event) for Days 1-8
- Review and confirm continued study eligibility (Section 4.2)
- Obtain temporal artery temperature.
- Record any SAEs, febrile seizures occurring between day 9 after Visit 1 and Visit 2
- Record concomitant medications
- Ensure participants receive IIV Vaccine Information Sheets (VIS) during visit.
- For subjects in the sequential study group, trained, licensed research staff will administer IIV.
- Observe child in the clinic for at least 15 minutes after vaccination
- Administer educational intervention and provide toothbrush to all study participants
- No concomitant immunizations will be allowed or administered unless deemed a personal or public health priority by the health care provider caring for this patient or the study team.
- Confirm preferred method of contact for follow-up (email or telephone) including continued preference for submitting memory aid information by REDCap or by mail.
- Confirm subjects still have previously dispensed thermometer; if not, provide new thermometer for the parent to keep. Dispense new paper memory aid. Review instructions for use of thermometer and memory aid completion

- Review use of REDCap for those preferring to submit memory aid information by internet and verify email address
- For those parent(s)/LAR(s) electing to use a paper memory aid, they will be provided survey regarding preferences for spacing of vaccinations. Give these parent(s)/LAR(s) a pre-addressed postage paid envelope to return the memory aid and survey.
- Confirm date of next scheduled telephone appointments.
 - Parent(s)/LAR(s) electing to use REDCap will only be called/contacted on Day 3 following Visit 2 if missing fever information or if out of range fever values and will only be called/contacted on Day 9 if any memory aid information is missing.
 - Remind parents using REDCap that they will receive a parental perceptions survey on Day 9 to be completed using REDCap
 - Parent(s)/LAR(s) electing to use the paper memory aid only will be called/contacted on Day 3 following Visit 2.
 - Remind parents using paper memory aid only to complete the parental perceptions survey and mail in the memory aid on Day 9 following Visit 2.

Visit 2A, Study Day 3 Post Visit 2 (window Days 3-6) Memory Aid Check Phone Call/E-mail Follow-up

- *REDCap Follow-Up for Memory Aid Information*
 - Review of REDCap information submitted for fever only on Day 1 and Day 2 following Visit 2 for completeness and out of range values for fever.
 - If missing fever information or out of range fever values, contact parent(s)/LAR(s) to review the memory aid data for Day 1 and Day 2 and obtain any missing fever information or clarify any out of range fever values.
 - Instruct parent to enter any missing days of data in REDCap
 - Record missing information regarding fever on paper case report form (CRF)
 - If missing days of information for solicited adverse events, medical care utilization, antipyretic use, occurrence of febrile seizure or occurrence of a serious event remind parent to complete information in REDCap,
- *Paper Memory Aid Completion*
 - Contact parent(s)/LAR(s) to review and obtain Day 1 and Day 2 memory aid information for fever only (completeness and out of range values)
 - Record information regarding fever on paper CRF
 - Remind parent(s)/LAR(S) to use the pre-addressed postage paid envelope to mail in the paper memory aid and parental preference survey at Day 9 following Visit 2

Visit 2B, Study Day 9 Post Visit 2 (window Days 9-15) Memory Aid Check Phone Call/E-mail Follow-up

- *REDCap Follow-Up for Memory Aid and Parental Preference Information*
 - Parent will receive parental preference survey on Day 9 after Visit 2 to complete through REDCap or verbally over the phone
 - Review of electronically submitted memory aid information (fever, solicited adverse events, medical care utilization, antipyretic use, occurrence of febrile seizure, or occurrence of a serious adverse event) for Days 1-8 and parental preference survey for completeness

- If missing information, contact parent(s)/LAR(s) to review the memory aid data for Days 1-8 and parental preference survey and obtain missing information
- Instruct parent to enter missing days of data into REDCap
- Record missing information on a paper CRF
- Review medical record for occurrence of any SAEs or febrile seizures during the enrollment period
- Complete end of study form once memory aid information and parental preference survey is completely entered in REDCap or has been obtained and medical record has been reviewed.
- **Paper Memory Aid Completion**
 - No scheduled follow-up for this visit
 - If parent fails to send in paper memory aid or parental preference survey they can be contacted by phone or e-mail to remind them to return the memory aid and parental preference survey using pre-addressed postage paid envelope or complete verbally over the phone
 - Review medical record for occurrence of any SAEs or febrile seizures during the enrollment period
 - Complete end of study form once memory aid information and parental perceptions survey have been received and medical record has been reviewed.

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 questions before and after permission is obtained. Parent(s)/LAR(s) will be given as much time as needed after being approached about their child participating in the study and needing to decide whether or not to participate. We anticipate that the initial consent discussion, including presenting the information in the consent document and answering questions will take about 30 minutes. Parent(s)/LAR(s) will have the opportunity to take the consent form home and discuss the document with other family members or friends. During the consent process, it will be stressed that participation is voluntary and that parents 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. 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 also be assessed.

5.3 Demographic Information, Medical History, Immunization History

The participant's age, race/ethnicity, day care attendance and the number of other children in the household will be obtained from parent/guardian report at the time of enrollment. The insurance payer status for the child will be obtained from the electronic health record (EHR). The participant's medical history including: birthweight; history of prematurity; seizure disorder (including febrile seizure history and family history of febrile seizure in sibling or parent); significant medical conditions (cardiac disease, pulmonary disease including asthma or recurrent wheezing or chronic lung conditions, renal disease, diabetes, anemia, hemoglobinopathies) and concomitant medications taken within 2 weeks of enrollment will be obtained by review of the electronic health record

(EHR) and will be reviewed and confirmed by the parent/guardian at the time of enrollment. Concomitant medications, history of intercurrent hospitalizations or febrile seizures will also be verified at Visit 2.

Information on prior history of IIV receipt and on prior receipt of Diphtheria Tetanus Toxoid (DT), Diphtheria, Tetanus and acellular Pertussis vaccine (DTaP), and PCV13 will be obtained at the time of study enrollment. 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 IIV, DTaP, and PCV13 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.

Vaccines received as part of the study and concomitant immunization received during the study, will be documented by the research staff. Documentation will include: product brand, lot number, site and date/time of vaccine administered during study participation.

At the end of the study, the medical record will be reviewed to assess and record the occurrence of any serious adverse events or febrile seizures that occurred during the period of study enrollment.

5.4 Temporal Artery Temperature Measurement and Fever Assessments

Participants' 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. Temperatures will be collected during both Visit 1 and Visit 2. Thereafter, parent(s)/LAR(s) will measure and record the participant's temperature at approximately the same time each day (preferably after 6:00 PM or right before participant goes to bed) beginning on Day 1 (day of vaccination) and will do so through Day 8 following Visits 1 and 2. In addition, parents will be instructed to take a temperature using a temporal artery thermometer if their child feels warm or feverish at any time from Days 1-8 after Visit 1 and 2 and to record the temperature on the memory aid. Temperature measurements will be done for both the simultaneous and sequential groups in a similar fashion such that those children in the simultaneous group, who do not receive vaccinations at Visit 2, will also have temperatures measured. If at any time a temperature $\geq 100.4^{\circ}\text{F}$ ($\geq 38^{\circ}\text{C}$) or $\leq 95^{\circ}\text{F}$ ($\leq 35^{\circ}\text{F}$) is recorded, a second measurement will be taken within 20 minutes. The highest of those two temperature measurements will be recorded. If more than one temperature is taken on the same day (prior to bedtime), the highest temperature for that day should be recorded on either the paper memory aid or entered into REDCap. Any temperature measured after your child's 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 temporal artery thermometer (Exergen Medical Scanner Model TAT-2000C)^{18,19}. Although parents may elect to use an alternate method for measuring temperatures, they will be required to measure temporal artery temperature measurements as specified above.

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. All parent(s)/LAR(s) will be encouraged to use the paper memory

aid as a tool to initially record temperatures and then enter information into REDCap. However, they can directly enter temperature information into REDCap if desired without using paper. 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 9 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 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 8-day post-visit 2 period. The study team will review the paper memory aid at the time of receipt.

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 receive PCV13, DTaP and IIV vaccines. The specific vaccines administered are based on availability from manufacturers prior to the 2017-2018 influenza season (see section 5.5.3).

5.5.1 Randomization

Participants will be randomized (1:1) to receive either PCV13, DTaP and IIV simultaneously or sequentially (PCV13 and DTaP followed by IIV ~2 weeks later) using a permuted block randomization scheme stratified by study site (i.e. Duke University Medical Center and Kaiser Permanente Northern California). The first 10 children enrolled in the pilot at Duke University will be randomized in a block of 10 such that 5 children will receive simultaneous vaccination and 5 will receive sequential vaccination. The project statistician at Duke University 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.

5.5.2 Blinding

This study will be open label and study staff and subjects will not be blinded to treatment arm assignments.

Vaccine (Supply, Storage, and Administration) and Educational Materials

Vaccine Supply and Storage

For consistency, the same formulations of DTaP, IIV and PCV13 vaccines will be used throughout this study to the extent feasible. There are multiple products on the market for DTaP and IIV vaccines. In the United States, only one PCV13 product (Wyeth

Pharmaceuticals, Inc) is licensed (package inserts, available at <https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm>)

Because Duke and Kaiser Study clinics may not stock the same DTaP and IIV products in their routine supply, DTaP and IIV (single dose vials or prefilled syringes) will be purchased for this study using contract Task Order funds. DTaP and IIV will be maintained either at the respective primary research center or their affiliated clinic sites in a monitored medication refrigerator at 2-8°C in accordance with package insert guidelines. Study supplied vaccines should be segregated from the clinic's routine vaccine supply. Study supplied vaccine may be transported between the primary research center and clinic sites using each site's Standard Operating Procedure for Study Product Transport as long as the cold chain is maintained.

- Infanrix® (GSK) will be purchased for use as the DTaP vaccine to be administered in this study. However, if there are vaccine supply issues at the time of the conduct of this study, Daptacel® (Sanofi) may be purchased and used in the place of Infanrix®.
- 2017-2018 Quadrivalent Fluzone® (Sanofi) will be purchased for use as the IIV administered in this study. If not available, an alternate US licensed IIV with an indication for this age group will be used.
- PCV13 (Wyeth) will be used as in this study. This is the only US FDA licensed PCV13 product available. Because both study sites routinely use the Wyeth PCV13 vaccine in their clinics, PCV13 will be supplied by the participant's clinic site from their usual vaccine supply for use in the study and will not be purchased using contract Task Order funds. PCV13 will be maintained at the respective clinic sites in a monitored medication refrigerator at 2-8°C in accordance with package insert guidelines and clinic standard operating procedures. The cost of PCV13 will be billed to patient's insurance.

Vaccine Administration

- To assure adherence to study randomization assignment, US licensed PCV13, DTaP, and IIV vaccines will be administered as study procedures. Young children meeting eligibility criteria for the study will either receive
 - 1) A single intramuscular (IM) 0.5 mL dose of PCV13 vaccine, a single IM 0.5 mL dose of DTaP vaccine and a single IM 0.25 or 0.50 mL dose (depending upon IIV product used but used according to package insert directions) of IIV at Visit 1 (simultaneous vaccination group)
OR
 - 2) A single IM 0.5 mL dose of PCV13 vaccine and a single IM 0.5 mL dose of DTaP at Visit 1, followed by a single IM 0.25 or 0.50 mL dose (depending upon IIV product used but used according to package insert directions) of IIV vaccine ~ 2 weeks later (sequential vaccination group).
- Following randomization assignment within the electronic data capture system, a licensed provider (RN, NP, PA, MD) from the study team will administer all vaccines. IIV and DTaP will be administered in the vastus lateralis muscle (anterolateral thigh). PCV13 and other concomitantly administered vaccines will be administered in the other vastus lateralis muscle (anterolateral thigh).

Concomitant vaccines such as MMR, Varicella and MMRV vaccine may be administered in either thigh or in the deltoid area as well, consistent with ACIP General Best Practice Guidelines for Immunization
<https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html>

When more than one vaccine is given in the same limb, 1 inch or more should separate the injection sites, if possible, so that any local reactions can be differentiated. Concomitant vaccine administration will be allowed at Visit 1 but not Visit 2 unless deemed a personal or public health priority by the health care provider caring for this patient or the study team. Influenza vaccine may be administered outside of the study window in case of public health emergency or personal exposure.

- 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). Vaccination information will also be entered into the Immunization Registry and Medical Record.
- Receipt and disposition of study supplied DTaP and IIV 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.

Educational Materials Provided to Parent(s)/LAR(s) at Visit 2

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 (http://www.mychildrensteeth.org/education/parent_fact_sheet_on_caries_bacteria/) will be given to parent(s)/LAR(s). Parent(s)/LAR(s) will also be provided with a free small soft bristle toothbrush for their child.

5.6 Solicited Systemic Adverse Events (Days 1-8 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 **Table 2** beginning on the evening of Study Visits 1 and 2 (Day 1) and for the next 7 days following the study visits (i.e. through Day 8). Each of the following symptoms fussiness or irritability, change in eating habits and sleepiness, 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 8 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 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 2: Fever Assessment and Solicited Systemic Adverse Events				
	None	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Temporal Artery Temperature °C °F	≤ 37.9 ≤ 100.3	≥ 38.0 - ≤ 38.5 ≥ 100.4 - ≤ 101.3	≥ 38.6 - ≤ 39.5 ≥ 101.4 - ≤ 103.1	≥ 39.6 ≥ 103.2
Fussiness or Irritability	None	Less playful than usual but not requiring more attention and able to console	Requiring increased attention but able to console	Unable to console
Change in eating habits	None	Eating less than normal for 1 to 2 feeds/meals	Missed 1 or 2 feeds/meals completely	Refuses ≥3 feeds/meals or refuses most feeds/meal
Drowsiness or Sleepiness	None	Drowsiness but still interested in surroundings and did not miss feed or meal	Not interested in surroundings or did not wake up for a feed or meal	Sleeps most of the time or difficult to wake up

*Cut off values for fever referenced from *Fluzone Quadrivalent Package Insert* (https://www.vaccineshoppe.com/image.cfm?pi=fluQIV&image_type=product_pdf)

For this study, solicited adverse events 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. All parent(s)/LAR(s) will be encouraged to use the paper memory aid as a tool to initially record solicited adverse events and then enter information into REDCap. However, they can directly enter solicited adverse event information into REDCap if desired without using paper. For parents electing to use REDCap, missing solicited adverse event data will be verified with the parent(s)/LARS on day 9 as needed following Visits 1 and 2. Parents/LAR using the paper memory aid alone will submit the Visit 1 memory aid to study staff during Visit 2, and will mail the study Visit 2 memory aid to the study team following the 8-day post-visit 2 period. The study team will review the paper memory aid at the time of receipt.

For parent(s)/LAR(s) entering data into REDCap, if there are data discrepancies for solicited adverse event entered directly into REDCap or obtained over the phone, the information provided by the parent in REDCap will be counted as the correct 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 solicited adverse events recorded on the memory aid, the information on the memory aid should be taken as the correct adverse event information unless verified as otherwise by study staff.

5.7 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 7 days following the study visits (through Day 8). On the evening of Visit 1 and Visit 2, medical care utilization related to fever, use of antipyretic medications, and febrile seizure occurrence should be rated from the time of Visit 1 or 2 until the information is recorded. For each subsequent day through Day 8, 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		
	Yes	No
Did you give your child fever or pain medicine?	Yes	No
If yes, was it for fever?	Yes	No
If yes, was it for pain?	Yes	No
If yes, check type or types of medicine given		
<input type="checkbox"/> Acetaminophen (e.g. Tylenol)		
<input type="checkbox"/> Ibuprofen (e.g. Motrin, Advil)		
<input type="checkbox"/> Other		
Did your child receive medical attention?	Yes	No
If yes, was it related to fever?	Yes	No
	Yes	No
If yes, check type or types of attention received		
<input type="checkbox"/> Telephone call for medical advice		
<input type="checkbox"/> Medical office visit including urgent care visit		
<input type="checkbox"/> Emergency department visit		
<input type="checkbox"/> Hospital admission		
If yes, provide reason for medical attention		
Did your child have a seizure?	Yes	No
If yes, was it related to fever?	Yes	No

For this study, medical care utilization, antipyretic use and the occurrence of febrile seizures 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. All parent(s)/LAR(s) will be encouraged to use the paper memory aid as a tool to initially record information and then enter information into REDCap; however, they can directly enter information into REDCap if desired without using paper. For parents electing to use REDCap, missing data will be verified with the parent(s)/LARS on day 9 as needed following Visits 1 and 2. Parents/LAR using the paper memory aid alone will submit the Visit 1 memory aid to study staff during Visit 2, and will mail the study Visit 2 memory aid to the study team following the 8-day post-visit 2 period. The study team will review the paper memory aid at the time of receipt.

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

5.8 Additional Safety Assessments (Visit 1 Day 1 – Visit 2 Day 8)

While completing the memory aid and during the in-person visit (Visit 2), parent(s)/LAR(s) will be prompted to report unsolicited serious adverse events (SAEs) and occurrence of febrile seizures. This will include asking: Has your child been seen for any medical visits? Has your child been evaluated in an emergency department or admitted to the hospital? If so, state reason why.” Parent(s)/LAR(s) who at any time express any concern about symptoms or serious 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.

Medical records will be obtained and reviewed for any medical appointment/s other than for routine scheduled visits (preventive care visits or planned specialty care visits), febrile seizures, and serious adverse events (SAEs) from Visit 1 Day 1 through Visit 2 Day 8.

IIV, PCV13 and DTaP administration for children are routinely recommended such that we do not anticipate having a significant issue with SAEs. However, we will monitor study participants for SAEs during the protocol-defined surveillance period from enrollment through 8 days following Visit 2. 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 scheduled hospital admission)
- 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,

Study site investigators will assess relatedness to study vaccine (related, possibly related, unlikely related, or not related) for SAEs and febrile seizure. A febrile seizure judged to be related to a non-study vaccine would not be considered related to, or probably related to vaccine. SAEs will be reported to the CDC’s Immunization Safety Office within 48 hours of study staff awareness of the event, and the respective institutional review boards or human subject reviewing officials at DUHS, Kaiser and CDC per local IRB reporting requirements. If indicated, SAEs will be reported through the CDC’s Vaccine Adverse Event Reporting System (VAERS) <https://vaers.hhs.gov/index>.

Given that this study involves administering US-licensed vaccines that are included as part of routine clinical care, there will not be a designated data safety monitoring board for this study. If deemed necessary, we will designate an independent safety monitor with relevant expertise, in collaboration with the CDC.

5.9 Parental Perceptions

At Visit 2, we will provide parent(s)/LAR(s) electing to use the paper memory aid with a paper survey to be completed 8 days after Visit 2 about their preferences regarding receiving influenza vaccine at the same time or separately from other routinely administered pediatric vaccines. Parents/LARs electing to use REDCap will receive the survey electronically at Day 9 following Visit 2 to be completed over the internet using REDCap. We will collect information about the parent's relationship to the child (mother, father, guardian). Parent(s)/LAR(s) using the paper survey will mail it to the study team and the data will be entered into REDCap by study staff upon receipt of the survey. If survey information is not obtained in REDCap or sent by mail, the information may be obtained over the phone.

6 STATISTICAL CONSIDERATIONS

In collaboration with the CDC and Kaiser Permanente Northern California sites, the research team at Duke will oversee the statistical analysis. The first 10 children enrolled in the study are considered part of a pilot to assess study feasibility and make adjustments in study design if necessary. As such we will measure some key feasibility benchmarks as noted in **Table 4**. Children enrolled in the feasibility component of the study will be included in the main study.

Table 4: Benchmarks for Pilot	
Benchmark	Target
Valid temperature obtained for D1 following Visit 1	80%
Valid temperature obtained for D2 following Visit 1	80%
Completion of Visit 2	80%
Valid temperature obtained for D1 following Visit 2	80%
Valid temperature obtained for D2 following Visit 2	80%
The thermometer was easy or very easy to use	80%
Reporting child's information (temperature and side effects) to the study team was easy or very easy	80%

The main study is designed based on prior data¹⁴ suggesting that the proportion of children who have fever on day 1 and/or day 2 after the first and/or second visit in the sequential group will be approximately 18% and that the proportion of children with fever observed following simultaneous administration during the comparable time periods will be at least twice as high (36%).

For 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 dataset for the study without personal identifiers will be made available to the CDC upon request.

6.1 Sample Size and Power Estimation

Allowing for a 10% drop out rate given an initial N=280, there should be approximately 252 children enrolled into the study. If the true proportion of children who have fever on day 1 and/or day 2 after the first and/or second visit in the simultaneous group is 36%

and the true proportion in the sequential group is 18%, then there is 90% power to reject the null hypothesis of no difference with N=126 per group with a two-sided alpha 0.05 level. This is based upon using a Mantel-Haenszel statistic in a stratified analysis to control for sites.

6.2 Analysis Plan

- 6.2.1 Study Populations** – There will be two study populations, the Intent-to-Treat (ITT) and Per Protocol populations. The ITT Population includes any participant that was enrolled, randomized into the study, and received at least one study vaccine at Visit 1. The Per Protocol Population is a subset of the ITT Population excluding those participants 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 proportions of children with fever following simultaneous versus sequential vaccination with PCV13, DTaP, and IIV during 2 visits. Children in the sequential vaccination group will receive PCV13 and DTaP at Visit 1 followed by IIV and health education at Visit 2. Children in the simultaneous vaccination group will receive PCV13, DTaP, and IIV at Visit 1, followed by a health education visit without vaccination at Visit 2. Fever will be assessed on the visit day of, and the day after (days 1-2) each visit.

Temperatures will be measured in children on the evening of, and for 7 subsequent evenings following Visit 1 and Visit 2. For the primary objective we will compare the proportions of children with fever (Temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1 and Visit 2 between the simultaneous and the sequential vaccination groups. Fever on day 1 and/or day 2 after either visit will be counted as positive for this analysis. The proportions will be compared using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. The relative risk and corresponding 95% confidence interval for the occurrence fever will also be calculated.

- 6.2.3 Secondary Objective 1** – To compare the proportions of children with fever on day 1 and/or day 2 after Visit 1 and Visit 2 separately, in the simultaneous versus sequential vaccination group.

For this secondary objective we will present the proportions of children with any fever on day 1 and/or day 2 following vaccination for Visit 1 and separately for Visit 2. Fever on day 1 and/or day 2 after either visit will be counted as positive for this analysis. Proportions at each visit will be compared between the simultaneous and the sequential vaccination groups using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks. The relative risk and corresponding 95% confidence interval for the occurrence of any fever on day 1 and/or day 2 after Visit 1 and/or Visit 2 will also be calculated.

6.2.4 Secondary Objective 2 – To compare the clinical importance of fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever.

To evaluate the severity of fever, we will present the proportions of children with the highest level of fever defined as Grade 2 and/or 3 ($\geq 38.6^{\circ}\text{C}$ and/or $\geq 39.6^{\circ}\text{C}$) on day 1 or day 2 following Visit 1, Visit 2 and Visit 1 and 2 combined by simultaneous and sequential vaccination groups.

To evaluate the duration of fever, the following analysis will be performed: The mean duration of any fever (in days) will be compared by simultaneous and sequential vaccination groups for children with fever that began on days 1 or 2 following Visit 1, Visit 2 and Visit 1 and 2 combined. Each consecutive day of fever on the memory aid will be counted per child per visit. Thus, a child could contribute a maximum of 8 days per study visit, should a fever be reported at each day on the memory aid.

Furthermore, we will present and compare the proportion of children with medical care utilization for fever (telephone contact, medical office visit, emergency department visit or hospital admission) on day 1 and/or day 2 following Visit 1, Visit 2 and Visit 1 and 2 combined.

Proportions will be compared between the simultaneous and the sequential vaccination groups using a Mantel-Haenszel statistic in a stratified analysis by center to control for the randomization blocks. The duration of fever will be compared between groups using a Mann-Whitney U/Wilcoxon rank-sum test. No adjustments will be made to the alpha level (two-sided $\alpha=0.05$) for these secondary objectives.

6.2.5 Exploratory Objectives

For exploratory objective 1 the average peak temperature on day 1 and/or 2 following Visit 1, Visit 2 and Visit 1 and 2 combined will be presented by simultaneous and sequential vaccination groups. To evaluate the duration of fever, the number of fever degree-days on day 1 or 2 following Visit 1, Visit 2 and Visit 1 and 2 combined will be presented by simultaneous and sequential vaccination groups. Comparisons will be made using a Mann-Whitney U/Wilcoxon rank-sum test.

For exploratory objective 2 we will present the use of antipyretics for fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group in tables for presentation. The proportion of children with antipyretic use on day 1 and/or day 2 following Visit 1, Visit 2 and Visit 1 and 2 combined will be compared using a Mantel-Haenszel statistic in a stratified analysis by site between the simultaneous and sequential vaccination groups.

Exploratory objective 3 that evaluates the level of severity of fever at various time points, will be presented and compared using a Mantel-Haenszel statistic in a stratified analysis by site.

Exploratory objectives 4 and 5 evaluate fever on days 3-8 and the clinical importance of fever on days 3-8, respectively. We will present and compare the proportions in

objectives 4 and 5 using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks. We will adjust for MMR and MMRV receipt at Visit 1 if necessary when analyzing the following outcome measures- EOM5.1, EOM5.2, and EOM 5.3 due to the possibility that a measles-containing vaccine may be administered at Visit 1 to infants in both the simultaneous and sequential group. Also for objective 5, we will present and compare the mean duration of any fever starting on days 3-8 using a Mann-Whitney U/Wilcoxon rank-sum test. Other analysis to further evaluate the clinical importance of fever onset 3-8 days after Visit 1 and/or Visit 2 will be performed if necessary.

Adverse event tables and listings will be prepared to assess Exploratory Objective 6 and 7. The group proportions of solicited systemic adverse events (excluding fever) occurring 1-8 days after Visit 1 and 2 will be compared as described above using a Mantel-Haenszel statistic in a stratified analysis. The Mantel-Haenszel statistic will also be used for group proportions of febrile seizure, and serious adverse events determined to be related to vaccination. If the cell sizes are too small (i.e., less than 5) then Fisher's exact test will be used.

Summary tables of acceptability will be produced to address Exploratory Objective 8. Likert scale questions will be compared between the study groups using an extended Mantel-Haenszel mean score statistic in a stratified analysis.

No adjustments will be made to the alpha level (two-sided $\alpha=0.05$) for these exploratory analyses.

6.2.6 Sensitivity Analyses

Sensitivity analyses will be performed under two conditions: 1) to exclude those who received antipyretics on day 1 and/or day 2 following Visit 1 and/or Visit 2; 2) to extend the risk window for fever to day 3 after Visit 1 and Visit 2. These sensitivity analyses will be performed for the primary objective in both study populations (ITT and Per Protocol). The statistical comparison will be made using a Mantel-Haenszel statistic in a stratified analysis by center to control for the randomization blocks. No adjustments will be made to the alpha level (two-sided $\alpha=0.05$) for these sensitivity analyses.

6.3 Data Management

The amount of data that will be collected for the proposed project will be substantial and will require a sophisticated, practical and flexible system that can accommodate different modes of data collection and several separate linked surveys. The novel Vanderbilt-designed resource developed specifically for online collection of research information, the Research Electronic Data Capture (REDCap) platform, will be used to design study forms, including the reaction forms, and short customized questionnaires to collect information from study subjects. This system will be used by Duke and Kaiser for data management. All electronic linkages will fulfill regulations for protection of human subjects and requirements to minimize the risk of breach of confidentiality. After initial set-up, the work load required for electronic data collection will be substantially reduced (description of REDCap resources below).²⁰ Duke investigators have previously used the REDCap system for collection and analysis of large quantities of data. Participants will be given the option to fill out their reactogenicity diary either directly in the REDCap system or on paper. The preferred method of data capture for this study is REDCap.

Regardless of the method of data entry chosen, all parents(s)/LAR(s) will be encouraged to use the paper memory aid to initially record information. Parents(s)/LAR(s) who choose the paper form will receive phone calls or be contacted by e-mail on Day 3 (Visits 1A, 2A) to collect the fever information recorded on their diary card, which will then be entered by study personnel onto a paper CRF. Participants who choose to enter the information directly into REDCap will receive phone calls or be contacted by e-mail as needed on Day 3 and/or Day 9 if they fail to enter their fever information for Days 1 and 2 or if they are missing information for days 1-8 respectively. All study-related documents containing protected health information, e.g. enrollment logs, case report forms, memory aids (**Appendices A-D**) completed by study participants, will be maintained in secure research offices at Duke and Kaiser, which are accessible to research staff only.

6.3.1 Research Electronic Data Capture (REDCap)

Investigators within the NIH-funded Clinical and Translational Research Unit at Vanderbilt have developed REDCap (<http://project-redcap.org/>), to collect and manage 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. Of particular interest for this project, a subcomponent of REDCap, the REDCap Survey is designed for studies where data are collected directly from the research participant. This will be used with the web-based reaction forms that will be completed by the study subjects. 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 2318 active institutions. The REDCap currently supports 68,000 projects with over 89,000 users spanning numerous research focus areas across the consortium. The current project will use this software application for the design of electronic forms to collect information from study participants, to link the baseline data, sample collection date, and laboratory results in an automated database family, to perform data cleaning and data quality assurance efficiently, and to design an analytical dataset for the analysis of the project data.

Data will be entered into the REDCap database by parents or by members of the study team, from Duke 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. Only the assigned identifiers will be used in REDCap. Therefore, personal health identifiers will not appear in the REDCap database.

In order to perform data cleaning and data quality assurance efficiently, numerous built-in filters and checks for consistency of the data including range and limit checks,

branching logic and pull down menus to limit choices for categorical variables to a pre-specified list will be implemented and performed automatically to minimize data entry error. The data will be randomly sampled and checked against source records on a regular basis. The data and related analytical datasets will also be stored at the lead and contributing sites with secured password-protected computers. Coded data without personal identifiers will be made available to the CDC and transferred using a secure transfer method.

6.4 Role of the CDC Investigators in the Project

This study is funded by a CDC contract with Duke University and Kaiser Permanente as Task Orders in the CISA Project Contract. The Duke University PI (Emmanuel “Chip” Walter) will oversee the study in partnership with the Kaiser Permanente PI (Nicola Klein). CDC staff will collaborate with both 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 and Kaiser investigators will be responsible for submitting the protocol, informed consent (**Appendix A**), memory aids (**Appendix B**), recruitment letters, flyers (**Appendix C**), and any written or verbally conveyed materials (**Appendix D**) 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 information 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 (**Appendix B**). 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 febrile seizures or serious adverse events during the entire study period.

7.3 Potential Risks and Benefits

PCV13, DTaP and IIV are FDA licensed vaccines approved for use in children 12-16 months of age. These vaccines are standard clinical practice and recommended by the CDC and ACIP. Participants will be provided with the CDC Vaccine Information Statements (VIS) for PCV13, DTaP and IIV (<http://www.cdc.gov/vaccines/hcp/vis/vis-statements/dtap.html>) and <http://www.cdc.gov/vaccines/hcp/vis/vis-statements/pcv13.html>).

IIV risks include minor problems such as soreness, redness, swelling, or pain where the shot was given, hoarseness, sore, red or itchy eyes, cough, fever, aches, headache, itching, fatigue, all of which usually occur within 1-2 days of vaccination and are self-limiting. Syncope (fainting) can occur in association with administration of injectable vaccines but is less likely in young children. More serious problems including a small increased risk of Guillain-Barré Syndrome estimated at 1 or 2 additional cases per million people vaccinated. This is much lower than the risk of severe complications from influenza infection, which can be prevented by IIV. In addition, any medication can cause a severe allergic reaction, or anaphylaxis, which is estimated at ~1 in a million doses of IIV (<http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.html>).

DTaP risks include mild problems such as redness, swelling, and pain where the shot was given, redness or swelling where the shot was given, fever, chills, sore joints, headache, body aches, fatigue, nausea, vomiting, diarrhea, stomach ache, rash, and swollen glands, all of which usually occur within 1-2 days of vaccination and are self-limiting. Moderate problems include higher severity of mild problems and swelling of the entire arm or leg in which the injection was given. Rarely, local injection site symptoms limit the ability to perform usual activities and require medical attention.

PCV13 risks include mild problems such as drowsiness, temporary loss of appetite, redness, swelling, or tenderness where the shot was given, fever, increase in fussiness and irritability. Young children may be at increased risk for febrile seizure.

Problems that could happen after any injected vaccine:

- People sometimes faint after a medical procedure, including vaccination. Sitting or lying down for about 15 minutes can help prevent fainting, and injuries caused by a fall. Subjects should inform their doctor should they feel dizzy, or have vision changes or ringing in the ears. This is unlikely in small children.
- Any medication can cause a severe allergic reaction. Such reactions from a vaccine are very rare, estimated at about 1 in a million doses, and would happen within a few minutes to a few hours after the vaccination. As with any medicine, there is a very remote chance of a vaccine causing a serious injury or death.
- The Advisory Committee on Immunization Practices (ACIP) does not make specific recommendations about simultaneous or sequential administration of PCV13, DTaP and IIV for young children. However, based on the ACIP General Recommendations, PCV13, DTaP and IIV (all inactivated vaccines) may be administered to young children either simultaneously or sequentially. The current General Best Practice Guidelines for Immunization (assessed at <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html>)

Simultaneous administration of vaccines is defined as administering more than one vaccine on the same clinic day, at different anatomic sites, and not combined in the same syringe. Experimental evidence and extensive clinical experience provide the scientific basis for administering vaccines simultaneously. Simultaneously administering all vaccines for which a person is eligible at the time of a visit increases the probability that a child, adolescent, or adult will be vaccinated fully by the appropriate age.

Pneumococcal conjugate, Diphtheria toxoid, tetanus toxoid and acellular pertussis (DTaP), and quadrivalent inactivated influenza vaccine (IIV) can be administered simultaneously.

There is the potential risk of loss of confidentiality about information obtained as part of this study. There is a potential risk of a short delay in influenza protection by delaying the receipt of influenza vaccine 2 weeks. If parents are concerned that their child has an influenza-like illness (characterized by fever and irritability, cough, sore throat, or vomiting), they should seek care for their child with their child's health care provider. If their child's provider suspects or determines that their child has influenza, there are medications to treat influenza illness and their provider may opt to treat their child with one of these medications.

7.4 Adequacy of Protection Against Risks

7.4.1 Protections against Risk

Subjects will be counseled on possible side effects following vaccination and followed closely during the 8 days post-vaccination for assessment of moderate to severe systemic reactogenicity. Subjects with a prior history of any severe reaction following IIV, PCV13 or DTaP will be excluded from study enrollment.

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.

7.4.2 ClinicalTrials.gov Requirements

The project is registered on ClinicalTrials.gov. (NCT03165981).

7.5 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.

7.5.1 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. Because the children are so young, 12 through 16 months, they are not capable of providing assent.

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

A Prospective, Randomized, Open-label Clinical Trial to Assess Fever Following Simultaneous versus Sequential Administration of 13-valent Conjugate Pneumococcal Vaccine, Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccine and Inactivated Influenza Vaccine in Young Children

Short Title: Fever after Simultaneous versus Sequential Vaccination in Young Children

Final Statistical Analysis Plan

Version 1.0

February 06, 2018

1 INTRODUCTION

This document describes the statistical procedures that will be utilized for the CISA protocol Fever after Simultaneous versus Sequential Vaccination in Young Children. This statistical analysis plan (SAP) describes the methods of statistical analysis. The initial draft SAP (Version 0.1) was written prior to any data being analyzed in order to avoid bias. Any subsequent changes that occur to the study protocol warranting changes to the analysis procedures will be documented in the SAP. Table 1 below will be used for tracking changes to the SAP (both draft versions (0.X) and the final version (X.0)).

Table 1. Statistical Analysis Plan Versions

Version	Date of Approval	Major Changes from Prior Version
0.1	NA	NA
0.2	NA	Minor edits with the addition of linear regression analysis to address Secondary Objective b.2 average peak temperature. See addition to Section 8.2.
0.3	NA	Updates made to Secondary and Exploratory objectives based on CDC review. See Version 2.0 of the protocol from October 12, 2017.
0.4	NA	Minor edits and clarification based on call with CDC on December 13, 2017 and comments from an email on January 29, 2018.
1.0	February 6, 2018	Final SAP

2 PROTOCOL OBJECTIVES

2.1 Primary

- a) PO 1: To compare the proportions of children with fever following simultaneous versus sequential vaccination with PCV13, DTaP, and IIV during 2 visits. Children in the sequential vaccination group will receive PCV13 and DTaP at Visit 1 followed by IIV and health education at Visit 2. Children in the simultaneous vaccination group will receive PCV13, DTaP, and IIV at Visit 1, followed by a health education visit without vaccination at Visit 2. Fever will be assessed on the visit day of, and the day after (days 1-2) each visit.

2.2 Secondary

- a) SO 1: To compare the proportions of children with fever on day 1 and/or day 2 after Visit 1 and Visit 2 separately, in the simultaneous versus sequential vaccination group.
- b) SO 2: To compare the clinical importance of fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever.

2.3 Exploratory

- a) EO 1: To compare the height and duration of fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group.
- b) EO 2: To compare the use of antipyretics for fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group.
- c) EO 3: To describe and compare the level of severity of fever following Visit 1 and Visit 2 (separately) in the simultaneous versus sequential group.
- d) EO 4: To compare the proportions of children with fever 3-8 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group.
- e) EO 5: To compare the clinical importance of fever occurring 3-8 days after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever.
- f) EO 6: To describe and compare the occurrence of solicited systemic adverse events on day 1-8 after Visit 1 and Visit 2 in the simultaneous versus sequential group.
- g) EO 7: To describe and compare the occurrence of febrile seizure and/or serious adverse events during the period of enrollment (i.e. from Visit 1 through 8 days after Visit 2) in the simultaneous versus sequential group.
- h) EO 8: To describe and compare the perceptions among parents/ legally authorized representatives (LARs) of the simultaneous versus sequential schedule experience.

3 STUDY ENDPOINTS

3.1 Primary

- a) POM 1.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1 and/or Visit 2.

3.2 Secondary

- a)
 - 1. SOM 1.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1.
 - 2. SOM 1.2: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 2.
- b)
 - 1. SOM 2.1: Proportions 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.
 - 2. SOM 2.2: Average number of consecutive days of fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) per subject for fever starting on day 1 or 2 following Visit 1, Visit 2 and Visit 1 and Visit 2 combined. Note: fever starting on day 1 or 2 could continue through day 8.
 - 3. SOM 2.3: Proportion of children with medical care utilization (telephone call, 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.

3.3 Exploratory

a)

1. EOM 1.1: Average peak temperature of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined.
2. EOM 1.2: Total number of fever degree-days (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 per subject following Visit 1, Visit 2, and Visit 1 and Visit 2 combined.

b) EOM 2.1: Proportion 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.

c)

1. EOM 3.1: Proportions of children with fever at different levels of severity (Grades 1, 2, and 3) on day 1 and/or day 2 following Visit 1 and Visit 2.
2. EOM 3.2: Proportions of children with fever at different levels of severity (Grades 1, 2, and 3) on days 3-8 following Visit 1 and Visit 2.
3. EOM 3.3: The proportion of children with fever at different levels of severity (Grades 1, 2,3 and all Grade) on days 1-8 following Visit 1 and Visit 2.

d)

1. EOM 4.1: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on at least one day on day 3-8 following Visit 1.
2. EOM 4.2: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on at least one day on day 3-8 following Visit 2.
3. EOM 4.3: Proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on at least one day on day 3-8 following Visit 1 and Visit 2 combined.

e)

1. EOM 5.1: Proportions of children with moderate/severe fever (GRADE 2 and/or 3) on at least one day during days 3-8 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined.
2. EOM 5.2: Average number of consecutive days of fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) per subject for fever starting on 3-8 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined. *Note: fever starting on day 3-8 could continue through day 8.*
3. EOM 5.3 Proportion of children with medical care utilization (telephone call, medical office visit, emergency department visit, or hospital admission) for fever on 3-8 days following Visit 1, Visit 2, and Visit 1 and Visit 2 combined).

f) EOM 6.1: The proportion of children with solicited systemic adverse events (excluding fever) at different levels of severity (Grades 1, 2, 3, and all Grades) on day 1-8 following Visit 1 and Visit 2.

g) EOM 7.1: The proportion of children with febrile seizure and/or serious adverse events during the period of enrollment (i.e. from Visit 1 through 8 days after Visit 2).

- h) EOM 8.1: Proportion of parents reporting positive and negative perceptions about their vaccination schedule experience will be determined for each survey item.

4 STUDY DESIGN

4.1 Study Description

This study is a prospective, randomized open-label clinical trial that will be conducted during the 2017-2018 influenza season. During the 2017-2018 season, approximately 280 children will be enrolled at Duke University Medical Center and Kaiser Permanente Northern California. Young children aged 12-16 months will be enrolled over a period of approximately 7 months. Children will be followed for up to 37 days following enrollment. Eligible children will be randomized to receive simultaneous or sequentially administered US-licensed PCV13, US-licensed DTaP vaccine, and US-licensed inactivated influenza vaccine (IIV). Children in the simultaneous group will receive PCV13, DTaP, and IIV vaccines at Visit 1, and then return for a health education visit without vaccination about 2 weeks later (Visit 2). Children in the sequential group will receive both PCV13 and DTaP without IIV at Visit 1, and then will receive IIV and health education about 2 weeks later (Visit 2). At Visit 1, children may also receive age- appropriate vaccines as recommended in the ACIP childhood immunization schedule. After Visit 1, non-study vaccines (U.S. licensed or investigational) are prohibited unless deemed a personal or public health priority by the health care provider caring for this patient or the study team.

Parents will record the occurrence of fever, solicited adverse events, medical care utilization, and receipt of antipyretics over 8 days following Visit 1 and Visit 2. In addition, febrile seizures and serious adverse events will be recorded for the entire study period (from enrollment through 8 days following the Visit 2) and will be assessed through parental report and chart review.

The first 10 children enrolled at Duke University Medical Center will be enrolled in a study pilot to quickly assess study feasibility benchmarks and make protocol adjustments if necessary. Data from pilot participants will also contribute to the analysis of primary, secondary and exploratory outcomes.

4.2 Sample Size and Power

Allowing for a 10% drop out rate given an initial N=280, there should be approximately 252 children enrolled into the study. If the true proportion of children who have fever on day 1 and/or day 2 after the first and/or second visit in the simultaneous group is 36% and the true proportion in the sequential group is 18%, then there is 90% power to reject the null hypothesis of no difference with N=126 per group with a two-sided alpha 0.05 level. This is based upon using a Mantel-Haenszel statistic in a stratified analysis to control for sites.

4.3 Randomization

Participants will be randomized (1:1) to receive either PCV13, DTaP and IIV simultaneously or sequentially (PCV13 and DTaP followed by IIV ~2 weeks later) using a permuted block randomization scheme stratified by study site (i.e., Duke University Medical Center and Kaiser Permanente Northern California). The first 10 children enrolled in the pilot at Duke University will be randomized in a block of 10 such that 5 children will receive simultaneous vaccination and 5 will receive sequential vaccination. The project statistician at Duke University 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. This study will be open label and study staff and subjects will not be blinded to treatment arm assignments.

5 PARAMETERS OF ANALYSIS

5.1 Data Collection and Storage

Data will be handled according to the Duke Vaccine and Trials Unit SOP (DVTU M010). Data will be captured on paper CRFs and entered into the REDCap database. Diary data may be entered directly into REDCap, if the parent of the participant chooses to use this method.

5.2 Analytic Issues

There are two sites participating in the study and analysis of the primary objective will be stratified by site to account for this unit of randomization. Secondary data objectives may be stratified by site when applicable. There is one primary objective evaluated at the alpha 0.05 level and no adjustments to the alpha level will be made for secondary and exploratory analyses.

6 ANALYSIS POPULATIONS

6.1 Intent-to-Treat (ITT)

The ITT Population includes any participant that was enrolled, randomized into the study, and received at least one study vaccine at Visit 1.

6.2 Per Protocol

The Per Protocol Population is a subset of the ITT Population which excludes participants who do not provide valid temperature data on days 1 and 2 following Visit 1 and Visit 2 and/or participants with major protocol violations, as determined by the study investigators. The list of major protocol violations is located in **Appendix 1**.

Statistical analyses will be performed for both study populations, or the ITT Population only if no participants are excluded from the Per Protocol Population.

7 BASELINE DATA AND FLOW CHART

7.1 Presentation of Baseline Data

The following baseline data will be presented by site and vaccination group: age, gender, gestational age, day care attendance, number of children living in the home, insurance payer status, ethnicity, race, receipt of first dose of influenza vaccine, receipt of inactivated influenza vaccine at Visit 1, and receipt of live vaccines at Visit 1. Summary statistics (e.g., mean, median, standard deviation, interquartile range) will be presented for continuous variables. Categorical variables will be described with frequencies and percentages.

7.2 Flow Chart

The number of enrolled participants will be presented in a flow chart by site and vaccination group. The number of visits completed and missed will be presented, along with a breakdown of the two analysis populations.

8 ANALYSIS OF STUDY OBJECTIVES

8.1 Primary Objective

The primary objective (PO 1) of the study is to compare the proportion of children with fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) on day 1 and/or day 2 following Visit 1 and/or Visit 2. This information is captured on the memory aid form which is captured in the REDCap database. Fever on day 1 and/or day 2 after either visit will be counted as positive (1) for this analysis and no fever reported will be negative (0). The proportions will be compared between the simultaneous versus the sequential group using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks at the two-sided alpha 0.05 level. The relative risk and corresponding 95% confidence interval for the occurrence fever will also be calculated.

8.2 Secondary Objectives

There are two secondary objectives for this study.

- a) The first secondary objective (SO 1) is to compare the proportions of children with fever on day 1 and/or day 2 after Visit 1 and Visit 2 separately, in the simultaneous versus sequential vaccination group. Fever on day 1 and/or day 2 after either visit will be counted as positive (1) for this analysis and no fever reported will be negative (0). Proportions at each visit will be compared between the simultaneous and the sequential vaccination groups using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks. The relative risk and corresponding 95% confidence interval for the occurrence of any fever on day 1 and/or day 2 after Visit 1 and Visit 2 separately will also be calculated. There are two separate statistical tests being performed at the alpha 0.05 level.
- b) The secondary objective (SO 2) is to compare the clinical importance of fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever. This information is captured on the memory aid form in the REDCap database.
 1. Severity of fever: To evaluate the severity of fever, we will present the proportions of children with the highest level of fever defined as Grade 2 and/or 3 ($\geq 38.6^{\circ}\text{C}$) on day 1 or day 2 following Visit 1, Visit 2 and Visit 1 and 2 combined by simultaneous and sequential vaccination groups.
 2. Duration of fever: To evaluate the duration of fever, the following analysis will be performed: The mean duration of any fever (in days) will be compared by simultaneous and sequential vaccination groups for children with fever that began on days 1 or 2 following Visit 1, Visit 2 and Visit 1 and 2 combined. Each consecutive day of fever on the memory aid will be counted per child per visit. Thus, a child could contribute a maximum of 8 days per study visit, should a fever be reported at each day on the memory aid. A child having fever on day 1, no fever on day 2, and fever on day 3 only has 1 day of fever.
 3. Medical care utilization for fever: We will present and compare the proportion of children with medical care utilization for fever (telephone contact, medical

office visit, emergency department visit or hospital admission) on day 1 and/or day 2 following Visit 1, Visit 2 and Visit 1 and 2 combined. Medical utilization for fever will be counted as positive for this analysis if onset of fever on day 1 and/or day 2 plus medical utilization on day 1, day 2 or day 3 after fever. Medical care related to fever will be determined by report on the diary.

Proportions will be compared between the simultaneous and the sequential vaccination groups using a Mantel-Haenszal statistic (three tests) in a stratified analysis by site to control for the randomization blocks. The duration of fever will be compared between groups using a Mann-Whitney U/Wilcoxon rank-sum test (three tests).

No adjustments will be made to the alpha level (two-sided alpha=0.05) for these secondary objectives.

8.3 Exploratory Objectives

There are eight exploratory objectives for this study.

- a) The first exploratory objective (EO 1) is to compare the height and duration of fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. The average peak temperature of each child with fever during the risk window of days 1 and 2 (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) and the total number of fever degree-days (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) following Visit 1, Visit 2 and Visit 1 and 2 combined will be presented by simultaneous and sequential vaccination groups. These six comparisons will be made using a Mann-Whitney U/Wilcoxon rank-sum test.
- b) The second exploratory objective (EO 2) is to compare the use of antipyretics for fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. The use of antipyretics for fever on day 1 and/or day 2 after Visit 1 and Visit 2 (separately and combined) will be presented for the simultaneous versus sequential group in tables. These three proportions of children with antipyretic use on day 1 and/or day 2 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined will be compared using a Mantel-Haenszal statistic in a stratified analysis by site between the simultaneous and sequential vaccination groups.
- c) The third exploratory objective (EO 3) is to describe and compare the level of severity of fever following Visit 1 and Visit 2 separately, in the simultaneous versus sequential group. Fever will also be assessed at different levels of severity (Grades 1, 2, and 3) on day 1 and/or day 2 and days 3-8 following Visit 1 and separately for Visit 2. The grade levels are defined in Table 2.

Temporal Artery Temperature	None	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
°C	≤ 37.9	$\geq 38.0 - \leq 38.5$	$\geq 38.6 - \leq 39.5$	≥ 39.6
°F	≤ 100.3	$\geq 100.4 - \leq 101.3$	$\geq 101.4 - \leq 103.1$	≥ 103.2

There will be six (day 1 and/or day 2, days 3-8, and days 1-8 following Visit 1 and separately for Visit 2) statistical comparisons performed at the alpha 0.05 level. These group comparisons will be made using a Mantel-Haenszel statistic (row mean scores difference with standardized midranks scores [modified ridit scores]) in a stratified analysis by site to control for the randomization blocks.

- d) The fourth exploratory objective (EO 4) is to compare the proportions of children with fever on at least one day during days 3-8 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. This information is captured on the memory aid form in the REDCap database. There will be three statistical comparisons performed at the alpha 0.05 level. These group comparisons will be made using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks.
- e) The fifth exploratory objective (EO 5) is to compare the clinical importance of fever occurring on at least one day during days 3-8 after Visit 1 and Visit 2 (separately and combined) in the simultaneous versus sequential group. Clinical importance is assessed based on severity of fever, duration of fever, and medical care utilization for fever. This information is captured on the memory aid form in the REDCap database.

1. Severity of fever: To evaluate the severity of fever, the proportions of children with moderate/severe fever (GRADE 2 and/or 3 see Table 2 above) on at least one day during days 3-8 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined will be presented in a tabular format. This group comparison will be made using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks.
2. Duration of fever: To evaluate the duration of fever, the average number of consecutive days of fever (temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 100.4^{\circ}\text{F}$) per subject for fever starting on day 3-8 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined will be calculated. A fever starting on day 3-8 could continue through day 8. The mean duration of any fever will be presented in days for children with fever that began on days 3-8 after Visit 1 and Visit 2 (separately and combined). Each consecutive day of fever on the memory aid will be counted per child per visit. Thus, a child could contribute a maximum of 6 days per study visit, should a fever be reported at each day on the memory aid. The longest duration of any fever occurring for a child will be counted for that child. e.g. If a child has fever on days 3 and 4, no fever on day 5, and fever occurring on days 6, 7, and 8 the duration of fever will be counted as 3 days for that child.

There will be three statistical comparisons performed (mean duration of any fever starting on days 3-8 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined) at the alpha 0.05 level. These group comparisons will be made using a Mann-Whitney U/Wilcoxon rank-sum test.

3. Medical care utilization for fever: The proportion of children with medical care utilization determined by report on the diary (telephone call, medical office visit, emergency department visit, or hospital admission) for fever on at least one

day during days 3-8 following Visit 1, Visit 2, and Visit 1 and Visit 2 combined, will be presented in tables or the simultaneous versus sequential group. There will be three statistical comparisons performed. These group comparisons will be made using a Mantel-Haenszal statistic in a stratified analysis by site to control for the randomization blocks.

- f) The sixth exploratory objective (EO 6) is to describe and compare the occurrence of solicited systemic adverse events (excluding fever) on days 1-8 after Visit 1 and Visit 2 in the simultaneous versus sequential group. Table 3 below lists the solicited adverse events to be collected.

Table 3: Solicited Systemic Adverse Events				
	None	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fussiness or Irritability	None	Less playful than usual but not requiring more attention and able to console	Requiring increased attention but able to console	Unable to console
Change in eating habits	None	Eating less than normal for 1 to 2 feeds/meals	Missed 1 or 2 feeds/meals completely	Refuses ≥ 3 feeds/meals or refuses most feeds/meal
Drowsiness or Sleepiness	None	Drowsiness but still interested in surroundings and did not miss feed or meal	Not interested in surroundings or did not wake up for a feed or meal	Sleeps most of the time or difficult to wake up

Listings of all solicited adverse events will be produced showing vaccination group, date of onset, date of resolution, and highest grade level. The frequency and percentage of the highest grade level for participants will be presented by each of the three solicited adverse events. There will be three statistical comparisons made using a Mantel-Haenszal statistic (row mean scores difference with standardized midranks scores [modified ridit scores]) in a stratified analysis by site to control for the randomization blocks.

- g) The seventh exploratory objective (EO 7) is to describe and compare the occurrence of febrile seizure and/or serious adverse events during the period of enrollment (i.e., from Visit 1 through 8 days after Visit 2) in the simultaneous versus sequential group. Listings of all febrile seizure and/or serious adverse events will be produced showing vaccination group, description, relatedness, date of onset, date of resolution, and SAE category. The frequency of the occurrence of febrile seizure and/or serious adverse events by vaccination group will be compared using a Fisher's Exact test because the expected number of events is very low (i.e., small cell counts).
- h) The eighth exploratory objective (EO 8) is to describe and compare the perceptions among parents/ legally authorized representatives (LARs) of the simultaneous versus sequential schedule experience. Summary tables of acceptability will be produced by vaccination group. Likert scale questions will be compared between the vaccination groups using a Mantel-Haenszal statistic (row mean scores difference with standardized midranks scores [modified ridit scores]) in a stratified analysis by site to control for the randomization blocks.

No adjustments will be made to the alpha level (two-sided $\alpha=0.05$) for these exploratory analyses.

8.4 Potential Adjustments to Exploratory Objectives

- a) It might be necessary to adjust for MMR and MMRV receipt at Visit 1 for the following outcome measures: EOM 3.2, EOM 3.3, EOM 4.1, EOM 4.3, EOM 5.1 and EOM 5.2. This is due to the possibility that a measles-containing vaccine may be administered at Visit 1 to infants in both the simultaneous and sequential group. If there is an imbalance (detected by a Mantel-Haenszel statistic in a stratified analysis by site) between the vaccination groups in the percentages of MMR and/or MMRV receipt at Visit 1, the aforementioned exploratory outcome measures will be evaluated by subgroups of those with MMR and/or MMRV receipt at Visit 1 and those without MMR and/or MMRV receipt at Visit 1.

9 SENSITIVITY ANALYSES

Sensitivity analyses will be performed under three conditions:

- to exclude those who received antipyretics on day 1 and/or day 2 following Visit 1 and/or Visit 2.
- to extend the risk window for fever to day 3 after Visit 1 and Visit 2.
- to compare the effect of the first versus second dose of current seasonal influenza vaccine

These sensitivity analyses will be performed for the primary objective in both study populations (ITT and Per Protocol). The statistical comparison will be made using a Mantel-Haenszel statistic in a stratified analysis by site to control for the randomization blocks. No adjustments will be made to the alpha level (two-sided $\alpha=0.05$) for these sensitivity analyses.

Appendix 1

Major Protocol Violations

Study Title: A Prospective, Randomized, Open-label Clinical Trial to Assess Fever Following Simultaneous versus Sequential Administration of 13-valent Conjugate Pneumococcal Vaccine, Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccine and Inactivated Influenza Vaccine in Young Children

Short Title: Fever after Simultaneous versus Sequential Vaccination in Young Children

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

Lead Site Principal Investigator: Emmanuel B. Walter, MD, MPH

Contributing Site Principal Investigator: Nicola Klein, MD

Centers for Disease Control and Prevention (CDC) Principal Investigator: Karen R. Broder, MD

CDC Sub-principal Investigator: Patricia Wodi, MD

NCT #: 03165981

Purpose: To define major protocol violations that will be used to establish the Per Protocol Population for the Fever after Simultaneous versus Sequential Vaccination in Young Children study

Background: Per the protocol analysis plan there will be two study populations, the Intent-to-Treat (ITT) and Per Protocol populations. The ITT Population includes any participant that was enrolled, randomized into the study, and received at least one study vaccine at Visit 1. The Per Protocol Population is a subset of the ITT Population excluding those participants 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.

This document stands to serve as a general guideline for the study investigators to a priori define major protocol violations. Participants with major protocol violations will not be included in the Per Protocol Population.

Major Protocol Violations Defined:

1) Inclusion/Exclusion Criteria Violations

Did Not Meet Study Inclusion Criteria	At Study Entry Visit 1	During Period of Enrollment¹
1. 12 through 16 months of age (i.e. from the 1-year birthday until the day before 17 months of age) at the time of vaccination	X	X
2. Stable health as determined by investigator's clinical examination and assessment of child's medical history	X	
3. Has received all immunizations recommended by Advisory Committee for Immunization Practices (ACIP) during the first year of life with the exception of rotavirus and influenza vaccines.* <i>*Immunizations recommended during the first year of life include: 3 doses of DTaP, 3 doses of PCV13, 2- 3 doses of inactivated polio virus vaccine, 3 doses of Hepatitis B vaccine, and 2 or 3 doses of Hib vaccine such that the primary Hib series is complete depending upon the brand used. (https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html).</i>	X	X
4. The parent(s)/ legally authorized representative(s) LAR(s) intend for the child to receive DTaP and PCV13 in addition to this season's IIV	X	
5. The parent(s)/LAR(s) must be willing and capable of providing permission for their child to participate through the written informed consent process	X	
6. The parent(s)/LAR(s) must be able to comply with the requirements of the protocol (e.g., completion of the memory aid (either electronic or paper diary), return for follow-up visits, respects intervals between the visits and have telephone access.	X	
7. The parent(s)/LAR(s) must be English speaking	X	
8. The parent(s)/LAR(s) 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)	X	
Met Exclusion Criteria		
1. History of any seizure (including febrile seizure) in the child or a febrile seizure in a first degree relative* <i>*First degree relatives include biological parents or siblings</i>	X	X
2. Has already completed influenza vaccination during the current season per ACIP recommendations* <i>*Children needing two doses of influenza vaccine per ACIP recommendations and who are receiving a second dose of</i>	X	X

<i>influenza vaccine may be enrolled; however, an attempt will be made to preferentially enroll children needing two doses at the time of receipt of their first dose of influenza vaccine</i>		
3. Receipt of more than 3 previous doses of DTaP	X	X
4. Received the 3 rd dose of DTaP within 6 months of Visit 1	X	X
5. Receipt of more than 3 previous doses of PCV13	X	X
6. Received the 3 rd dose of PCV13 within 8 weeks of Visit 1	X	X
7. History of a severe allergic reaction (e.g. anaphylaxis) to a previous dose of any influenza, diphtheria toxoid-, tetanus toxoid-, or pertussis-containing vaccine, or pneumococcal vaccine	X	
8. History of a severe allergic reaction (e.g., anaphylaxis) to any component (including egg protein) of any of the three vaccines used in this study.	X	
9. History of Guillain-Barré syndrome within 6 weeks following a prior dose of influenza, DTaP, or tetanus toxoid containing vaccine	X	
10. History of a progressive neurologic disorder	X	
11. History of encephalopathy within 7 days of a previous pertussis-containing vaccine	X	
12. History of collapse within 3 days after a prior dose of DTaP	X	
13. Received any other licensed vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Visit 1* <i>*Concomitant vaccine administration for ACIP recommended vaccines are allowed to be administered on the first vaccination day in this study but at no other time in this study period unless deemed a personal or public health priority by the health care provider caring for this patient or the study team.</i>	X	X
14. Received an experimental/investigational agent (vaccine, drug, biologic, device, blood product, or medication) within 28 days prior to Visit 1, or expects to receive an experimental/investigational agent during the study period (up to 8 days after visit 2)	X	X
15. A moderate to severe acute illness within 72 hours of Visit 1* <i>*All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection without fever.</i>	X	X
16. A reported temperature greater than or equal to 100.4°F (38.0°C) within 72 hours prior enrollment or a temperature (measured by temporal artery thermometer) greater than or equal to 100.4°F (38.0°C) at the time of enrollment* <i>*This may result in a temporary delay of vaccination</i>	X	X
17. Receipt of an antipyretic medication (acetaminophen or ibuprofen) within 24 hours prior to enrollment* <i>*This may result in a temporary delay of vaccination</i>	X	X
18. Parent(s)/LAR is planning to administer a prophylactic antipyretic or medication on the day of, and/or within 7 days following Visit 1 or Visit 2* <i>*This exclusion does not apply if the caretaker indicates he/she might administer antipyretics or analgesics after vaccination to reduce fever or pain</i>	X	
19. Long term (at least 14 consecutive days) oral corticosteroids (prednisone 2 mg/kg/day or equivalent other glucocorticoid), any parenteral steroids, high-dose inhaled steroids (>800 mcg/day of beclomethasone)	X	X

dipropionate or equivalent) or other immune-modifying drugs or immunosuppressants within the preceding 6 months prior to Visit 1* <i>*Topical and nasal steroids are allowed</i>		
20. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and or their provider's routine physical examination* <i>*No laboratory testing required</i>	X	X
21. Has an active neoplastic disease, a history of any hematologic malignancy, current bleeding disorder, or taking anticoagulants.	X	X
22. Unable to receive an intramuscular injection in the thigh* <i>* For example – a broken bone or cast for treatment of broken bone in a lower extremity, congenital anomaly in lower extremity precluding administration in the affected extremity or if deemed inappropriate by the study investigator</i>	X	
23. Any condition deemed by the investigator to place the child at increased risk as a result of their participation in the study	X	
24. Any child or grandchild of a study investigator or study team member	X	X

If study team during the period of enrollment subsequent to Visit 1 becomes aware subject did not meet inclusion criteria or met exclusion meets the definition of a major violation

Met Study Exclusion Criteria	At Visit 2	After Visit 2 During Period of Enrollment²
1. Has already completed influenza vaccination during the current season per ACIP recommendations	X	X
2. History of a severe allergic reaction (e.g. anaphylaxis) to a previous dose of any influenza vaccine.	X	
3. History of a severe allergic reaction (e.g., anaphylaxis) to any component (including egg protein) of the influenza vaccine used in this study	X	
4. History of Guillain-Barré syndrome within 6 weeks following a prior dose of any influenza vaccine	X	
5. Received an experimental/investigational agent (vaccine, drug, biologic, device, blood product, or medication) after randomization or expects to receive an experimental/investigational agent during the remaining study period (up to 8 days after visit 2)	X	X
6. A moderate to severe acute illness within 24 hours of Visit 2* <i>* This may result in a temporary delay of Visit 2 and/or vaccination. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection without fever.</i>	X	X
7. A reported temperature greater than or equal to 100.4°F (38.0°C) within 24 hours prior to Visit 2 or a temperature (measured by temporal artery thermometer) greater than or equal to 100.4°F (38.0°C) at the time of Visit 2* <i>*This may result in a temporary delay of Visit 2 and/or vaccination</i>	X	X

8. Receipt of an antipyretic medication (acetaminophen or ibuprofen) within 24 hours prior to Visit 2* <i>*This may result in a temporary delay of Visit 2 and/or vaccination</i>	X	X
9. Parent(s)/LAR is planning to administer a prophylactic antipyretic or medication on the day of, and/or within 7 days following Visit 2* <i>*This exclusion does not apply if the caretaker indicates he/she might administer antipyretics or analgesics after Visit 2 to reduce fever or pain</i>	X	
10. Unable to receive an intramuscular injection in the thigh* <i>* For example – a broken bone or cast for treatment of broken bone in a lower extremity, congenital anomaly in lower extremity precluding administration in the affected extremity or if deemed inappropriate by the study investigator</i>	X	
11. Any condition deemed by the investigator to place the child at increased risk as a result of their participation in the study	X	

²If study team during the period of enrollment subsequent to Visit 2 becomes aware subject met exclusion meets the definition of a major violation

Procedural Violations

Visit 1

- Written informed consent not obtained
- Study eligibility not reviewed
- Temperature using the temporal artery thermometer not obtained
- Assigned study products administered prior to randomization
- Assigned study products not administered according to respective package insert specifications
- Study products received were not according to randomization assignment
- Study products not administered in thighs

Visit 2

- Visit 2 not done
- Study eligibility not reviewed
- Temperature using the temporal artery thermometer not obtained
- Assigned study product (IIV if in sequential group) not administered according to package insert specifications
- Study products received were not according to randomization assignment
- Concomitant vaccine/s administered
- Study product not administered in thighs

Interval Between Visits 1 and 2

- The protocol notes that the maximal interval between Visit 1 (Day 1) and Visit 2 (Day 15 (+7)) is 21 days. If Visit 2 occurs between Day 15 and Day 25, it will not be considered a major Protocol Violation.

Parental assessments

- Parents did not measure temperature using temporal artery method

Other Major Protocol Violations

- Vaccines administered during any point during study period but not at Visit 1 or Visit 2
 - Emergency response
 - For other reason
- Use of immunosuppressive steroid dose (i.e. ≥ 14 days of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent.) or other immune-modifying drugs or immunosuppressants from Visit 1 through 8 days after Visit 2