

Protocol Title: Clinical Study of the Safety of Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) in Children with Asthma of Varying Levels of Severity

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Clinical Study of the Safety of Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) in Children with Asthma of Varying Levels of Severity

Abbreviated Title: Safety of LAIV4 in Children with Asthma

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 (U.S.) 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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1 BACKGROUND

CDC's Advisory Committee on Immunization Practices (ACIP) has long recommended annual influenza vaccination for all persons aged ≥ 6 months who do not have contraindications. In June 2018, ACIP voted to reaffirm this core recommendation for the 2018-2019 influenza season. Specifically, ACIP stated that: *For the 2018-19 season, immunization providers may choose to administer any licensed, age-appropriate, inactivated influenza vaccine (IIV), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent live attenuated influenza vaccine (LAIV4). LAIV4 is an option for those for whom it is otherwise appropriate*¹. Influenza vaccination is particularly important for persons at high risk for medical complications attributed to severe influenza.¹ It is anticipated that the recommendations will be similar for the 2019-20 season. ACIP designates persons with asthma to be at higher risk for severe influenza.¹

Asthma, a chronic, inflammatory disease of the pulmonary airways, can be life-threatening if not adequately managed.² According to the U.S. National Health Interview Survey (NHIS), in 2016, 8.4 million children <18 years (9.3%) had (current) asthma, with increased prevalence of asthma among older, compared with younger children [0-4 years (3.8%); 5-11 years (9.6%); 12-17 years (10.5%)].³ Children in economically disadvantaged families were also more likely to have asthma (10.7%) than children in families that were not disadvantaged (6.7%).³ Furthermore, children with asthma are more likely to require hospitalization for influenza, and to experience asthma exacerbations after influenza illness.^{4,5} Despite this, NHIS data for the 2012-2013 influenza season revealed that influenza vaccination among children with asthma 2-17 years averaged almost 55%, up from 32% in 2004-2005, yet, this proportion still falls short of the Healthy People 2020 influenza vaccination goal of 80% for children with asthma (aged 6 months-17 years).⁶⁻⁸

Live attenuated influenza vaccine (LAIV) is administered intranasally, and replication of the vaccine virus occurs primarily in nasopharyngeal epithelial cells. This replication can lead to symptoms of nasal congestion.^{9,10} Since 2013, all LAIV formulations used in the United States have been quadrivalent LAIV (LAIV4) (FluMist® Quadrivalent). The Warnings and Precautions section of the FDA package insert for LAIV4 states that, "persons of any age with asthma may be at increased risk of wheezing following the administration (of LAIV)".¹⁰ Similarly, ACIP considers asthma in persons aged ≥ 5 years a precaution for LAIV use.¹ Because of the potential for increased risk of wheezing after LAIV, the use of LAIV in persons with asthma has been an area of vaccine safety research for many years; the safety issue remains unresolved. Broadening the LAIV recommendation to include persons with asthma could have several advantages: 1. Ease of program implementation, especially in busy clinic or school-based vaccination settings; 2. Ease of implementation and greater options for influenza pandemic preparedness; and 3. Greater options for children with needle phobia. A clinical study to assess the safety of LAIV4 in children with asthma could expand the evidence base and inform clinical decision-making and public health policy. Below we present a summary of the safety data of LAIV in children and recent changes in ACIP recommendations for use of LAIV.

Review of Safety Evidence for LAIV in Children. In 2014, after completing a review of available evidence, ACIP concluded that for healthy children aged 2-8 years, risks for harms assessed (including fever, wheezing, and serious adverse events) appeared to be similar for LAIV and IIV.¹¹ However, for

children with chronic medical conditions placing them at higher risk for influenza complications, including asthma, data on the relative safety of LAIV and IIV were limited.¹¹ Most studies suggested that LAIV was not associated with an increased risk of wheezing events after vaccination in children who are at least 2 years of age and that did not have a prior history of asthma and wheezing.¹² However, data regarding LAIV safety in persons with a history of asthma or wheeze were less clear.¹²⁻¹⁴ One study of LAIV safety specified in the methods that children with severe asthma were included; no safety concerns were identified, but the small study (N=48) conducted in one season limited the ability to draw conclusions.¹³ There is even less information about the safety of LAIV4 in persons with asthma when compared with trivalent LAIV; LAIV4 has been the only live influenza vaccine product available in the United States since the 2013-14 influenza season.

In an effort to further assess the safety of LAIV in participants with asthma, several clinical trials have been conducted over the past decade. These will be briefly summarized to provide a context for the proposed study. Redding et al. assessed the safety and tolerability of LAIV in children > 9 years of age with moderate to severe asthma.¹³ They enrolled 48 subjects (24 participants and 24 controls) into a randomized, double blind, placebo-controlled study; spirometry was performed twice before vaccination to establish a baseline forced expiratory volume (FEV1) and once 2 to 5 days thereafter. The primary outcome was the percent change in percent-predicted FEV1 before and after vaccination; a reduction of $\geq 15\%$ was the prespecified endpoint. Peak flows, clinical asthma symptom scores and nighttime awakening scores were also measured daily from 7 days pre- to 28 days post-vaccination. There was no difference in the primary outcome measure (percentage change in percent predicted FEV1) between the treatment and placebo groups ($P = 0.78$). Secondary outcomes did not differ between the two groups either; these included the number of participants with a decrease in FEV1, reductions in peak flows, use of beta-adrenergic rescue medications, asthma exacerbations and clinical asthma symptom scores before and after vaccination. The same proportion of participants in each group experienced post-vaccination symptoms within 10 days (92% and 91%, respectively; $P = 1.0$). No serious adverse events occurred. These data were reassuring for the safety of LAIV in asthmatic children but were of small sample size.¹³

To further evaluate the safety of LAIV in children and adolescents, a larger randomized, double blind, placebo-controlled safety trial in healthy children age 12 months to 17 years was conducted by Bergen et al., in a large health maintenance organization.¹⁵ Children were randomized 2:1 to receive either LAIV or placebo. Children <9 years of age received a second dose of LAIV or placebo 28 to 42 days after the first dose. Enrolled children were followed for 42 days after each vaccination for all medically attended events. A total of 9689 evaluable children were enrolled in the study. Of the 4 pre-specified diagnostic categories (acute respiratory tract events, systemic bacterial infection, acute gastrointestinal tract events, and rare events potentially associated with wild-type influenza), none was associated with vaccine receipt. However, a significantly increased relative risk (4.06; 90% confidence interval, 1.29 to 17.86) of reactive airway disease was observed in children 18 to 35 months of age.¹⁵

Given these concerns regarding the triggering of asthma by LAIV, Piedra et al. conducted an even larger open-label, non-randomized, community-based trial of LAIV in children 18 months to 18 years of age over a four-year period.¹⁶ In the four years of the study 18,780 doses of LAIV were administered to 11,096 children. Medical records of all children were surveyed for serious adverse events (SAEs) and health care utilization was evaluated for medically attended acute respiratory illness and asthma. No

increased risk of asthma events for 0 to 14 days after vaccination was observed in children of any age group. In vaccine year 1, children who were 18 months to 4 years of age did have a significantly higher risk for asthma events 15 to 42 days after vaccination (RR 2.85; 95% CI: 1.01-8.03), but this was not seen in year 2. The authors concluded, "...although the possibility for a true increased risk for asthma was observed in one of the four years of the study in children who were 18 months to 4 years of age at 15 to 42 days after vaccination, it is more likely that the association is a chance effect because of the 190 comparisons made without adjustment for multiple comparisons." They also concluded that LAIV was safe and not associated with an increase in asthma events in children who are younger than 5 years.¹⁶

Utilizing the same population as Piedra, Gaglani et al. administered a single LAIV dose to healthy children aged 1.5-18 years with history of intermittent wheezing.¹⁷ As in the earlier study, they assessed the rates of medically attended acute respiratory illnesses, including acute asthma exacerbation, during 0-14 and 0-42 days post-LAIV and also assessed the risk of new-onset asthma in LAIV recipients. During each of the 4 study years, a total of 454, 656, 656, and 430 children with intermittent wheezing who received LAIV, respectively, had no increased risk for medically attended acute respiratory illnesses, including asthma exacerbation. First-dose LAIV recipients, including those aged 1.5-4 years, and those receiving 2-4 consecutive annual doses had no increased risk. Children with parental report of intermittent wheezing and those with administrative database codes for asthma during the two prior years had no increased risk of wheezing. In addition, during the 4 years of the study, 2,952, 3,092, 2,953, and 2,478 children without history of wheezing, respectively, had no increased risk of new-onset asthma. The authors concluded that "LAIV administration in children aged 1.5-18 years with a history of intermittent wheezing was safe, and was not associated with increased risk for medically-attended acute respiratory illnesses, including acute asthma exacerbation during any of the study years."¹⁷

Ashkenazi et al. compared the safety of LAIV and trivalent inactivated influenza vaccine (TIV) in young children with a history of recurrent respiratory tract infections.¹⁸ Children 6 to 71 months of age were randomized to receive 2 doses of LAIV (n = 1101) or TIV (n = 1086), 35 +/- 7 days apart before the start of the 2002-2003 influenza season. They were followed for vaccine effectiveness and safety. Overall, 52.7% (95% confidence interval [CI] = 21.6%-72.2%) fewer cases of influenza caused by virus strains antigenically similar to vaccine were observed in LAIV than TIV recipients. Greater relative efficacy for LAIV was observed for the antigenically similar A(H1N1) (100.0%; 95% CI = 42.3%-100.0%) and B (68.0%; 95% CI = 37.3%-84.8%) strains but not for the antigenically similar A(H3N2) strains (-97.1%; 95% CI = -540.2% to 31.5%). Relative to TIV, LAIV reduced the number of respiratory tract infection healthcare provider visits by 8.9% (90% CI = 1.5%-15.8%) and missed days of school, kindergarten, or day care by 16.2% (90% CI = 10.4%-21.6%). Rhinitis and rhinorrhea, otitis media, and decreased appetite were the only events that were reported more frequently in LAIV recipients (monitored for 11 consecutive days after vaccination). There was no difference between groups in the incidence of wheezing after vaccination (during the 42 days after vaccination). LAIV was well tolerated in these children and demonstrated superior relative efficacy compared with TIV in preventing influenza illness.¹⁸

Given the concern about the safety of LAIV administration in patients with asthma, a large open-label study was conducted among 2,229 asthmatic children aged 6 to 17 years by Fleming et al. during the 2002-2003 influenza season.⁴ Children receiving high-dose systemic corticosteroids were excluded from the study, but the study did not quantify the level of severity of the underlying asthma among study participants.

Nearly 70% of children were on inhaled corticosteroids. No significant differences were reported between the LAIV and TIV vaccine recipients in the incidence of asthma exacerbations (during 42 days after vaccination), mean peak expiratory flow rates, asthma symptom scores, or nighttime awakening scores. Rhinorrhea and nasal congestion were commonly reported symptoms among recipients of LAIV during the 15 days after study vaccination; injection site reactions were the most commonly reported symptoms among recipients of TIV. Overall, there was no evidence of a significant increase in adverse pulmonary outcomes for LAIV compared with TIV. LAIV had a significantly greater relative efficacy of 35% compared with TIV in this high-risk population.⁴ This well designed and conducted clinical trial serves as a model for the conduct of the proposed trial.

More recently, the Centers for Disease Control and Prevention's Vaccine Safety Datalink published a study assessing the safety of LAIV in persons with asthma.¹⁹ They assessed medically-attended respiratory events during the 14 days after LAIV (trivalent LAIV and monovalent 2009 H1N1 pandemic LAIV) compared with the 29 to 42 days after vaccination among persons 2 through 49 years over three influenza seasons (2008-2009; 2009-2010; 2010-2011). Most patients had intermittent or mild persistent asthma. Medically-attended upper or lower respiratory events (outpatient or inpatient) were not significantly increased after LAIV. This was true for younger children 2-8 years as well as older children 9-17 years.

Summary of recent history of ACIP guidance for use of LAIV. Based on influenza surveillance systems and published pre- and post-licensure clinical study data, ACIP recommendations for live attenuated influenza vaccine (LAIV) use in healthy children aged ≥ 2 years have changed over recent years. During 2007-2008 through the 2013-2014 influenza seasons, ACIP recommended that either live attenuated influenza vaccine (LAIV) or IIV could be used for these children.⁹ In 2014, after completing an evidence review, ACIP concluded that data supported the superior efficacy for LAIV versus IIV in children aged 2-8 years; in response ACIP recommended a preference for LAIV over IIV in this age group during the 2014-15 influenza season.¹¹ However, following this preferred recommendation, new data emerged suggesting that LAIV did not have superior efficacy over IIV.²⁰ Therefore for the 2015-16 influenza season, ACIP removed the preference and recommended that either LAIV or IIV could be used in healthy children aged ≥ 2 years.²⁰ Due to concerns regarding lack of effectiveness of quadrivalent LAIV (FluMist® Quadrivalent; LAIV4; MedImmune, Gaithersburg, MD) during the 2013-2014 and 2015-2016 influenza seasons, ACIP voted in June 2016 to recommend against use of LAIV4 in persons of any age during the 2016-2017 influenza season,²¹ and continued the recommendation against use of LAIV4 during the 2017-2018 influenza season.¹ The manufacturer (MedImmune/AstraZeneca) identified that a more immunogenic strain of post-pandemic A(H1N1) was needed to improve the immune response to LAIV4. The manufacturer changed the vaccine formulation and carried out clinical studies of viral shedding and antibody response to the new LAIV4 formulation in young children. Results of these studies were presented at the February 2018 ACIP meeting.²² Based on results of these studies and additional investigations, the ACIP voted on February 21, 2018, to recommend inclusion of the updated quadrivalent formulation of LAIV (FluMist®; LAIV4) among vaccines eligible for use during the 2018-2019 influenza season.^{22,23} On June 8, 2018, CDC published the updated recommendation for use of the Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) during the 2018-2019 influenza season: *“For the 2018–19 U.S. influenza season, providers may choose to administer any licensed, age-appropriate influenza vaccine (IIV, recombinant influenza vaccine [RIV], or LAIV4). LAIV4 is an option for those for*

whom it is otherwise appropriate. No preference is expressed for any influenza vaccine product."²³ It is anticipated that the recommendations will be similar for the 2019-20 season.

In September 2015, CDC's Immunization Safety Office-Clinical Immunization Safety Assessment (CISA) Project awarded 3 medical research centers a contract to conduct a clinical study to assess the safety of LAIV versus IIV in children 5-11 years diagnosed with persistent asthma. This study intended to enroll participants during the 2016-2017 influenza season; however, these plans were postponed temporarily during the 2016-2017 and 2017-2018 influenza seasons due to the ACIP recommendation against use of LAIV. ACIP's vote in February 2018 to recommend use of LAIV4 and expressed no preference for use of LAIV or IIV in children during the 2018-19 influenza season. This vote made it feasible for this CISA vaccine safety study to proceed, and it is anticipated that the recommendations will be similar for the 2019-20 season.

2 STUDY OBJECTIVES

2.1 Study Objectives

2.1.1 Primary Objective

1. To compare proportions of participants with asthma exacerbations during the 42 days (until day 43) after quadrivalent live attenuated influenza vaccine (LAIV4) versus quadrivalent inactivated influenza vaccine (IIV4) in children with asthma aged 5-17 years.

The hypothesis for this primary objective is that the proportion of asthma exacerbations after LAIV4 is non-inferior to the proportion of asthma exacerbations after IIV4 (proportion of asthma exacerbations is NOT higher in the LAIV4 group vs. the IIV4 group).

2.1.2 Secondary Objectives

1. To compare proportions of participants with asthma exacerbations during the 14 days after LAIV4 versus IIV4
2. To compare the proportions of participants with asthma symptoms and unscheduled albuterol use during the 14 days after receipt of LAIV4 or IIV4
3. To compare the proportion of participants that experience a clinically significant decrease in Peak Expiratory Flow Rate (PEFR) from baseline during the 14 days after receipt of LAIV4 or IIV4

2.1.3 Exploratory Objectives

1. To compare proportions of participants with asthma exacerbations during the 14 days and 42 days after receipt of LAIV4 or IIV4, by asthma severity group
2. To compare the proportions of participants with asthma symptoms and unscheduled albuterol use during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group
3. To compare the proportion of participants who experience a clinically significant decrease in PEFR from baseline during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group
4. To describe and compare changes in Peak Expiratory Flow Rate (PEFR) from baseline (pre-vaccination) PEFR after vaccination over time during the 14 days after LAIV4 versus IIV4, by asthma severity group
5. To compare change in Childhood Asthma Control Test (c-ACT) score (participants aged 5-11 years) or Asthma Control Test (ACT) score (participants aged 12-17 years) from baseline through 42 days after LAIV4 or IIV4, by asthma severity group

6. To compare asthma symptom days using **Preventative Omalizumab** or **Step-up Therapy** for Severe Fall Exacerbations (PROSE) from baseline during the 14 days after vaccination by asthma severity group
7. To compare rates of medical utilization for asthma-related symptoms during the 14 and 42 days after LAIV4 or IIV4, by asthma severity group
8. To describe and compare systemic reactogenicity events during the 14 days after receipt of LAIV4 or IIV4 by asthma severity group
9. To describe and compare serious adverse events after LAIV4 vs. IIV4 during the 42 days after vaccination and assess relatedness to vaccine
10. To describe and compare asthma symptoms and control among participants with and without a history of allergic rhinitis or hay fever, used as a proxy for allergic versus non-allergic asthma.

2.2 Study Outcome Measures

2.2.1 Primary Outcome Measure

1. Comparison of the proportion of participants experiencing an asthma exacerbation during the 42 days after LAIV4 vs. IIV4 (until day 43).

According to the 2007 *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*, asthma exacerbations, “are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness (or some combination of these symptoms). Exacerbations are characterized by decreases in expiratory airflow that can be documented and quantified by simple measures of lung function [spirometry or peak expiratory flow (PEF)]”.²⁴ For this study, asthma exacerbation will be defined as: any acute episode of progressively worsening shortness of breath (dyspnea), cough, wheezing, chest tightness, and/or respiratory distress during the 42 days (until day 43) after influenza vaccination for which the patient seeks unscheduled medical attention (e.g., healthcare provider office or Emergency Department visit or hospitalization) or receives a new prescription for systemic corticosteroids.

2.2.2 Secondary Outcome Measures

1. Comparison of the proportion of participants experiencing an asthma exacerbation during the 14 days after LAIV4 vs. IIV4.
For the purposes of this outcome measure, the above definition of asthma exacerbation (section 2.2.1) is modified to include the time period of 14 days after receipt of influenza vaccine (LAIV4 or IIV4)
2. Comparison of the proportion of participants with asthma symptoms and unscheduled albuterol use during the 14 days after receipt of LAIV4 or IIV4 (each is assessed separately).
 - a. Cough

- b. Wheezing
 - c. Tightness in chest
 - d. Nighttime awakening
 - e. Unscheduled albuterol use
3. Comparison of the proportion of participants who experience a clinically significant decrease in peak flow measurement* from baseline during the 14 days after LAIV4 or IIV4.
*For purposes of this measure, a clinically significant decrease in peak flow is defined as: a decrease of $\geq 20\%$ in PEFr from baseline PEFr.

2.2.3 Exploratory Outcome Measures

1. a. Comparison of the proportion of asthma exacerbations by asthma severity group (Mild vs. Moderate-Severe) during the 14 days after receipt of LAIV4 or IIV4
 - b. Comparison of the proportion of asthma exacerbations by asthma severity group (Mild vs. Moderate-Severe) during the 42 days after receipt of LAIV4 or IIV4
2. Comparison of the proportions of participants with asthma symptoms and unscheduled albuterol use by asthma severity group during the 14 days after receipt of LAIV4 or IIV4 (each symptom is assessed separately).
 - a. Cough
 - b. Wheezing
 - c. Tightness in chest
 - d. Nighttime awakening
 - e. Unscheduled albuterol use
3. Comparison of the proportion of participants that experience a clinically significant decrease in Peak Flow measurement any time during the 14 days after vaccination with LAIV4 or IIV4, by asthma severity group. For purposes of this measure, a clinically significant decrease in peak flow is defined as: a decrease of $\geq 20\%$ in PEFr from baseline PEFr.
4. A. Comparison of numerical changes in Peak Flow when compared to baseline during the 14 days after LAIV4 vs IIV4, by asthma severity group.
 - B. Description of changes in Peak Flow when compared to baseline during the 14 days after LAIV4 vs IIV4, by asthma severity group
5. Comparison of Change in Childhood Asthma Control Test (c-ACT) scores (participants aged 5-11 years) or Asthma Control Test (ACT) scores (participants aged 12-17 years) from baseline during the 42 days after LAIV4 or IIV4, by asthma severity group
6. Comparison of maximum number of asthma symptom days using **Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE)** from baseline during the 14 days after vaccination with LAIV4 or IIV4, by asthma severity group

7. Comparison of rates of medical utilization for asthma-related symptoms during the:
 - a. 14 days after LAIV4 or IIV4 by asthma severity group
 - b. 42 days after LAIV4 or IIV4 by asthma severity group
8. Description and comparison of systemic reactogenicity events during the 14 days after receipt of LAIV4 or IIV4 by asthma severity group
9. Description and comparison of serious adverse events during the 42 days after IIV4 or LAIV4 and performance of a relatedness assessment
10. Description and comparison of asthma symptoms and asthma control (PROSE, and c-ACT/ACT scores) among participants with and without a history of allergic rhinitis or hay fever, as a proxy for allergic versus non-allergic asthma

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Children between 5-17 years of age, inclusive, at enrollment
2. Participant must have a current diagnosis of persistent asthma¹
¹Physician diagnosis of asthma and current prescribed use of a long-acting controller medication. For purposes of this study, we have considered “controller” medications to be any single or combination use of long-acting medications used to prevent asthma exacerbations and to achieve long-term control of asthma (as compared to short-acting rescue medication). (see Table 2, Section 4.4).
3. Parent(s) or legal guardian(s) must provide written, informed consent and participant must provide assent as appropriate for age prior to initiation of study procedures and according to local IRB requirements
4. Parent(s) or legal guardian(s) and participant must be willing and able to comply with planned study procedures and be available for all study visits
5. Is in good health, other than their asthma, as determined by medical history
6. English or Spanish literate²
² only English-speaking participants will be included at the Cincinnati and Duke sites
7. Intention of being available for entire study period and complete all relevant study procedures, including follow-up using at least one of the following methods: phone calls, text messages, or emails

3.2 Exclusion Criteria

1. Acute illness and/or a reported oral temperature of $\geq 100.4^{\circ}\text{F}$ within 72 hours prior to enrollment (this may result in a temporary delay of vaccination)
2. Use of antipyretic medication during the preceding 24 hours that might mask a fever (this may result in a temporary delay of vaccination)
3. History of a severe allergic reaction (e.g., anaphylaxis) after a previous dose of any influenza vaccine or after any component of the influenza vaccine, including egg protein.
4. Receipt of any licensed vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to vaccination or planned receipt of any licensed vaccine within 42 days after vaccination

5. Receipt of current year's (2018-2019 or 2019-2020 influenza season) licensed influenza vaccine for children 9-17 years (*only*).

(Clarification: Children aged 5-8 years are permitted to be enrolled if they have received zero or one dose of the 2018-2019 or 2019-2020 influenza season's vaccine, and require two doses of the current year's (2018-2019 or 2019-2020 influenza season) influenza vaccines.) (see Fig 2, section 4.7.3)

6. Received an investigational agent (licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication) in the 28 days prior to enrollment or planned receipt before 42 days after vaccination
7. Have immunosuppression as a result of an underlying illness or treatment, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months
8. Have taken ≥ 20 mg/day of prednisone or its equivalent, for 14 days or more within the past 28 days
9. Have known active neoplasm or a history of any hematologic malignancy
10. Have had a previous exacerbation of their asthma symptoms requiring systemic steroids within the prior 28 days, or has had a life-threatening exacerbation of asthma in the past two years (e.g. hypoxic seizure, mechanical ventilation)
11. Received influenza antiviral medication within 48 hours prior to study vaccination
12. History of Guillain-Barré syndrome within 6 weeks of previous influenza vaccination
13. Have any condition that, in the opinion of the investigator, would interfere with the evaluation of the responses or would place the participant at unacceptable risk of injury
14. Has a positive urine or serum pregnancy test within 24 hours prior to vaccination in a post-menarchal female, as LAIV is not recommended for use in pregnant females.¹
15. Currently taking aspirin or aspirin-containing products
16. Any parent(s) or legal guardian(s) who is an immediate relative of study staff or is an employee supervised by study staff.
17. Previously enrolled in the study

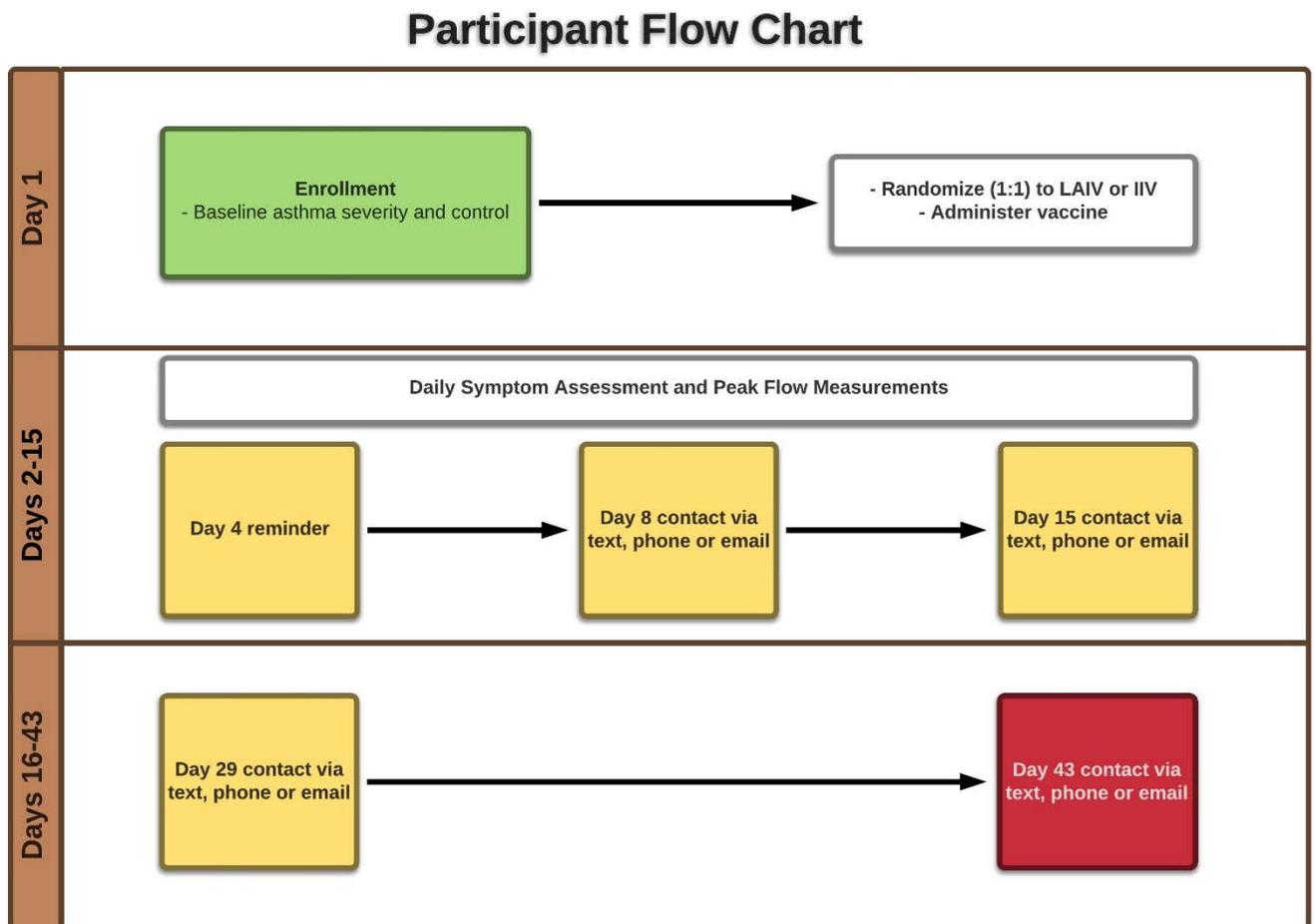
4 STUDY DESIGN AND PROCEDURES

4.1 Recruitment

This is a prospective randomized, open label clinical trial in approximately 300 children aged 5-17 years, inclusive, with a physician diagnosis of persistent asthma. The study will be conducted at three sites: Vanderbilt University Medical Center (Lead site), Cincinnati Children's Hospital Medical Center (contributing site), and Duke University Medical Center (contributing site) during the 2018-2019 and 2019-2020 influenza seasons. Participants will be randomized 1:1 to receive either a single intranasal dose of LAIV4 or an intramuscular injection of IIV4, stratifying by asthma severity (mild vs. moderate-to-severe) and by age group (5-11 years vs. 12-17 years of age). Vanderbilt will enroll approximately 100 participants, Cincinnati will enroll approximately 110 participants, and Duke will enroll approximately 90 participants. All sites will begin enrolling when study vaccines become available. Recruitment will occur at various clinics at the three study sites. At all sites, study participants will be compensated for the initial clinic visit at enrollment, and for each study visit follow-up (excluding reminder-only communications), as outlined in Section 4.3. A social security number will be requested for the parent, legal guardian, or child who receives monetary compensation for participating in this study. A child may participate in this study even if their parent or legal guardian chooses not to provide a social security number; however, the study will not be able to provide compensation to the parent, legal guardian, or child if a social security number is not provided.

4.2 Enrollment and Randomization

Participants will be randomized (1:1) to receive either a single intranasal dose of licensed quadrivalent LAIV4 or an intramuscular injection of quadrivalent inactivated influenza vaccine (IIV4), stratifying by asthma severity (mild vs. moderate-to-severe) and age (5-11 vs. 12-17 years of age). Asthma severity level will be assessed at Visit 1 (see Table 2, section 4.4). Randomization will be done separately for each site. Each site may have more than one clinic to recruit participants, and proportions of participants with mild or moderate-to-severe asthma can vary by clinics. Randomization will be accomplished using the REDCap System, hosted at Vanderbilt, or a back-up method if REDCap is temporarily unavailable. REDCap is a web-based system that is easily accessible to the other collaborating sites. This study will be open label and study staff and participants will not be blinded to treatment arm assignments.

Figure 1: Participant Flow Chart

4.3 Study Visits and Procedures

4.3.1 Visit 1 (Day 1) - Enrollment and Vaccination

- Obtain parent(s) or legal guardian(s) permission by written informed consent prior to performing any study procedures.
- Obtain child assent if applicable to site
- May read script about study to participants aged 5 to 6 years if applicable to site
- Medical history and medication history will be obtained, including a review of all current medications and medications taken within 28 days prior to enrollment.
- A targeted physical exam may be performed by clinical study staff, based on information gathered during medical history
- History of asthma and allergy disease
- Temperature will be recorded prior to immunization; oral temperature must be <math><100.4^{\circ}</math> F without use of antipyretic medication prior to administration of vaccine.

- Sex, height, weight, and BMI (demographics)
- Eligibility criteria will be reviewed to determine if child meets criteria for study.
- A urine or serum pregnancy test will be collected on post-menarchal females.
- For females, parent(s) or legal guardian(s) will be asked whether their child has had onset of menarche. If the answer is “yes”, a urine or serum pregnancy test will be performed as part of eligibility assessment, and conducted within 24 hours before vaccination. Results of a positive pregnancy test would be communicated with the female being tested in accordance with local institutional practices.
- Asthma severity will be assessed according to Table 2, section 4.4.
- Asthma control will be assessed with following tools:
 - Administration of the Childhood Asthma Control Test (c-ACT) or Asthma Control Test (ACT) score, as appropriate by age (Appendix, Fig. A1)
 - Clinical assessment to assess baseline asthma clinical symptoms [**Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) asthma symptom questionnaire**] (Appendix Figure A2)
- Patient and parent(s) or legal guardian(s) will be taught proper peak flow technique and will be provided with a digital peak flow meter by the study staff, even if they have another peak flow meter at home. A baseline peak flow measurement (standing, three attempts) will be collected. The patient (and parent(s) or legal guardian(s)) will be requested to use this same peak flow meter every day at home beginning on the day of vaccination and for 14 days following vaccination, (days 1 through 15). (see section 4.6 below)
- The child will be randomized to the respective treatment group (LAIV4 or IIV4) using the REDCap System. The Vaccine Information Sheet (VIS) for the respective vaccine administered will be provided to parent(s) or legal guardian(s) before the vaccine is administered (<https://www.cdc.gov/vaccines/hcp/vis/current-vis.html>). The VIS will be in the primary language of the parent(s) or legal guardian(s) consenting for the child to be enrolled in the study.
- An assessment of the number of influenza vaccine doses needed will be performed for children 5-8 years according to ACIP guidance. See FIG. 2, section 4.7.3.
- For children 5-8 years who are recommended to receive two doses of vaccine, study staff will document whether Dose #1 or Dose #2 will be given during the study. Additional guidance will be provided to the parent if Dose #2 is needed during the influenza season per section 4.7.3 below (*Seasonal Influenza Vaccine Single and 2-Dose Considerations for Participants aged 5-8 years*)
- The influenza vaccine will be administered according to the study randomization scheme.
- Documentation of influenza vaccine Dose #1 or Dose #2 will be provided to the parent(s) or legal guardian(s).
- Memory aid (daily symptom and peak flow diary on vaccination day, Day 1, and for the next 14 days, through Day 15, and on day 43) will be reviewed with the parent and the parent will demonstrate ability to take temperature and will be instructed in the collection of post-vaccination asthma clinical symptoms and symptom scores, adverse event, fever and concomitant medication administration data for 14 days (until day 15) after vaccination
- Parent(s) or legal guardian(s) will be given a thermometer to use for daily temperature recording
- Study staff will record any immediate adverse events (AEs) after vaccination occurring while still in the clinic. They will observe the child for at least 20 minutes after vaccination.

Study staff will instruct the parents/legal guardians to follow up with their child's healthcare provider if their child has a severe adverse event, worsening asthma symptoms or any other symptoms they find concerning

- Study staff will educate parents/legal guardians to notify the study staff if the patient requires an additional unscheduled medical visit for management of asthma symptoms (medical services utilization), has a severe adverse event, or a new asthma control medication that has been prescribed.

4.3.2 Visit 2 [Day 4 (-1 through +2)] – Reminder [phone call, email, or text message]

- Reminder message to parent(s) or legal guardian(s) to complete memory aid.

4.3.3 Visit 3 [Day 8 (-1 through +3)] – Contact [phone call(s), email(s), and/or text message(s)]

- Memory aid review for solicited symptoms
- Unsolicited symptoms review
- Obtain serious adverse event (SAE) information
- Concomitant medications review
- Medical services utilization review
- Peak flow measurements
- Parents/legal guardians will be instructed to follow up with their child's healthcare provider if their child has a severe adverse event, worsening asthma symptoms, or any other symptoms they find concerning
- Parents/legal guardians will be instructed to contact the study staff if the child has an unscheduled medical visit for management of asthma symptoms (medical services utilization), or has a new asthma medication prescribed, or experiences a severe adverse event

4.3.4 Visit 4 [Day 15 + 5] – Contact [phone call(s), email(s), and/or text message(s)]

- Memory aid review for solicited symptoms
- Unsolicited symptoms review
- Obtain serious adverse event (SAE) information
- Concomitant medications review
- Post-vaccination asthma clinical symptoms review and PROSE questionnaire
- Medical services utilization review
- Peak flow measurements
- Study staff will instruct the parents/legal guardians to follow up with their child's healthcare provider if their child has worsening asthma symptoms or any other symptoms they find concerning
- Parents/legal guardians will be instructed to contact the study staff if the child has an unscheduled medical visit for management of asthma symptoms (medical services utilization) or has a new asthma medication prescribed.

4.3.5 Visit 5 (Day 29 ± 3) – Contact [phone call(s), email(s), and/or text message(s)]

- Concomitant medications review
- Unsolicited symptoms review
- Medical services utilization review
- Obtain serious adverse event (SAE) information
- Study staff will instruct the parents/legal guardian to follow up with their child's healthcare provider if their child has worsening asthma symptoms or any other symptoms they find concerning
- Parents/legal guardians will be instructed to contact the study staff if the child has an unscheduled medical visit for management of asthma symptoms (medical services utilization) or has a new asthma medication prescribed.

4.3.6 Visit 6 (Day 43 + 7) – Contact [phone call(s), email(s), and/or text message(s)]

- Concomitant medications review
- Unsolicited symptoms review
- Medical services utilization review
- Obtain serious adverse event (SAE) information
- Post-vaccination asthma clinical symptoms review and symptom scores
 - Asthma control assessment (c-ACT/ACT, as appropriate by age)

Table 1: Schedule of Events

Study Visit	Enrollment Visit 1 (Vaccination)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Study Day	1	4	8	15	29	43
Visit Window (Days)	n/a	3-6	7-11	15-20	26-32	43-50
Type of Visit	In –person Clinic	Reminder only	Contact	Contact	Contact	Contact
Obtain Informed Consent through parental permission	X					
Obtain Assent (if applicable per site’s IRB requirement)	X					
Review Eligibility Criteria	X					
Document Prior Year Flu Vaccination and present year influenza vaccine status for children 5-8 years	X					
Review Medical History	X					
May perform targeted physical exam	X					
Review Asthma History	X					
Assess asthma clinical symptoms ^a (PROSE)	X			X		
Assess asthma control ^b (c-ACT/ACT)	X					X
Asthma severity classification ^c	X					
Concomitant Medications ^d	X		X	X	X	X
Urine or serum pregnancy test ^e	X					
Oral temperature	X					
Sex, Height, Weight, BMI	X					
Peak Flow Measurement ^f	X		X	X		
Enrollment and Randomization ^g	X					
Study Vaccination	X					
Post vaccination evaluation period (at least 20 minutes)	X					
Distribute Memory Aid and other Materials	X					
Memory Aid Review (solicited symptoms)			X	X		
SAE, unsolicited symptoms, and Medical Services Utilization ^h	X		X	X	X	X

^a Asthma clinical symptoms assessed using the PROSE questionnaire.

^b Asthma control assessed using the c-ACT or the ACT, as appropriate by age.

^c See section 4.4 in the protocol, for categories of asthma severity.

^d All current medications taken within 28 days prior to signing the informed consent form and through Day 43 (Visit 6).

^e Will be performed on all post-menarchal females within 24 hours before vaccination.

^f The highest of 3 peak flow measurements will be recorded.

^g Participants will be randomized 1:1 to LAIV4 or IIV4; stratified by asthma severity and age stratum

^h Medical services utilization to include visits to doctor, urgent care, emergency room, hospitalization.

4.4 Assignment of Asthma Severity

After the informed consent process, asthma severity will be assessed for each child according to the classification schema described on Table 2, section 4.4.1.

4.4.1 Characterizing Asthma Severity

Prior to randomization, it will be necessary to characterize asthma severity in each patient (see Table 2). For this study, we will only recruit participants with persistent asthma and will recruit within the full clinical spectrum of asthma severity described in Table 2 (mild, moderate, and severe). For this study, we have created distinct categories of asthma severity levels, using existing literature and clinical judgement. Study staff should use these definitions at time of enrollment to identify if the children have mild-, moderate-, or severe-persistent asthma. For the purposes of our study, the categories of asthma severity reflect the intensity of medical treatment needed to: 1) obtain optimal control of asthma, and 2) minimize impairment and risk resulting from asthma. This categorization was adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 that was issued in September 2011 and the associated Quick Reference Guide

https://www.nhlbi.nih.gov/sites/default/files/media/docs/asthma_qrg_0_0.pdf²⁴

Table 2: Asthma severity categories and prescription long-acting controller medications* for children with persistent asthma, aged 5-17 years

Classification of Asthma Severity		
Treatment of Persistent Asthma		
Mild Persistent	Moderate Persistent	Severe Persistent
Low-dose ICS OR Montelukast OR Cromolyn sodium	Low-dose ICS + Montelukast OR Low-dose ICS + LABA OR Medium-dose ICS	Medium-dose ICS + Montelukast or LABA OR Any High-dose ICS OR Omalizumab/Xolair OR Mepolizumab/Nucala OR Chronic systemic steroids

Abbreviations: LABA: long-acting beta-agonist; ICS: inhaled corticosteroids

*Controller medications include inhaled corticosteroids, oral corticosteroids, leukotriene receptor antagonists, long-acting beta agonists, and biologics.

4.5 Baseline demographic and health data

All patients enrolled in the study will have baseline demographic and clinical data obtained from their parents/legal guardian at the time of enrollment and clarified with available medical records if necessary. These data will include age, gender, height, weight, BMI, allergy history, conditions for which the child takes prescribed or over-the-counter medications or supplements, and the list of medications or supplements. If these data are not available from the clinic record, they will be obtained from the parent(s) or legal guardian(s).

4.6 Individual Peak Expiratory Flow Rate (PEFR) Evaluations

Participants will be trained on the “at home” performance of PEFR using a digital hand held device purchased by study funds and that participants will get to keep after completing the study. The device is easily learned, and it can provide an objective measure of control of asthma symptoms. Typically, a participant’s PEFR is measured while standing by the highest of 3 efforts. These measurements should be completed in the evening, before taking daily controller medication, to minimize variations that may be influenced by diurnal changes. Additionally, the PEFR maneuver should be attempted after completion of the two surveys that assess asthma control (c-ACT/ACT and PROSE) to avoid bias in the recording of daily symptoms. All efforts will be made to minimize variation in technique; training in proper digital peak flow meter use will be accomplished at study enrollment and reviewed at each study call.

For this study, all sites will provide participants with a digital peak flow meter. This device has an automatic memory for peak flow measurements and each entry is marked with a time stamp; thus, participants will be instructed to record their daily PEFR data measurements on their memory aid until day 15.^{25,26}

4.7 Vaccine Delivery

Only U.S.-licensed vaccines will be used in this study. These vaccines will be used according to the approved FDA package insert. The vaccines will be obtained from the study site pharmacies and will be administered by a licensed provider (RN, NP, PA, MD) from the study team. Both of the vaccines will be quadrivalent. The summaries from the package inserts of the two proposed vaccines are shown below. The influenza vaccines formulated for use during the 2018-2019 or 2019-2020 influenza season shall be used in this study for the respective season. Vaccines will be administered in a manner that is consistent with ACIP General Best Practice Guidelines for Immunization.²⁷

4.7.1 FluMist® Quadrivalent (Influenza Vaccine Live, Intranasal)

FluMist® Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FluMist® Quadrivalent is approved for use in persons 2 through 49 years of age for intranasal administration by a healthcare provider.¹⁰ FluMist® Quadrivalent is not contraindicated for asthmatics, although persons of any age with asthma may be at increased risk of wheezing following the administration of this vaccine. In

the United States there is only one licensed formulation of live attenuated influenza vaccine (LAIV4; FluMist® Quadrivalent; AstraZeneca), and this will be used in all sites for the study.

4.7.2 Fluzone® Quadrivalent Influenza Vaccine (suspension for intramuscular injection)

Fluzone® Quadrivalent influenza vaccine (IIV4; Sanofi Pasteur) is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.²⁸ Fluzone® Quadrivalent is approved for use in persons 6 months of age and older for intramuscular administration by a healthcare provider. There is no precaution or contraindication against using Fluzone® Quadrivalent in persons with asthma. In the event of lack of availability of Fluzone® Quadrivalent, another U.S.-licensed age-appropriate quadrivalent IIV product may be used according to the FDA package insert.²⁹

4.7.3 Seasonal Influenza Vaccine Single and 2-Dose Considerations for Participants aged 5-8 years

Evidence from several studies indicates that children aged 6 months through 8 years require 2 doses of influenza vaccine (administered a minimum of 4 weeks apart) during their first season of vaccination for optimal protection.¹ For children aged 5-8 years, the ACIP recommends 2 doses of seasonal influenza vaccine, administered at least 4 weeks apart, if they have not previously received 2 or more total doses of trivalent or quadrivalent influenza vaccine before July 1 of the current influenza season. For purposes of this study, July 1, 2018 would be used as the cutoff date for the 2018-2019 influenza season, and July 1, 2019 would be used as the cutoff date for the 2019-2020 influenza season. The two doses need not to have been received during the same season or consecutive seasons. See Fig 2, (*Influenza vaccine dosing algorithm for children aged 6 months through 8 years- Advisory Committee on Immunization Practices, United States, 2018*).²⁰ If a child needs two doses, it is acceptable for one dose to be LAIV4 and the other dose to be IIV3 or IIV4.

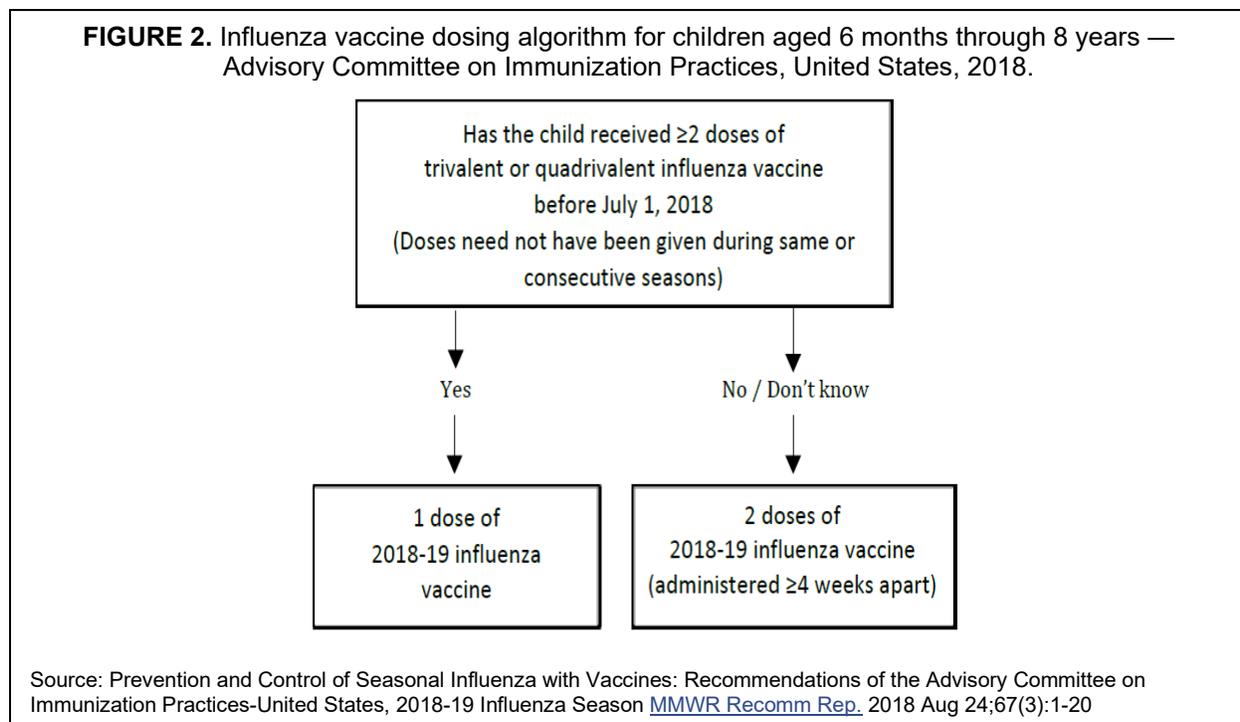
Among participants 5 through 8 years otherwise eligible for enrollment into this study, Vanderbilt, Cincinnati, and Duke will assess during the pre-enrollment process and at the time of enrollment whether one or two doses of seasonal influenza vaccine is recommended for each of these potential study participants. For study participants in the 5-to-8year age category who are recommended to receive two doses of seasonal influenza vaccine during 2018-2019 or 2019-2020 influenza seasons, the following guidance will be used:

- For those receiving dose #1 of influenza vaccine at Visit #1 during the study, the parent(s) or legal guardian(s) will be educated to seek the second dose from their usual healthcare provider; administration of the second dose will not be a study procedure. Study staff may facilitate, but will not be responsible for, making the appointment for the child to receive the second dose of the seasonal influenza vaccine at the healthcare provider office. The parent(s) or legal guardian(s) must also be informed that the child would be eligible to receive Dose #2 beginning 4 weeks after Dose #1, but that the study will request that Dose #2 be administered after Day #43 to allow for the study to assess asthma symptoms during a complete 6-week timeframe after the vaccination. If during the study a parent(s) or legal guardian(s) changes their mind, and the child receives the second dose before day #43, the parent or legal guardian will be instructed to inform the study staff. In addition, if there is widespread circulation of influenza virus in the local community at the time of enrollment (as assessed by the study site investigator(s), in consultation with local public health experts), this request

to postpone Dose #2 will be removed. In 74% of influenza seasons from 1982–83 through 2015–16, peak influenza activity did not occur until January or later, and in 59% of seasons, the peak was in February or later.¹

- For children aged 5-8 years who have already received dose #1 during the 2018-2019 or 2019-2020 influenza seasons before enrollment in this study, and who are recommended to receive Dose #2, study staff will ensure that at least 4 weeks have elapsed since Dose #1 before administering Dose #2 during this study. Study staff will document if Dose #1 or Dose #2 was administered during this study (at Visit #1)

Figure 2: Influenza vaccine dosing algorithm for children aged 6 months through 8 years—Advisory Committee on Immunization Practices, United States, 2018. [Note: This recommendation is anticipated to be similar (using the July 1, 2019 cutoff) for the 2019-2020 season]



The seasonal influenza vaccine (quadrivalent live attenuated influenza vaccine or quadrivalent inactivated influenza vaccine) will be administered at baseline (Day 1 of study) according to the study randomization scheme.

4.8 Monitoring Vaccine Safety in the First 15 Days

On the vaccination day and for the next 14 days post-vaccination (until day 15), all participants will be monitored daily by their parent(s) or legal guardian(s) and the information will be recorded using memory aids provided at the enrollment visit. Daily reactogenicity, including measurement of nighttime awakening, and unscheduled albuterol use and two validated questionnaires will be completed (c-ACT/ACT and PROSE). PROSE will be assessed at baseline (Day 1) and on Day 15.

In addition to the two questionnaires above, several predefined events that could occur after vaccine administration will also be recorded for 14 days after vaccination (through day 15). These will include fever (oral temperature $\geq 100.4^{\circ}\text{F}$), asthma symptoms, and other respiratory and systemic symptoms. Medication receipt, new prescriptions for asthma medications, and any previously unscheduled healthcare utilization (medical office visits, ED visits, hospitalizations) will also be documented on the reaction form. To ensure compliance with the reaction assessment, parents will be called, emailed through REDCap, or receive text messages on Days 4, 8 and 15 by the study staff.

On the day of vaccination and during the first 14 days (until day 15) after vaccination, if the participant reports an increase in their symptoms and an increase in the need for medications for their asthma, the family will be instructed to contact the study staff, so medical records can later be collected, if needed. If at any point a study participant is experiencing symptoms of any asthma exacerbation, the participant or their parent will be instructed to contact their primary care provider (PCP) and inform study staff of this encounter.

4.9 Extended follow-up for days 16-43

After the initial 15-day follow up after vaccination, there will be an extended surveillance period for safety assessment from day 16 after vaccination for a total of 42 days (Day 43). This will be accomplished by a telephone call, text messaging, or email through the REDCap system to the parents of the participants, depending on their preference and their availability, at day 29 and at day 44 to determine the status of asthma control. On Day 29, participants will be queried about concomitant medications, unsolicited symptoms, serious adverse events, and medical services utilization. On day 44, participants will be queried about concomitant medications, unsolicited symptoms, serious adverse events, and medical services utilization, as defined above. The c-ACT/ACT score will also be completed at day 44.

During the extended follow up period, parents/legal guardian will be instructed to contact the study staff if the participant has an unscheduled medical visit for management of asthma symptoms or a new asthma medication prescribed.

4.10 Adverse Events and Serious Adverse Events

Adverse events (AEs) will be recorded on the memory aid and will include the need for new prescription or nonprescription medications for the control of asthma, an unscheduled healthcare provider visit or consultation within 42 days (until day 43) after vaccination, any other clinically significant event occurring at any point during the study period. Serious AEs (SAEs) will also be monitored through 42 days (until day 43) after vaccination and will include events that result in death, were life threatening, result in participant hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity. Additionally, important medical events that may not have resulted in death, were not life threatening, or did not require hospitalization might be considered SAEs when, according to appropriate medical judgment, they jeopardize the patient or participant and require medical or surgical intervention to prevent one of the outcomes listed above. Medical records will be requested and reviewed to evaluate SAE and assess relatedness of SAEs to receipt of LAIV4 or IIV4

5 RISKS

5.1 Vaccines

All participants will receive the CDC Vaccine Information Statements (VIS) (<https://www.cdc.gov/vaccines/hcp/vis/current-vis.html>) before vaccination. With any medicine, including vaccines, there is a chance of reactions. These are usually mild and go away on their own, but serious reactions are also possible. Any medication or vaccine can cause a severe allergic reaction, including anaphylaxis. 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 small chance of a vaccine causing a serious injury or death.

5.1.1 Inactivated Influenza Vaccine (IIV)

ACIP routinely recommends IIV for children with asthma^{9,11,20} and risks after IIV would be expected to be no higher than those encountered through usual care. Most people who get a flu shot do not have any problems with it. Minor problems following a flu shot may include: soreness, redness, or swelling where the shot was given, hoarseness, sore, red or itchy eyes, cough, fever, aches, headache, itching, fatigue. If these problems occur, they usually begin soon after the shot and last 1 or 2 days. More serious problems following a flu shot can include the following: There may be a small increased risk of Guillain-Barré Syndrome (GBS) after inactivated flu vaccine. This risk has been estimated at 1 or 2 additional cases per million people vaccinated, primarily in adults. This is much lower than the risk of severe complications from flu, which can be prevented by flu vaccine. Problems could happen after any injected vaccine: People sometimes faint after a medical procedure, including vaccination. Sitting or lying down for about 15 minutes after vaccination can help prevent fainting and injuries caused by a fall. Some people get severe pain in the shoulder and have difficulty moving the arm where a shot was given.

5.1.2 Live, attenuated influenza vaccine (LAIV)

ACIP considers use of LAIV as a precaution for children aged ≥ 5 years with asthma.¹ In addition to the usual risks as described in the VIS (<https://www.cdc.gov/vaccines/hcp/vis/current-vis.html>), children with asthma might experience higher rates of asthma exacerbations after LAIV than with IIV.^{9,11,20} Most people who get LAIV do not have any problems with it. Reactions to LAIV may resemble a very mild case of flu. Some of the most common symptoms that have been reported following LAIV in children and adolescents 2-17 years of age are runny nose, nasal congestion, sore throat, cough, fever, headache, muscle aches, wheezing, abdominal pain, vomiting, or diarrhea.¹⁰

There is also the potential risk of loss of confidentiality about the information obtained as part of this study (see section 9).

6 REPORTING OF ADVERSE EVENTS

Parent(s) or legal guardian(s) who at any time express any concern about symptoms or serious unsolicited events will be encouraged to follow up with their child's health care provider.

Serious adverse events (SAEs) will be reported to CDC and all participating IRBs according to institutional requirements.

If indicated, adverse events will be reported to CDC's Vaccine Adverse Event Reporting System (VAERS). The National Childhood Vaccine Injury Act requires healthcare providers to report:

- Any adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine; or
- Any adverse event listed in the VAERS Table of Reportable Events Following Vaccination (https://vaers.hhs.gov/docs/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf) [link accessed 5/2/2019) that occurs within the specified time period after vaccination.

In addition, CDC encourages reporting of any clinically significant adverse event that occurs in a patient following a vaccination, even if there is uncertainty regarding if a vaccine caused the event.

As noted in section 4.10, a SAE is an AE meeting one or more of the following criteria

- Life-threatening illness
- Death
- Hospitalization - An event requiring inpatient hospitalization
- Prolongation of existing hospitalization
- Persistent or significant disability or incapacity

Additionally, important medical events that may not have resulted in death, were not life threatening, or did not require hospitalization might be considered SAEs when, according to appropriate medical judgment, they jeopardize the patient or participant and require medical or surgical intervention to prevent one of the outcomes listed above. These will be reported to the IRBs. SAEs will be assessed for relatedness to vaccine: related or not related.

Participants who report severe solicited AEs or SAEs or express any concern about symptoms, and/or unsolicited events will be encouraged to follow up with their pediatrician or primary care provider. Severe solicited or unsolicited adverse events are those that prevent daily activity and/or require a doctor's office visit or a missed day of school or daycare.

7 STUDY WITHDRAWAL AND DISCONTINUATION

Participants may voluntarily withdraw their consent for study participation at any time and for any reason, without penalty.

A participant may withdraw or be withdrawn from this study for any of the following reasons:

- Medical disease or condition, or any new clinical findings for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would compromise the safety of the participant, or would interfere with the participant's successful completion of this study, or would interfere with the evaluation of responses.
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Participant withdrawal of consent.
- Participant lost to follow-up.
- Termination of this study.
- New information becomes available that makes further participation unsafe.

Participants may withdraw their consent for study participation at any time and for any reason, without penalty.

7.1 Handling of Withdrawals

Participants who withdraw from the study before randomization will be replaced. Participants who withdraw from the study after randomization will not be replaced. Every attempt should be made to collect all data specified by the protocol relative to study vaccine received up to the time of withdrawal. Data collected before withdrawal will still be used for analysis.

7.2 Termination of Study

This study may be terminated for safety concerns of the PI, CDC, or participating IRBs.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Calculations

This study aims to enroll approximately 300 participants (at least 100 from Vanderbilt, at least 110 from Cincinnati, and at least 90 from Duke). We assume that the proportion of asthma exacerbations in 42 days (until day 43) after vaccination is 12% after LAIV4 and IIV4.⁴ We also assume that ~10% of the children may drop out, yielding a total sample of at least 270 (135 LAIV4 and 135 IIV4).

We expect the proportion of asthma exacerbation in LAIV4 (experimental group) will be at least as high as IIV group (control group). The power estimate is shown below, given delta of 10% and one-sided alpha is set at 5% level.

Proportion of asthma exacerbation in control IIV4 group (pc)	Proportion of asthma exacerbation in LAIV4 experimental group (pe)	Estimated power to reject H0: $pe - pc \geq 10\%$
12%	12%	81.1%

The null hypothesis will be rejected (and delta margin non-inferiority claimed) when the upper bound of the 95% one-sided confidence interval for the PE-PC is less than 10%. IBM SPSS SamplePower software version 3.0.1 was used for the power calculation which was not adjusted for stratifying by site.

8.2 Analysis plan

Descriptive analyses will be summarized for continuous variables with mean, standard deviation, median, and interquartile range. Categorical variables will be summarized with frequencies and percentages. Explanatory figures will be generated to evaluate the data distribution. Comparisons of demographic characteristics between LAIV4 and IIV4 groups will be conducted using Pearson Chi-square and Wilcoxon tests appropriately.

We will prepare three datasets for analyses populations for main analysis of the primary and secondary objectives. These are defined below.

Intent-to-Treat (ITT) Population:

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

Per Protocol Population for 43 Days:

The Per Protocol Population for 43 days is a subset of the ITT Population. This is defined as all participants who were randomized, vaccinated, completed study procedures through day 43, had no protocol violations that are likely to affect the objectives, and did not receive a second dose of influenza vaccine before day 43.

Per Protocol Population for 15 Days

The Per Protocol Population for 15 days is a subset of the ITT Population. This is defined as all participants who were randomized, vaccinated, completed study procedures through day 15, and have no protocol violations that are likely to affect the objectives.

The Per Protocol population for 43 days is the primary analysis population for the Primary Objective. Statistical analyses for the Primary Objective will be performed for the ITT population and the Per Protocol for 43 days, or the ITT Population only if no participants are excluded from the Per Protocol Population. The Per Protocol population for 15 days is the primary analysis population for the Secondary Objectives. Statistical analyses for the Secondary Objectives will be performed for the ITT population and Per Protocol population for 15 days, or the ITT Population only if no participants are excluded from the Per Protocol Population. The list of major protocol violations for analysis will be provided in the Statistical Analysis Plan (SAP).

In the ITT and Per Protocol populations, participants will be analyzed according to randomization assignment, rather than treatment group. If applicable, sensitivity analyses on primary and secondary objectives will be done on datasets defined by treatment group. For example, if a participant was assigned to LAIV4 and inadvertently received IIV4 that participant would be reassigned to the IIV4 treatment group in the sensitivity analyses.

Adjustments for enrollment site and/or other covariates for study objectives will be described in the comprehensive Statistical Analysis Plan (SAP). The analysis methods for the exploratory objectives, as well as sensitivity analyses, will be also be detailed in the SAP.

All analyses will be performed using R 3.5.0 (r-project.org), SAS version 9.4, or STATA version 15, or updated software from these programs.

8.2.1 Primary Objective

1. To compare proportions of asthma exacerbations during the 42 days (until day 43) after LAIV4 versus IIV4 in children with asthma aged 5-17 years.

The hypothesis for this primary objective is that the proportion of asthma exacerbations after LAIV4 is non-inferior to the proportion of asthma exacerbations after IIV4 (proportion of asthma exacerbations is NOT higher in the LAIV4 group vs. the IIV4 group).

8.2.2 Primary Outcome Measure

1. Proportions of asthma exacerbations in recipients of LAIV4 and IIV4 during the 42 days post-vaccination (until day 43).

The asthma exacerbation proportion within 42 days (until day 43) post-vaccination will be calculated for children receiving LAIV4 or IIV4 influenza vaccine. For this calculation a child with an asthma

exacerbation (as defined earlier in the protocol) on one or more days during day 1-43 would be considered to have had an asthma exacerbation (dichotomous yes or no). We propose a one-sided test for non-inferiority of asthma exacerbation in children receiving LAIV4 vs. children receiving IIV4. More precisely, we hope to reject the null hypothesis H_0 indicating a higher proportion of children with asthma exacerbation (above an acceptable margin $DELTA=10\%$) in the experimental (LAIV4) group as compared to the control (IIV4) group. Namely, PE is the true probability of event (asthma exacerbation) in the experimental group, PC is the true probability of event in the control group, and $DELTA$ indicates maximum clinically acceptable absolute increase in the probability of event in the experimental group over probability of event in the control group. We hope to reject: $H_0: PE \geq PC + DELTA$ in favor of alternative hypothesis $H_1: PE < PC + DELTA$. The null hypothesis H_0 will be rejected (and $DELTA$ margin non-inferiority claimed) when the upper limit of the 95% one-sided confidence interval for the $PE-PC$ is less than $DELTA$. More explicitly, if pe is the estimated event proportion in the experimental group; pc is the estimated event proportion in the control group; ne is the number of children in the experimental group; and nc if the number of children in the control group, then H_0 is rejected if

$$\left((pe - pc) + z(0.95) \sqrt{\frac{pe(1-pe)}{ne} + \frac{pc(1-pc)}{nc}} \right) < DELTA$$

8.2.3 Secondary Objectives and Secondary Outcome Measures (SOM)

1. The first secondary objective (SO 1) is to compare the proportion of participants with asthma exacerbations during the 14 days (until day 15) after receipt of LAIV4 or IIV4.

Outcome measure: Comparison of the proportion of participants experiencing an asthma exacerbation during the 14 days after LAIV4 vs. IIV4.

The analysis is similar to primary objective 1 using a one-sided non-inferiority test with the alpha level set at 0.05 and non-inferiority margin of 10% though asthma exacerbation proportions during the 14 days post-vaccination is the outcome.

2. The second secondary objective (SO 2) is to compare the proportion of participants with asthma symptoms and unscheduled albuterol use during the 14 days after receipt of LAIV4 or IIV4.

Outcome measures:

SOM 2a: Proportions of participants with asthma symptoms of cough after LAIV4 vs. IIV4 during the 14 days post-vaccination.

SOM 2b: Proportions of participants with asthma symptoms of wheezing after LAIV4 vs. IIV4 during the 14 days post-vaccination.

SOM 2c: Proportions of participants with asthma symptoms of tightness in chest after LAIV4 vs. IIV4 during the 14 days post-vaccination.

SOM 2d: Proportions of participants with asthma symptoms of nighttime awakening after LAIV4 vs. IIV4 during the 14 days post-vaccination.

SOM 2e: Proportions of participants with unscheduled albuterol use to treat asthma symptoms after LAIV4 vs. IIV4 during the 14 days post-vaccination.

Proportions of participants with each asthma symptom (yes or no) along with unscheduled albuterol use to treat asthma symptoms (yes or no) will be compared between two treatment groups using Chi-square tests. Proportions and difference of proportions between two treatment groups will be reported along with their 95% CIs. No adjustments will be made to the alpha level (two-sided $\alpha=0.05$) for this secondary objective.

3. The third secondary objective (SO 3) is to compare the proportion of participants who experience a clinically significant decrease in Peak Expiratory Flow Rate (PEFR) from baseline during the 14 days after receipt of LAIV4 or IIV4.

Outcome measure: Proportions of participants that experience a clinically significant decrease in peak flow measurement from baseline ($\geq 20\%$ in PEFR from baseline) after LAIV4 vs. IIV4 during the 14 days post-vaccination

Proportions of participants with a clinically significant ($\geq 20\%$) decrease in PEFR from baseline (yes or no) will be compared between two treatment groups using a Chi-square test. Proportions and difference of proportions by two treatment groups will be reported along with their 95% CIs. No adjustments will be made to the alpha level (two-sided $\alpha=0.05$) for this secondary objective.

9 PRIVACY AND CONFIDENTIALITY ISSUES

Participant confidentiality is strictly held in trust by the site principal investigators, other study personnel, the sponsor, and their agents. Participants will have code numbers and will not be identified by name.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning this study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the sponsor and all data and information generated by the participating as part of this study (other than a participant's medical records) will be kept confidential by the site principal investigators and other study personnel to the extent permitted by law. This information and data will not be used by the site principal investigator or other study personnel for any purpose other than conducting this study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the site principal investigator or other study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of this study; (3) information which is necessary to disclose in order to provide appropriate medical care to a study participant; or (4) study results which may be published.

A Certificate of Confidentiality from the Centers for Disease Control and Prevention (CDC) covers this study. Under this Certificate, the researchers may not disclose or use information or documents that may identify participants in any legal, administrative, legislative, or other action, unless the participant has consented for this use or the information is required to be reported by federal, state or local law such as child abuse or some infectious diseases.

10 DATA HANDLING AND RECORDS RETENTION

Study records and reports, including, but not limited to, electronic case report forms (eCRFs), source documents, informed consent forms, laboratory test results, and medication inventory records, shall be retained locally by each site in accordance with institutional record keeping requirements. Across all sites, records will be retained for a minimum of 3 years after the study is closed, as is required under 45 CFR 46.115(b).

10.1 Data collection and 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 REDCap platform, will be used to design study forms, including the memory aid forms, and short customized questionnaires to collect information from study participants. This system will be used by Vanderbilt, Cincinnati and Duke for data management. All electronic linkages will fulfill regulations for protection of human participants and requirements to minimize the risk of breach of confidentiality. After initial set-up, the workload required for electronic data collection will be substantially reduced (description of REDCap resources below).³⁰ The Vanderbilt, Cincinnati and Duke investigators have previously used the REDCap system for collection and analysis of large quantities of data. Participants' parent(s) or legal guardian(s) will fill out their paper memory aid and will be contacted via phone calls, emails, and/or a text messages according to the visit schedule in section 4.3. The data will be entered by study personnel onto REDCap. All study-related documents containing protected health information, e.g. enrollment logs, case report forms, will be maintained in secure research offices at Vanderbilt, Cincinnati and Duke, respectively, which are accessible to research staff only.

10.1.1 Vanderbilt Research Electronic Data Capture (REDCap)

Investigators within the NIH-funded Clinical and Translational Research Unit at Vanderbilt have developed REDCap, to collect and manage data for diverse clinical and translational research studies.³⁰ 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. REDCap includes secure institutional data hosting and full audit-trails in compliance with HIPAA security requirements. The REDCap Consortium is comprised of 647 active institutions, including CCHMC and Duke Health Technology Solutions. 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, in an automated database family, to perform data cleaning and data quality assurance efficiently, and to design analytical datasets for the analysis of the project data.

Periodic data enrollment audits will be conducted through the recruitment period to help monitor study progress.

10.1.2 Data cleaning and data quality assurance

To maximize data cleaning and data quality assurance, built-in filters and checks for consistency of the data including range and limit checks and branching logic and pull-down menus to limit choices for categorical variables to a pre-specified list will be 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 in the Department of Biostatistics with secured password-protected computers at Vanderbilt University. Data cleaning check and error reports will be generated on a regular basis for all sites.

10.1.3 Role of the CDC Investigators in the Project

This study is funded by a CDC contract with Vanderbilt University, Cincinnati Children's Hospital Medical Center and Duke University as Task Orders in the CISA Project Contract. Vanderbilt University (C. Buddy Creech and Andrew Sokolow) will oversee the overall study and direct activities at Vanderbilt University. Duke University (Emmanuel (Chip) Walter and Amy Stallings) will contribute participants and direct activities at Duke, and Mary Staat and Carolyn Kerckmar will contribute participants and direct activities at Cincinnati. CDC personnel will collaborate with the three study sites to develop the protocol, conduct the study, ensure the study is aligned with CDC public health priorities, and analyze the data and disseminate the results. CDC may receive access to coded data.

11 ETHICS AND PROTECTION OF HUMAN SUBJECTS

11.1 Ethical Standard

The site principal investigators will ensure that this trial is conducted in full conformity with principles of the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979)* and codified in 45 CFR 46 and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The site principal investigator's Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

11.2 Institutional Review Board

Prior to enrollment of participants into this trial, the approved protocol and informed consent-parental permission documents will be reviewed and approved by the appropriate IRB.

11.3 Informed Consent Process

11.3.1 Parental Permission

The site principal investigator or designee will choose participants in accordance with the eligibility criteria detailed in Section 3. Before any study procedures are performed, the investigators must obtain and document the permission of the child's parent(s) or legal guardian(s), in accordance with the requirements of 45 CFR 46 and the local IRB.

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, participants' parent(s) or legal guardian(s) will receive a comprehensive explanation of the proposed study procedures and study intervention, study products (influenza vaccines), including the nature and risks of the trial, alternate therapies, any known AEs, and the other elements that are part of obtaining proper informed consent. Participants' parent(s) or legal guardian(s) will also receive a detailed explanation of the proposed use and disclosure of their protected health information. Participants' parent(s) or legal guardian(s) will be allowed sufficient time to consider participation in the study, after having the nature and risks of the study explained to them, and have the opportunity to discuss the trial with their family, friends or legally authorized representative or think about it prior to agreeing to participate.

Parental permission forms describe in detail the study intervention, study products, study procedures, risks and possible benefits that are given to participants. Parental permission forms will be IRB-approved and the participant's parent(s) or legal guardian(s) will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the site principal investigator (or designee) will explain the research study to participants and their parent(s) or legal guardian(s) and answer any questions that may arise. If the participant's parent(s) or legal guardian(s) agrees, he, she, or they will be asked to sign the parental permission document. Written documentation of parental permission is required prior to

starting any study procedures or interventions being done specifically for the trial, including administering study product (seasonal influenza vaccine). The parent(s) or legal guardian(s) will be given a copy of all parental permission forms that they sign.

By signing the parental permission form, parent(s) or legal guardian(s) give permission on behalf of their children to participate in all aspects of the study.

The rights and welfare of participants will be protected by emphasizing to participants that the quality of their medical care will not be adversely affected if they decline to participate in or withdraw from this trial.

11.3.2 Assent Process

This study includes children aged 5 through 17 years. Assent will be obtained following local IRB policies and standard practice for obtaining and documenting assent. During the consent/assent process, study staff will discuss the study with both the parent and child. For children who require assent based on local IRB policies, study staff will actively solicit the assent (affirmative agreement) of the child. A child's failure to object will not will not be sufficient to demonstrate assent.

Vanderbilt	Cincinnati	Duke
5 and 6 year olds: a simple script will be read describing the study. Assent will not be obtained	5 year olds: assent will not be obtained	5 year olds: assent will not be obtained
7-17 year olds: written assent will be obtained using an assent form. The assent process includes reading the assent form and engaging the parent and participant in a discussion about the study.	6-10 year olds: verbal assent will be included as part of obtaining parental permission. A verbal assent script will be used to describe the study to the child	6-11 year olds: verbal assent will be included as part of obtaining parental permission. A verbal assent script will be used to describe the study to the child
	11-17 year olds: written assent will be obtained using an assent form	12-17 year olds: written assent will be included as part of obtaining parental permission. They will be asked for written assent during the informed consent discussion process with the parent and child.

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13 APPENDIX

13.1 Figure A1. Childhood Asthma Control Test (c-ACT)

Patient Name:

Date:

Patient ID#:

Primary Care Provider:

Childhood Asthma Control Test for children 4 to 11 years.

How to take the Childhood Asthma Control Test

- ▶ **Step 1** Let your child respond to the first four questions (1 to 4). If your child needs help reading or understanding the question, you may help, but let your child select the response. Complete the remaining three questions (5 to 7) on your own and without letting your child's response influence your answers. There are no right or wrong answers.
- ▶ **Step 2** Write the number of each answer in the score box provided.
- ▶ **Step 3** Add up each score box for the total.
- ▶ **Step 4** Take the test to the doctor to talk about your child's total score.

19
or less

If your child's score is 19 or less, it may be a sign that your child's asthma is not controlled as well as it could be. No matter what the score, bring this test to your doctor to talk about your child's results.

Have your child complete these questions.

1. How is your asthma today?

 0 Very bad	 1 Bad	 2 Good	 3 Very good
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SCORE

2. How much of a problem is your asthma when you run, exercise or play sports?

 0 It's a big problem, I can't do what I want to do.	 1 It's a problem and I don't like it.	 2 It's a little problem but it's okay.	 3 It's not a problem.
---	---	--	-------------------------------------

3. Do you cough because of your asthma?

 0 Yes, all of the time.	 1 Yes, most of the time.	 2 Yes, some of the time.	 3 No, none of the time.
---------------------------------------	--	--	---------------------------------------

4. Do you wake up during the night because of your asthma?

 0 Yes, all of the time.	 1 Yes, most of the time.	 2 Yes, some of the time.	 3 No, none of the time.
---------------------------------------	--	--	---------------------------------------

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday
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6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday
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7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday
------------------------	----------------------	-----------------------	------------------------	------------------------	----------------------

TOTAL



13.2 Figure A2. Asthma Control Test (ACT)

Asthma Control Test™ for teens 12 years and older. Know the score.

If your teen is 12 years or older have him take the test now and discuss the results with your doctor

Step 1 Write the number of each answer in the score box provided.

Step 2 Add up each score box for the total.

Step 3 Take the test to the doctor to talk about your child's total score.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5	<input type="text"/>
-----------------	---	------------------	---	------------------	---	----------------------	---	------------------	---	----------------------

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	<input type="text"/>
----------------------	---	------------	---	---------------------	---	----------------------	---	------------	---	----------------------

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5	<input type="text"/>
-------------------------	---	----------------------	---	-------------	---	---------------	---	------------	---	----------------------

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5	<input type="text"/>
-------------------------	---	----------------------	---	-----------------------	---	---------------------	---	------------	---	----------------------

5. How would you rate your asthma control during the past 4 weeks?

Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	<input type="text"/>
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AMERICAN LUNG ASSOCIATION The American Lung Association supports the Asthma Control Test and wants everyone 12 years of age and older with asthma to take it.

Copyright 2002, by QualityMetric Incorporated.
Asthma Control Test is a trademark of QualityMetric Incorporated.

Total

What does it mean if my child scores 19 or less?

- If your child's score is 19 or less, it may be a sign that your child's asthma is not under control.
- Make an appointment to discuss your child's asthma score with their doctor. Ask if you should change your child's asthma treatment plan.
- Ask your child's doctor about daily long-term medications that can help control airway inflammation and constriction, the two main causes of asthma symptoms. Many children may need to treat both of these on a daily basis for the best asthma control.

13.3 Figure A2. Preventative Omalizumab or Step-Up Therapy For Severe Fall Exacerbations (PROSE) Questionnaire

Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations			Place ID label here
ASTHMA SYMPTOMS			
Participant's Initials _____	Interviewer's Initials _____	Visit Date ___/___/___	Visit _____

[Form values are used in MEDS Program at E&M Visits.]

"Now I want to talk with you about how asthma affects [you/PARTICIPANT] each day. The next few questions are about [your/PARTICIPANT'S] symptoms and medication use in the last two weeks, that is, the past 14 days, from [14 days ago] to today." [Show calendar.]

1. In the last 14 days, how many days did [you/PARTICIPANT] have wheezing or tightness in the chest or cough?
 ___ ___ days
2. In the last 14 days, how many days did [you/PARTICIPANT] have to slow down or stop play or activities because of asthma, wheezing or tightness in the chest, or cough?
 ___ ___ days
3. During the last 14 days, how many days did [you/PARTICIPANT] use albuterol/levalbuterol by puffer or breathing machine/nebulizer during the day for relief of asthma symptoms? Please do not include albuterol/levalbuterol taken prior to physical activities such as playing sports or exercising.
 ___ ___ days
4. In the last 14 nights, how many nights did [you/PARTICIPANT] wake up because of asthma, wheezing or tightness in the chest, or cough?
 ___ ___ nights
5. During the last 14 nights, how many nights did [you/PARTICIPANT] wake up and use albuterol/levalbuterol by puffer or breathing machine/nebulizer after going to sleep?
 ___ ___ nights
6. [Are you/Is PARTICIPANT] currently in school?
 Yes1
 No0 [SKIP TO 7]
- 6a. How many days was school in session in the last 14 days? [Response cannot be greater than 10 days.]
 ___ ___ days [IF 0, SKIP TO 7]
- 6a1. How many times in the last 14 days did [you/PARTICIPANT] miss school due to asthma?
 ___ ___ times

"The following questions ask about the effect of [PARTICIPANT'S] asthma on your ability to work in the last two weeks; that is, the past 14 days, from [14 days ago] to today." **[Show calendar.]**

7. **[To be asked of caretaker]** Are you currently employed (working for pay)?

Yes1
No.....0 **[SKIP TO NEXT FORM]**

7a. **[To be asked of caretaker]** In general, how many hours per week do you usually work?

___ ___ hours/week

7a1. **[To be asked of caretaker]** During the last 14 days, how many hours did you miss from work because of problems associated with [PARTICIPANT'S] asthma? **[If necessary, review the number of hours per week he/she works.]**

___ ___ hours