

**Feasibility study to assess the safety of quadrivalent, live attenuated influenza vaccine (LAIV4) versus quadrivalent inactivated influenza vaccine (IIV4) in children aged 5-11 years with persistent asthma of varied severity (cell culture quadrivalent IIV used as surrogate for LAIV4)**

## Short Title: Influenza vaccine feasibility study in children with persistent asthma

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#### **STATEMENT OF COMPLIANCE**

- This trial will be conducted in compliance with the protocol, the International Conference on Harmonization (ICH) Guideline E6-Good Clinical Practice (GCP), and the applicable guidelines and

regulatory requirements from the United States (US) Code of Federal Regulations (CFR), 45 CFR Part 46.

- All study personnel with subject contact have completed Human Subjects Protection Training.

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# 1 BACKGROUND

Asthma, a chronic, inflammatory disease of the pulmonary airways, can be life-threatening if not adequately managed.<sup>1</sup> According to the US National Health Interview Survey (NHIS), in 2012, 6.8 million children <18 years (9.3%) had (current) asthma, with increased prevalence of asthma among older, compared with younger children [0-4 years (5.4%); 5-11 years (11.0%); 12-17 years (10.5%)].<sup>2</sup> Children in economically disadvantaged families were also more likely to have asthma (13%) than children in families that were not disadvantaged (8%).<sup>2</sup> Furthermore, children with asthma are more likely to require hospitalization for influenza, and to experience asthma exacerbations after influenza illness.<sup>3,4</sup> Despite this, NHIS data for the 2010-2011 influenza season revealed that influenza vaccination among children with asthma 2-17 years averaged almost 53%, up from 29% five years earlier, 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).<sup>5,6</sup> The Advisory Committee on Immunization Practices (ACIP) designates asthma to be a 'high-risk' condition for which annual vaccination with the inactivated influenza vaccine (IIV) is recommended.<sup>7</sup> In addition, due to the elevated morbidity and mortality associated with influenza virus infection (including pandemic influenza virus) in persons with asthma, the US Department of Health and Human Services' [Guidance on Allocating and Targeting Pandemic Influenza Vaccine](#) notes that children with asthma are Tier 2 priority recipients (scale of Tier 1 highest to Tier 5 lowest) for receipt of pandemic influenza vaccine.

## Studies assessing the safety of live attenuated influenza vaccine (LAIV) in children with asthma

Most studies conducted to date have suggested that LAIV is not associated with an increased risk of wheezing events after vaccination in children who are at least 2 years of age and that didn't have a prior history of asthma or wheezing (Belshe).<sup>10</sup> However, data regarding LAIV safety in persons with a history of asthma or wheeze are less clear, particularly among children with severe asthma.<sup>10-12</sup> In an effort to address this important vaccine safety data gap, and to assess the safety of LAIV in subjects with asthma, several clinical trials have been conducted over the past decade. Redding and colleagues assessed the safety and tolerability of LAIV in children > 9 years of age with moderate to severe asthma.<sup>11</sup> They enrolled 48 subjects into a randomized, double blind, placebo-controlled study and compared pre-study baseline to post-vaccination measurements of FEV1, peak flow, clinical asthma scores, and nighttime awakening scores. They found no difference in the primary outcome measure (% change in FEV1) or secondary outcomes (decrease in FEV1, reductions in peak flows, use of beta-adrenergic rescue medications, asthma exacerbations and clinical asthma symptom scores before and after vaccination) between the two groups. Bergen et al conducted a randomized, double blind, placebo-controlled safety trial in 9689 healthy children age 12 months to 17 years.<sup>13</sup> Enrolled children were followed for 42 days after each vaccination for all medically-attended events. 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.<sup>13</sup>

Given these concerns regarding the possible triggering of asthma by LAIV, Piedra and colleagues conducted an open-label, non-randomized, community-based trial of LAIV in 11,906 children 18 months to 18 years of age over a four-year period; children were followed for 42 days post-vaccination.<sup>14</sup> Investigators found no increase in asthma events during the 0 to 14 days after vaccination in children of any age group, and though they found a significantly increased risk for asthma events in children 18 months to 4 years during the 15 to

42 days after vaccination (RR 2.85; 95% CI: 1.01-8.03), during the first year (only) of the study, after final analysis of all data, the authors concluded that LAIV was safe and not associated with an increase in asthma events in children who are younger than 5 years.<sup>14</sup>

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.<sup>15</sup> 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.”<sup>15</sup>

Finally, 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.<sup>3</sup> Nearly 70% of children were on inhaled corticosteroids. No significant differences were reported between the LAIV and trivalent inactivated influenza vaccine (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. 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.<sup>3</sup>

#### ACIP recommendations for LAIV use in healthy children and children with asthma

ACIP recommendations for LAIV use in healthy children aged  $\geq 2$  years have changed in recent years. During 2007/08 through the 2013/14 influenza seasons, ACIP recommended that either live attenuated influenza vaccine (LAIV) or IIV could be used for these children.<sup>7</sup> 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.<sup>8</sup> However, following this preferred recommendation, new data emerged suggesting that LAIV did not have superior efficacy over IIV.<sup>9</sup> 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  $\geq 2$  years.<sup>9</sup>

In 2014, after completing a review of available evidence, ACIP also 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.<sup>8</sup> 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.<sup>8</sup> 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 didn't have a prior history of asthma and wheezing.<sup>10</sup> However, data regarding LAIV safety in persons with a history of asthma or wheeze were less clear.<sup>10-12</sup> 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.<sup>11</sup> There is even less information about the safety of quadrivalent LAIV (LAIV4) in persons with asthma when compared with trivalent LAIV.

Since the 2013-14 influenza season, LAIV4 has been the only live influenza vaccine product available in the United States. ACIP recommendations specified that LAIV should not be used for, “Children aged 2 through 4 years, who have asthma or who have had a wheezing episode noted in the medical record within the past 12

months, or for whom parents report that a health care provider stated that they had wheezing or asthma within the last 12 months”.<sup>8</sup> However, ACIP considered asthma in persons aged  $\geq 5$  years to be a “precaution” for the use of LAIV, leaving the vaccination decision to clinicians.<sup>9</sup> Anecdotal experiences from front-line US pediatricians suggest that deciding whether or not to vaccinate children aged  $\geq 5$  years with asthma with LAIV4 may be difficult. Broadening the LAIV recommendation to include persons with asthma could have several advantages: ease of program implementation, especially in busy clinic or school-based vaccination settings; ease of implementation and greater options for influenza pandemic preparedness; and 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.

*ACIP interim guidance regarding use of LAIV4 for the 2016-2017 influenza season following the June 2016 ACIP vote, and FDA information regarding FluMist® Quadrivalent (LAIV4) vaccine*

At the June 22, 2016 meeting, ACIP voted that “no live attenuated influenza vaccines (LAIV) should be used in any setting” during the 2016-2017 influenza season (<http://www.cdc.gov/media/releases/2016/s0622-laiv-flu.html>). This interim recommendation resulted primarily from findings from two US-based observational studies. Data from the US Influenza Vaccine Effectiveness (VE) Network and from a US-based manufacturer (MedImmune) post-marketing study demonstrated that LAIV4 had lower vaccine effectiveness in youth 2-17 years than IIV, and LAIV4 provided no statistically significant effectiveness against Influenza A (H1N1) during the 2015-2016 influenza season. According to the VE Network data, LAIV4 vaccine effectiveness against any influenza virus among children (2-17 years) was estimated at only 3 percent (95% confidence interval -49% - 37%). In comparison, IIV had a VE estimate of 63 percent (95% confidence interval: 52% - 72%) against any influenza virus among children in this same age group.

The US Food and Drug Administration (FDA) reviewed the data presented to ACIP and continues to find that the benefits of FluMist® Quadrivalent outweigh any potential risks. [FDA has stated](#) that specific regulatory action is not warranted at this time; as a result, LAIV4 remains a licensed vaccine in the United States. The FDA noted that though the CDC VE Network data did not demonstrate statistically significant effectiveness for all influenza strains combined, three other observational studies (MedImmune study; study from Finland; study from the United Kingdom) did demonstrate statistically significant effectiveness of FluMist® Quadrivalent against all influenza strains combined, ranging from 46% to 58% effectiveness. The FDA indicates that this level of overall effectiveness is considered comparable to vaccine effectiveness against vaccine-similar strains for both FluMist® and inactivated influenza vaccines in prior seasons. Reasons for discordant results among the studies, particularly between the two U.S. studies, are not clear but may include limitations inherent in observational studies. The FDA continues to work with MedImmune to understand the factors that may be contributing to the lower than expected effectiveness of FluMist® Quadrivalent.

*Clinical Immunization Safety Assessment (CISA) Project Proposed Feasibility Study with Flucelvax® Quadrivalent during 2016-2017 Influenza Season*

The Centers for Disease Control and Prevention’s Clinical Immunization Safety Assessment (CISA) planned to address a data safety gap regarding use of LAIV4 vaccine in children with asthma by conducting a 3-site randomized, non-inferiority prospective study. The main goal was to compare the safety of LAIV4 versus IIV in children 5-11 years with persistent asthma during the 2016-2017 influenza season. CDC and the CISA study sites developed a protocol and associated materials, and were poised to begin enrollment early during the 2016-2017 influenza season. However, after the June 22, 2016 ACIP vote recommending against use of

LAIV4 during the 2016-2017 influenza season, CDC and study investigators decided to defer implementing a study using LAIV4 during the 2016-2017 influenza season. Investigators will reconsider initiating this study during the 2017-2018 influenza season if ACIP votes to reinstate LAIV4 use or new data become available; ACIP makes recommendations annually.

The planned LAIV4 study had unique features in its design that previously had not been implemented in vaccine safety studies, including: 1) enrolling a substantial proportion of children with moderate-severe asthma 2) using digital peak flow meters and 3) collecting clinical data through multiple, complementary, measures for 42 days after vaccination. To capitalize on progress made during development of the study protocol and associated documents and procedures, CISA is proposing to carry out a study at the three sites to assess the feasibility of recruiting, enrolling, retaining, and collecting clinical data on children 5-11 years with persistent asthma of varied levels of severity in an influenza vaccine safety study. Findings from this proposed feasibility study will facilitate improving the LAIV4 study in the future if it goes forward through the CISA Project or in another venue. In 2016-2017 season, FDA approved a new influenza vaccine for use in persons aged 4 years and older, Flucelvax® Quadrivalent (ccIV4); ACIP incorporated this vaccine into its [recommendations for the 2016-2017 influenza season](#). Therefore ccIV4 will be used in place of LAIV4 for this feasibility study. The feasibility study also offers an opportunity to gain some additional descriptive safety data for this new vaccine in asthmatic children.

On May 23, 2016, the quadrivalent formulation of Flucelvax® Quadrivalent (ccIV4) was approved for use in persons 4 to <18 years of age under the accelerated [approval of biological products regulations](#) (21 CFR 601.40-46). Flucelvax® Quadrivalent (ccIV4) is a non-egg, cell culture-based [Madin Darby Canine Kidney cells (MDCK)], non-adjuvanted, inactivated influenza 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. According to the [package insert](#), Flucelvax® Quadrivalent is antibiotic-, preservative-, and latex-free. ACIP considers Flucelvax® an appropriate option for vaccination in persons aged 4 years and older. Federal funding was provided to develop this non-egg based cell culture technology to allow for rapid scale-up of influenza vaccination production as needed to fulfill the needs during an influenza pandemic. Flucelvax® is the only FDA-licensed formulation of a non-egg-based influenza vaccine approved for use in children and adolescents.

The safety of Flucelvax® Quadrivalent in children was evaluated in a randomized, double-blind, controlled study conducted in the US. The safety population included a total of 2332 children 4 through 17 years of age; 1161 children 4 through 8 years of age and 1171 children 9 through 17 years of age. In this study, subjects received Flucelvax® Quadrivalent or one of the two formulations of Flucelvax® (trivalent) influenza vaccine (Flucelvax® Quadrivalent n=1159, TIV1c, n=593 or TIV2c n= 580). Children 9 through 17 years of age received a single dose of Flucelvax® Quadrivalent or a trivalent Flucelvax® formulation. Children 4 through 8 years of age received one or two doses (separated by 4 weeks) of Flucelvax® Quadrivalent or a Flucelvax® trivalent formulation based on determination of the subject's prior influenza vaccination history. The mean age of subjects who received Flucelvax® Quadrivalent was 9.6 years of age. In children ≥4 through <18 years of age, for the quadrivalent formulation, the most common injection-site reaction was pain (59%) and tenderness for subjects ≥4 to <6 years of age (55%). Most of the solicited local adverse events (AEs) had their onset from 6 hours to 2 days after the vaccination and were mild to moderate in severity. The most common solicited systemic adverse events in children >4 years to < 18 years, that occurred at rates >10%



were myalgia, headache, fatigue, sleepiness and irritability. Fevers  $\geq 38.0$  °C occurred in 3% of subjects; one subject who received cclIV4 had a febrile convulsion. In children 4 through 17 years of age, serious adverse events (SAEs) were collected throughout the study duration (until 6 months after last vaccination) and were reported by 0.5%, of the subjects who received Flucelvax® Quadrivalent. None of the SAEs were assessed as being related to study vaccine.

## 2 FEASIBILITY STUDY OBJECTIVES

### 2.1 Study Objectives

#### Primary Objective

To assess the feasibility of conducting a randomized prospective safety study of LAIV4 versus IIV4 during the 42 days after vaccination in children aged 5-11 years with persistent asthma of varied severity (ccIIIV4 will be used as a surrogate for LAIV4)

#### Secondary Objectives

1. To compare proportions of local and systemic reactogenicity events during the 14 days after ccIIIV4 versus IIV4 in children with asthma aged 5-11 years.
2. To describe the unsolicited and serious adverse events in children receiving ccIIIV4 and IIV during the 42 days.
3. To compare proportions of asthma exacerbations during the 14 days after ccIIIV4 versus IIV4 in children with asthma aged 5-11 years.
4. To compare proportions of asthma exacerbations during the 42 days after ccIIIV4 versus IIV4 in children with asthma aged 5-11 years.
5. To explore differences between the ccIIIV4 and IIV4 groups regarding clinical asthma symptoms after vaccination and changes in asthma control before and after vaccination in children with asthma of varied levels of severity.

### 2.2 Study Outcome Measures

#### Primary Outcome Measure

1. Assess the feasibility of conducting a randomized prospective safety study of LAIV4 versus IIV4 during the 42 days after vaccination in children with asthma (ccIIIV4 will substitute for LAIV4 in this feasibility study).
  - a. Qualitative information about best practices and lessons learned
  - b. Quantitative Benchmarks (Table A1 Appendix)

#### Secondary outcome measures:

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)]”.<sup>17</sup> For the purpose of 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 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.

1. Proportion of subjects with solicited local and systemic reactogenicity events for 14 days after vaccination between recipients of cclIV4 and IIV4.
2. Description of nature and frequency of unsolicited and serious adverse events in children receiving cclIV4 and IIV during the 42 days after vaccination with cclIV4 and IIV4.
3. Proportions of asthma exacerbations in recipients of cclIV4 and IIV4 during the 14 days post-vaccination.
4. Proportions of asthma exacerbations in recipients of cclIV4 and IIV4 during the 42 days post-vaccination.
5. Proportions of clinical symptoms after vaccination and changes in measurement of asthma control, before and after vaccination in children with asthma of varied levels of severity, between recipients of cclIV4 or IIV4. This will be assessed through four measures (see methods for schedule):
  - A. Proportions of subjects with asthma symptoms as assessed on memory aid (e.g., wheezing, nighttime awakenings, cough) during days 1 through 15
  - B. Change in Peak Expiratory Flow Rate (PEFR) after vaccination from baseline (pre-vaccination) PEFR
  - C. Change in Childhood Asthma Control Test (cACT) scores after vaccination from baseline (pre-vaccination) cACT
  - D. Change in Pediatric Respiratory Outcome PROSE after vaccination from baseline (pre-vaccination) PROSE
  - E. Rates of medical utilization for asthma-related symptoms in recipients of cclIV4 and IIV during the 42 days post-vaccination.

### 3 ELIGIBILITY CRITERIA

#### 3.1 Inclusion Criteria

1. Children between 5-11 years of age, inclusive, at enrollment

2. Participant must have a current diagnosis of persistent asthma<sup>1</sup>

<sup>1</sup> *Physician diagnosis of asthma and current prescribed use of a daily controller medication*

3. Parent/legal guardian must provide written informed consent and subject must provide assent as appropriate for age prior to initiation of study procedures and according to local IRB requirement
4. Parent/legal guardian and subject must be willing and able to comply with planned study procedures and be available for all study visits
5. Children aged 5-8 years must have received at least 2 doses of seasonal trivalent or quadrivalent influenza vaccine prior to the current influenza season. Children 9-11 years must have received at least 1 dose of seasonal trivalent or quadrivalent influenza vaccine prior to the current influenza season.<sup>2</sup>

<sup>2</sup> *Influenza vaccination history verification Figure 2 appendix*

6. Is in good health, other than their asthma, as determined by medical history and targeted physical examination based on medical history
7. English or Spanish literate<sup>3</sup>  
<sup>3</sup> *only English speaking participants will be included at the Cincinnati site*
8. Intention of being available for entire study period and complete all relevant study procedures, including follow-up phone calls and collection of information

#### 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 (temporary deferral)
3. History of a severe allergic reaction (e.g., anaphylaxis) to any component of study influenza vaccines or a known allergy to eggs
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 licensed influenza vaccine

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. Has immunosuppression as a result of an underlying illness or treatment, or use of anticancer chemotherapy or radiation therapy within the preceding 36 months
8. Has taken  $\geq 20$ mg/day of prednisone or its equivalent, for 14 days or more within the past 28 days
9. Has known active neoplasm or a history of any hematologic malignancy
10. Has 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. History of Guillian-Barré syndrome within 6 weeks of previous influenza vaccination
12. Has 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
13. Has any diagnosis, current or past, of schizophrenia, bipolar disease, or other major psychiatric disorder
14. Currently taking aspirin or aspirin-containing products

### 3.3 Characterizing Asthma Severity

Prior to vaccination, it will be necessary to characterize asthma severity and control in each patient (see figures A1 through A3 in the appendix). This characterization will be based on the chart from the National Asthma Education and Prevention Program Expert Panel Report 3 that was issued in October 2007.<sup>17</sup> For the purposes of the study, we will only recruit subjects with persistent asthma and within the full spectrum of severity. Subjects in well-controlled and not well-controlled categories will be enrolled; subjects with very poorly controlled asthma will be discussed with the physician prior to enrollment for their assessment as to whether these subjects can be safely enrolled, based on clinical judgment.

**Table 1. Classification of Asthma Severity<sup>17</sup>**

Lowest level of treatment required to maintain control	Classification of Asthma Severity			
	Treatment of Asthma			
	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Treatment Steps (includes prn SABA use)	Step 1	Step 2 Low dose ICS	Step 3 or 4 Low to Medium dose ICS  <u>AND/OR</u> LABA or Montelukast	Step 5 or 6 High dose ICS  <u>AND/OR</u> LABA or Montelukast
Additional considerations		Immunotherapy	Immunotherapy plus Asthma specialist	

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

## 4 STUDY DESIGN AND PROCEDURES

This is a prospective randomized, open label clinical trial in approximately 50 children aged 5-11 years 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). Subjects will be randomized 1:1 to receive either a single intramuscular dose of licensed Flucelvax® Quadrivalent (cclIV4) or a single intramuscular dose of licensed Fluarix® Quadrivalent (IIV4), stratifying by asthma severity (mild vs. moderate/severe).

### 4.1 Recruitment

Subject enrollment for this feasibility study will begin during September or October 2016. Site-specific information is described below.

#### **Vanderbilt**

Vanderbilt will enroll approximately 20 participants. The Vanderbilt Pediatric Pulmonary Clinic will be the source for the majority of patients enrolled. There are additional Allergy and General Pediatric Clinics that have patients with asthma but if enrolled, these patients will be referred to the Pulmonary Clinic or to the Clinical Research Center at the Children's Hospital where enrollment will occur.

The Pediatric Pulmonary Clinic has the necessary space and infrastructure to provide support for this study. Ongoing clinical research is conducted there and the investigators can integrate research enrollment in the same area as they are providing clinical care. During the months prior to enrollment, the research staff will inquire about the study interest, will assess the ability of the families to assess clinical symptoms and to perform home respiratory testing, and will identify parental preferences for recording reaction data. Drs. Moore and Sokolow will facilitate introduction of the patients to the study staff, and the patients will be informed about the study. During August and September 2016, when recruitment and enrollment is expected to begin, Vanderbilt Vaccine Research Program (VVRP) study staff will be actively involved in recruitment. All qualifying patients for the study will be given information and contact numbers to discuss the study in the months prior to the study onset. The research team will provide follow up contact information to discuss questions or concerns.

After informed consent, Vanderbilt study staff will target subjects with moderate or severe persistent asthma for the conduct of the study, which represents the majority of patients at this Vanderbilt clinic. Using the Severity and Control tables shown in the Appendix, subjects will be graded for each of these two parameters, severity and control, and these assessments will be recorded on the Case Report Form. Lists of children with an interest in the study will have been previously compiled prior to the availability of the vaccine. If the parents agree to participation, then the subjects will be seen in the outpatient clinic areas (e.g., Pediatric Pulmonary Clinic or Pediatric Clinical Research Center) at Vanderbilt Children's Hospital.

#### **Cincinnati**

Cincinnati will enroll approximately 20 participants. The study population will be children with asthma who are patients at Cincinnati Children's Hospital Medical Center (CCHMC) with primary recruitment from the Pulmonary Asthma and Pediatric Primary Care (PPC) Clinics at CCHMC. One of the ongoing quality management goals at CCHMC is to document the level of severity for all children cared for at CCHMC with

asthma. Of those not categorized, Cincinnati will be able to categorize their asthma severity and control if they interested in the study.

If influenza vaccine (ccIIIV4 and IIV4) is available, Cincinnati would like to start enrollment in September 2016 to maximize the number of weeks for enrollment. Using local and national data, we will determine the target weeks for enrollment to ensure this high-risk group of children with asthma are vaccinated for influenza well before the influenza season starts. The target enrollment period should be as soon as both vaccines are available and should end by the last week of November allowing for approximately 12-13 weeks for enrollment.

Cincinnati will recruit approximately 20 children, 5-11 years of age, diagnosed with asthma of varying degrees of severity. The primary strategy for recruitment will be through the Pulmonary Asthma Clinic and the Pediatric Primary Care Center. Cincinnati will advertise at these two sites, as well as through the asthma registry and their database of past research participants who have agreed to be e-mailed for future studies. Any written communication provided to the potential subjects' parents/legal guardians about the study will be submitted to the IRB for their approval before study initiation. Recruitment letters introducing the study will be sent to parents of asthmatic children shortly ahead of the influenza vaccination season. To assist with recruitment, parents will then be called 2 to 3 weeks after sending the letter to screen for interest, eligibility and enrollment (September-November 2016). Recruitment will also be coordinated with well child visits and clinic visits. Recruitment will be advertised by the use of flyers posted in pediatric/allergy/and pulmonary clinics.

Interested parents may call or email the Cincinnati study line and study personnel will discuss the study by phone or email with the parent. Subjects will be screened using a phone screening tool (eligibility and brief medical history questions) from the parents. If potentially eligible and interested, an appointment will be scheduled. Parents will be informed that their decision to participate or not to participate in the study will not have any effect on their child as a patient. If parental permission is given for participation, the subjects will be seen in the Research Clinic (Schubert Center) at Cincinnati Children's Hospital Medical Center. Cincinnati will enroll approximately 20 children with persistent asthma to include approximately 50% with mild, persistent asthma and 50% with moderate to severe asthma.

## **Duke**

Duke will enroll approximately 10 children age 5-11 years with persistent asthma. Duke study staff will obtain informed consent from parents/guardians of children with persistent asthma at clinical sites affiliated with Duke University in order to enroll, randomize and vaccinate approximately 10 children (5 with moderate to severe asthma and 5 with mild asthma). Children with persistent asthma will be enrolled at Duke Allergy/Immunology and Pulmonary Clinics located at Duke Children's and WakeMed Children's Specialty Services in Raleigh, NC.

Identification of children with persistent asthma will occur from providers at the clinic and through the use of the Duke patient data portal. With permission of their health care provider, recruitment letters introducing the study may also be sent to parents of asthmatic children. To assist with recruitment, parents will then be called 10 days after sending the letter to schedule children for screening and enrollment. Recruitment will also be



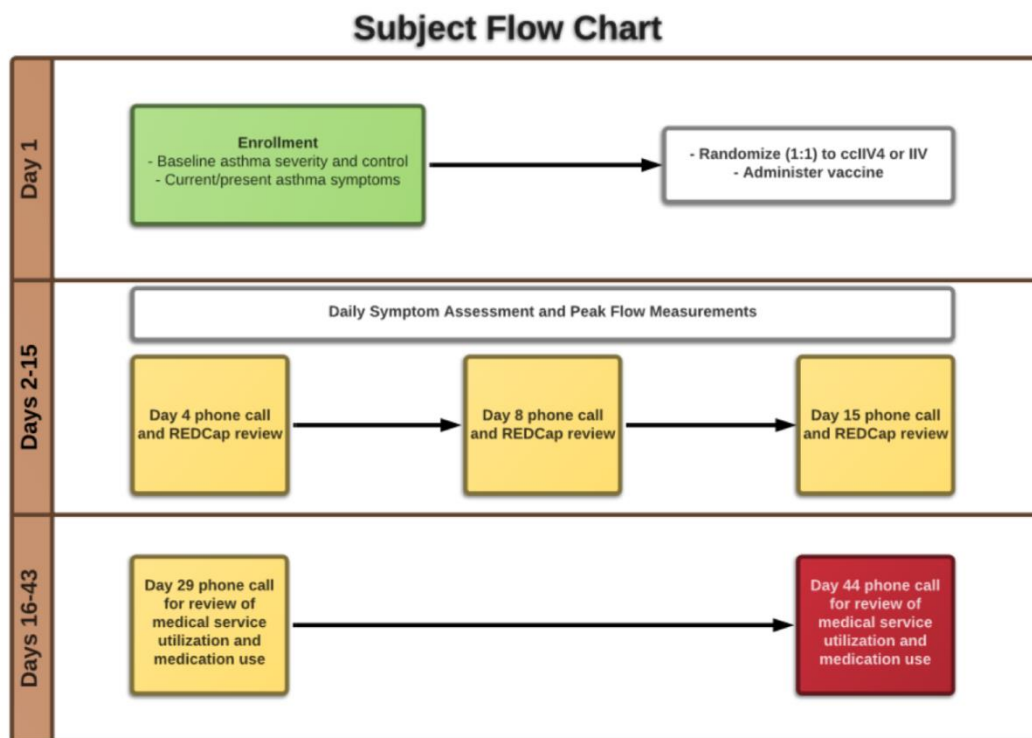
coordinated with clinic visits and or vaccination clinics. Recruitment will be advertised by the use of flyers posted in allergy/and pulmonary clinics.

At all sites, study participants will be compensated for each clinic visit (including enrollment) and for each follow-up telephone/email contact.

## 4.2 Enrollment/Randomization

In total, the study will enroll approximately 50 children between 5-11 years of age, inclusive, who have persistent asthma of varying levels of severity (~20 from Vanderbilt, ~20 from Cincinnati and ~10 from Duke). The study will aim to enroll equal proportions of participants (50%) with mild and with moderate/severe asthma.

Subjects will be randomized 1:1 to receive by intramuscular injection either a single dose of a licensed non-egg, cell culture-based, quadrivalent inactivated influenza vaccine (ccIIV4-Flucelvax® Quadrivalent) or an egg-based formulation of inactivated influenza vaccine, stratifying by asthma severity (mild vs. moderate/severe). 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/severe asthma can vary by clinics, but the targeted proportions of asthma severity at site level will be 50% for each. Therefore, overall enrollment with randomization will recruit the same proportions of asthma severity participants in each arm. Randomization will be accomplished using the REDCap System, hosted at Vanderbilt. Since this is a web-based system, it is easily accessible to the other collaborating sites as well.



### 4.3 Study Visits and Procedures

#### 4.3.1 Visit 1 (Day 1) - Enrollment and Vaccination

- Informed consent/assent will be obtained
- Medical history and medication history will be obtained, including a review of all current medications and medications taken within 28 days of enrollment.
- History of asthma and allergy disease (asthma triggers, environmental, food and other documented allergies, allergy testing results, household pets, exposure to secondhand smoke in the home or daycare or where subject spends considerable time during the day) will be captured.
- Temperature will be recorded prior to immunization; oral temperature must be  $<100.4^{\circ}\text{F}$  prior to administration of vaccine.
- Height and weight will be measured in order to calculate subject's BMI
- Eligibility criteria will be reviewed to determine if child meets criteria for study
- Asthma severity and control will be assessed
  - Clinical assessment to assess baseline asthma clinical symptoms [**Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE)** asthma symptom questionnaire]
  - Administration of the Childhood Asthma Control Test (cACT)
- Patient and parent(s)/guardian will be taught proper peak flow technique and will be provided with a 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/guardian) 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, and on day 43 after vaccination (days 1 through 15 and on day 43, respectively). (see section 4.7 below)
- The child will be randomized to the respective treatment group (ccIIV4 or IIV4) using the REDCap System. The Vaccine Information Sheet (VIS) for the respective vaccine administered will be provided to parents/guardians before the vaccine is administered. The VIS will be in the primary language of the parent/guardian consenting for the child to be enrolled in the study.
- The vaccine will be administered according to the study randomization scheme.
- 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/guardian will be given a thermometer and a ruler to use for daily temperature and local reactions recording, respectively
- Study staff will record any immediate adverse events (AEs) after vaccination occurring while still in the clinic
- Study staff will educate the family to notify the study staff if the patient requires an additional unscheduled medical visit for management of asthma symptoms (medical services utilization) or a new asthma control medication that has been prescribed.

#### 4.3.2 Visit 2 [Day 4 (-1 through +2)] – Call/email

- Memory aid review for solicited symptoms

- Unsolicited symptoms review
- Concomitant medications review
- Post-vaccination asthma clinical symptoms review and symptom scores
  - Asthma control assessment (cACT)
  - PROSE
- Medical services utilization review
- Peak flow measurements
- Parent will be instructed to contact the study staff if the child utilizes medical services, has a new asthma medication prescribed. or experiences a serious adverse event

#### **4.3.3 Visit 3 (Day 8 ± 2) – Call/email**

- Memory aid review for solicited symptoms
- Unsolicited symptoms review
- Concomitant medications review
- Post-vaccination asthma clinical symptoms review and symptom scores
  - Asthma control assessment (cACT)
  - PROSE
- Medical services utilization review
- Peak flow measurements
- Parent will be instructed to contact the study staff if the child utilizes medical services, has a new asthma medication prescribed, or experiences a serious adverse event

#### **4.3.4 Visit 4 [Day 15 (- 1 through +2)] – Call/email**

- Memory aid review for solicited symptoms
- Unsolicited symptoms review
- Concomitant medications review
- Post-vaccination asthma clinical symptoms review and symptom scores
  - Asthma control assessment (cACT)
  - PROSE
- Medical services utilization review
- Peak flow measurements
- Parent will be instructed to contact the study staff if the child utilizes medical services, has a new asthma medication prescribed, or experiences a serious adverse event

#### **4.3.5 Visit 5 (Day 29 ± 2) – Call/email**

- Concomitant medications review
- Medical services utilization review

#### **4.3.6 Visit 6 (Day 44 + 3) – Call/email**

- Concomitant medications review

- Medical services utilization review
- Post-vaccination asthma clinical symptoms review and symptom scores
  - Asthma control assessment (cACT)
  - PROSE
- Peak flow measurement
- Administer parent/guardian satisfaction survey

#### **4.4 Assignment of Severity**

After informed consent, asthma severity will be classified as previously described. Using the Severity and Control tables shown in the Appendix, subjects will be assessed for severity, and these assessments will be recorded on the Case Report Form.

#### **4.5 Baseline demographic data**

All patients enrolled in the study will have baseline demographic and clinical data available from their medical records or they will be obtained at the time of enrollment. These data will include age, gender, height and weight to determine the BMI; history of known asthma triggers, including exercise (i.e., exercise-induced bronchospasm), indoor/outdoor climate (e.g., cold, dry air; thunderstorms), allergies (environmental, food, medication, or other documented allergies); allergy testing results; other pertinent physician-diagnosed health conditions (e.g. gastroesophageal reflux disease); presence of household pets; daycare or school attendance; number of siblings/ persons in the household; and exposure to secondhand smoke in the home or other settings where the subject spends considerable time during the day. These details will be recorded in the Case Report Form for Visit 1. If these data are not available from the clinic record they will be obtained from the parents and entered into the REDCap case report form at the time of enrollment.

#### **4.6 Spirometry**

Spirometry will not be performed as a study procedure. All enrolled patients who have routine spirometry performed at baseline, as part of their clinical care, with a commercial spirometer will have that data recorded on the case report form. Recent joint statements issued by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) to standardize endpoints for clinical trials suggested that the measurement of Forced Expiratory Volume in 1 second (FEV1) in an ambulatory clinic setting provides the best objective measure of airway obstruction, which is the hallmark of asthma exacerbation. The statement also cautioned that the safety of this testing has been widely established and that reproducibility is high. Additional information regarding pulmonary health can also be obtained from the Forced Vital Capacity (FVC) and the ratio of FEV1/FVC from the spirometry data obtained in the clinic in the patients with asthma. For this study, spirometry data will be collected on all patients who have spirometry performed as standard of care (at any site) at enrollment and during any visit prompted by alterations in PEFR or home questionnaires to verify exacerbation.

#### **4.7 Individual Peak Expiratory Flow Rate (PEFR) Evaluations**

Subjects will be trained on the “at home” performance of PEFR using a hand held device purchased by study funds and that subjects will get to keep after completing the study. In addition, for all subjects who have spirometry performed at enrollment, it will be compared to the results obtained by the PEFR studies. Numerous longitudinal asthma studies have utilized the peak flow meter device to monitor control between study visits. The device is inexpensive, its use is easily learned, and it can provide an objective measure of

control of asthma symptoms. While PEFR testing with a peak flow meter is inferior to the determination of FEV1 by spirometry as a measure of airway obstruction, it can be very helpful and additive to home questionnaires in monitoring control. Typically, a subject'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 asthma surveys to avoid bias in the recording of daily symptoms. All efforts will be made to minimize variation in technique; training in proper peak flow meter use will be accomplished at study enrollment and reviewed/reinforced at each study visit.

For this study, all sites will provide participants with the same model of a digital peak flow meter. This device has an automatic memory of 240 data entries with a time stamp; thus, participants will be instructed to record their daily PEFR data measurements on their memory aid/REDCap until day 15 and again at day 43. The device can also be connected to a computer, and the values can be analyzed by using the Microlife Asthma analyzer software program.<sup>18,19</sup>

#### 4.8 Vaccine Delivery

Only US-licensed vaccines will be used in this study. The vaccines will be purchased from the study site pharmacies and will be administered by a vaccinator. Because ccIIIV4 is quadrivalent, using quadrivalent IIV (IIV4) in the comparison group will be used. Preferably, all three sites will use the same vaccines, although if this is not possible, similar products will be chosen. The details from the package inserts of the two proposed vaccines are shown below.

##### **Flucelvax® Quadrivalent**

Flucelvax® 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. In the United States, Flucelvax® Quadrivalent is antibiotic-, preservative-, and latex-free. Flucelvax® is the only FDA-licensed formulation of non-egg, cell culture-based inactivated influenza vaccine (ccIIIV) [approved for use in children and adolescents](#). The quadrivalent formulation of Flucelvax® (ccIIIV4) was approved for use in persons 4 years of age and older on May 23, 2016. Studies in children 4-17 years demonstrated non-inferior immunogenicity and comparable safety when compared to the Flucelvax® (trivalent) vaccine preparation. Data demonstrating a decrease in influenza disease after vaccination of this age group with Flucelvax® Quadrivalent are not available. Clinical benefit of Flucelvax® Quadrivalent for individuals 4 to <18 years of age is inferred from immunogenicity as a surrogate. It is our intention that half of the feasibility study subjects at the three CISA-contracted study sites will be randomized to receive Flucelvax® Quadrivalent vaccine.

##### **FLUARIX® Quadrivalent (Influenza Vaccine) Suspension for Intramuscular Injection**

FLUARIX® Quadrivalent is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLUARIX® Quadrivalent is approved for use in persons 3 years of age and older for intramuscular injection only.

There are multiple brands of inactivated influenza vaccine licensed and recommended for use in children aged 5-11 years, and ACIP does not state a preference. For consistency, Fluarix® Quadrivalent inactivated

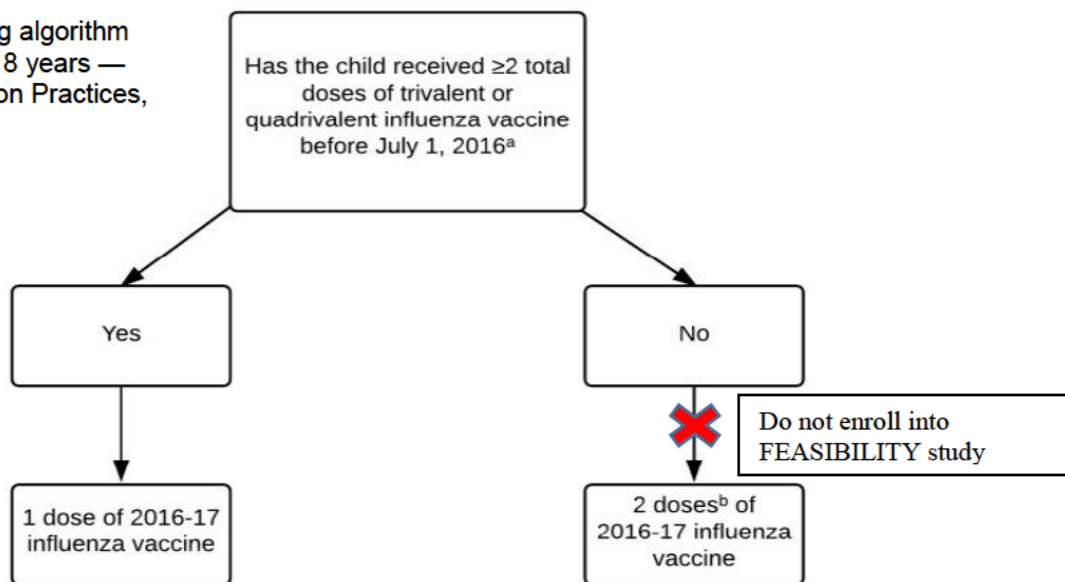
influenza vaccine (IIV4) will be the preferred brand and formulation of seasonal inactivated influenza vaccine administered to enrolled subjects at all three study centers. However, if for some unforeseen reason Fluarix® Quadrivalent is not available at all study sites, the study site may use any formulation of IIV4 that is indicated for use in the study age-group. If a site needs to use an alternative IIV formulation then that site shall use the same formulation until Fluarix® Quadrivalent vaccine becomes available again, to the extent feasible.

### Seasonal Influenza Vaccine Dose 2 considerations for Subjects aged 5-8 years

As stated above, children with persistent asthma aged 5 through 11 years, who have not already received a seasonal influenza vaccine during the 2016-17 influenza season, will be enrolled into this study. The ACIP recommends that children aged 6 months through 8 years receive 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 fall influenza season (For purposes of this study, July 1, 2016 would be used as the cutoff date for the 2016-2017 influenza season). The two doses need not to have been received during the same season or consecutive seasons. See Fig 1, modified from *Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2015-2016 Influenza Season*.<sup>9</sup>

Among subjects 5 through 8 years otherwise eligible for enrollment into this study, Vanderbilt, Cincinnati, and Duke will assess during the pre-enrollment process whether one or two doses of seasonal influenza vaccine is recommended for each of these potential study subjects. For the 2016-2017 feasibility, the study sites will enroll children with persistent asthma that have received at least 2 doses of seasonal influenza vaccine during prior influenza season(s), such that only one dose of seasonal influenza vaccine is recommended for

**FIGURE 2.** Influenza vaccine dosing algorithm for children aged 6 months through 8 years — Advisory Committee on Immunization Practices, United States.



<sup>a</sup>The two doses need not have been received during the same season or consecutive seasons.

<sup>b</sup>Doses should be administered ≥4 weeks apart.

the 2016-2017 influenza season. The quadrivalent seasonal inactivated influenza vaccine will be administered at baseline (Day 1 of study) according to the study randomization scheme.

#### **4.9 Monitoring Vaccine Safety in the First 15 Days**

On the vaccination day and for the next 14 days post-vaccination, all subjects will be monitored daily by their parents and the information will be recorded using memory aids provided at the enrollment visit. Daily reactogenicity, including measurement of nighttime awakening, and two asthma scoring systems will be completed (cACT score and the PROSE score).

In addition to the two symptom scores above, several predefined events that could occur after vaccine administration will also be recorded for 14 days after vaccination. These will include; fever (oral temperature  $\geq 100.4^{\circ}\text{F}$ ), runny nose/ nasal congestion, sore throat, cough, wheeze, vomiting, change in activity level, appetite change, irritability, abdominal pain/stomachache, headache, chills, and muscle aches. Local reactions after the intramuscular vaccination will also be captured and include: redness, swelling, and/or pain around the injection site. 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 or emailed through REDCap on Days 4, 8 and 15 by the study staff.

On the day of vaccination and during the first 14 days after vaccination, if the subject 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 applicable. 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 PCP and inform study staff of this encounter.

#### **4.10 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. This will be accomplished by a telephone call or email through the REDCap system to the parents of the subjects, depending on their preference and their availability, at day 29 and at day 44 to determine the status of asthma control. On Day 29, subjects will be queried about concomitant medications and medical services utilization. On day 44, subjects will be queried about concomitant medications and medical services utilization, as defined above. The cACT score and PROSE score will also be completed at day 44.

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 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 after vaccination and will include events that result in death, were life threatening, result in subject 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 subject and require medical or surgical intervention to prevent one of the outcomes listed above.

## 5 RISKS

### 5.1 Vaccines

All participants will receive the CDC VIS 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.

### 5.2 Inactivated Influenza Vaccine (IIV)

ACIP routinely recommends IIV for children with asthma<sup>7-9</sup> and risks after IIV would 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 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 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. This happens very rarely.

## 6 REPORTING OF ADVERSE EVENTS

SAE and AE reporting will occur consistent with routine practice. Vaccine-associated SAEs will be medically attended per standard procedures, and reported to the Vaccine Adverse Event Reporting System (VAERS) in accordance with standard procedures, and information about such events will be included in the study data (<https://VAERS.hhs.gov>). SAEs will be reported promptly to the overseeing IRBs in accordance with institutional procedures. Any unanticipated problems resulting from study conduct related to participation will be promptly reported to the reviewing IRBs including the CDC, in accordance with institutional procedures.

An 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/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 subject and require medical or surgical intervention to prevent one of the outcomes listed above. These will be reported to the IRBs.

Participants who report severe solicited AEs or SAEs or express any concern about symptoms/unsolicited events will be encouraged to follow up with their pediatrician or primary care provider. Study staff will assist with coordination of referral appointments as necessary.

## **7 STUDY WITHDRAWAL/DISCONTINUATION**

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

A subject 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 subject, or would interfere with the subject'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.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of this study.
- New information becomes available that makes further participation unsafe.

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

### **7.1 Handling of Withdrawals**

Subjects who withdraw from the study before receiving vaccine will be replaced. Subjects who withdraw from the study after receiving vaccine 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. All SAE's and AE's that require VAERS reporting will be followed to adequate resolution or until considered stable.

### **7.2 Termination of Study**

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

## 8 Statistical Analytic Plan

This study aims to enroll approximately 50 participants (~20 from Vanderbilt, ~20 from Cincinnati and ~10 from Duke). Since sample-sizes were predetermined and since this is a feasibility study, no power calculations were conducted. All analyses will be performed using R 3.2.3 (r-project.org), SAS version 9.4, or STATA version 14.

### Feasibility Analysis

The proportion of children meeting the outlined feasibility benchmarks (Appendix, Table A1) will be determined.

### Descriptive Statistics

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 cclIV4 and IIV4 groups will be conducted using Pearson Chi-square and Wilcoxon tests appropriately.

### Primary Objective

To assess the feasibility of conducting a randomized prospective safety study of LAIV4 versus IIV4 during the 42 days after vaccination in children aged 5-11 years with persistent asthma of varied severity (cclIV4 will be used as a surrogate for LAIV4)

### Primary Outcomes Measures

1. Assess the proportions of those achieving Feasibility Benchmarks (Table A1 Appendix)
2. Qualitatively describe best practices and lessons learned

### Secondary Objectives

1. To compare proportions of local and systemic reactogenicity events during the 14 days after cclIV4 versus IIV4 in children with asthma aged 5-11 years.
2. To describe the unsolicited and serious adverse events in children receiving cclIV4 and IIV4 during the 42 days.
3. To compare proportions of asthma exacerbations during the 14 days after cclIV4 versus IIV4 in children with asthma aged 5-11 years.
4. To compare proportions of asthma exacerbations during the 42 days after cclIV4 versus IIV4 in children with asthma aged 5-11 years.
5. To explore differences between the cclIV4 and IIV4 groups regarding clinical asthma symptoms after vaccination and changes in asthma control before and after vaccination in children with asthma of varied levels of severity.

**Secondary outcome measures**

1. Proportion of subjects with solicited local and systemic reactogenicity events for 14 days after vaccination between recipients of cclIV4 and IIV4.
2. The nature and frequency of the unsolicited and serious adverse events will be described in children receiving cclIV4 and IIV4 during the 42 days.
3. Proportions of asthma exacerbations in recipients of cclIV4 and IIV4 during the 14 days post-vaccination (until day 15). The asthma exacerbation proportion within 14 days post-vaccination will be calculated for children receiving cclIV4 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 1-15 would be considered to have had an asthma exacerbation (dichotomous yes or no). We will compare proportions in children receiving cclIV4 vs. IIV4.
4. Proportions of asthma exacerbations in recipients of cclIV4 and IIV4 during the 42 days post-vaccination (until day 43). The asthma exacerbation proportion within 42 days post-vaccination will be calculated for children receiving cclIV4 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 will compare proportions in children receiving cclIV4 vs. IIV4.
5. Proportions of clinical symptoms after vaccination and changes in measurement of asthma control, before and after vaccination in children with asthma of varied levels of severity, between recipients of cclIV4 or IIV4 will be assessed through five measures (see methods for schedule):
  - A. Proportions of subjects with asthma symptoms as assessed on memory aid (e.g., wheezing, nighttime awakenings, cough) during days 1 through 15.  
Proportions of subjects with each asthma symptom (dichotomous yes or no) by treatment group, and asthma severity level will be calculated and a 95% confidence interval of the difference in proportions between the treatment groups will also be presented.
  - B. Change in Peak Expiratory Flow Rate (PEFR) after vaccination from baseline (pre-vaccination) PEFR.

Peak Expiratory Flow Rate (PEFR) evaluations are recorded once every day starting on day 1 (baseline) through day 15; PEFR measurement will also be performed on day 43. Proportion of subjects with clinically important change of  $\geq 20\%$  decrease in PEFR (dichotomous yes or no) will be calculated at baseline (day 1), during days 2 through 15 (observed  $\geq 20\%$  decrease on one or more days) and on day 43. Comparisons of proportions between days 2 through 15 or day 43 with baseline will be conducted between the two treatment groups and 95% CIs of such proportion differences will be presented. Comparisons of mean/median between each day after vaccination with baseline will also be conducted between the two treatment groups and 95%CIs of such differences will be presented.

Each subject will have repeated PEFR measurements (baseline, once a day for days 1-15 and once on the last study day 43), which naturally provides a longitudinal data set. We plan to explore the change in PEFR after vaccination for up to 43 days between cclIV4 and IIV4 groups through a full likelihood longitudinal analysis such as a mixed effects model. We may adjust for covariates listed below while accommodating multiple random subject effects. We may apply restricted cubic splines for some continuous covariates to relax the linearity

assumption. Estimates of average treatment effects along with 95%CIs will be reported for day 15 and day 43.

C. Change in Childhood Asthma Control Test (cACT) scores after vaccination from baseline (pre-vaccination) cACT

The cACT scores are recorded at baseline, days 4, 8, 15 and 43; lower scores indicate poorer asthma control for the interval. Proportions of subjects with cACT scores <20 (dichotomous yes or no) will be calculated at baseline (day 1), on days 4, 8, 15, and 43. Comparisons of proportions between days 4, 8, 15 or day 43 with baseline will be conducted between the two treatment groups and 95%CIs of such proportion differences will be presented. Comparisons of mean/median between day 4, 8, 15, or 43 with baseline will also be conducted between the two treatment groups and 95%CIs of such differences will be presented.

Similar full likelihood longitudinal analysis (stated in 8.2.4, 2, B) may be conducted using cACT measurements as the outcome.

D. Change in Pediatric Respiratory Outcome PROSE after vaccination from baseline (pre-vaccination) PROSE

The PROSE score are recorded at baseline, days 4, 8, 15 and 43. Comparisons of mean/median between day 4, 8, 15, or 43 with baseline will be conducted between the two treatment groups and 95%CIs of such differences will be presented.

Similar full likelihood longitudinal analysis (stated in 8.2.4, 2, B) may be conducted using PROSE measurements as the outcome.

E. Rates of medical utilization for asthma-related symptoms in recipients of cclIV4 and IIV4 during the 42 days post-vaccination (until day 43).

The rate of medical utilization for asthma-related symptoms is defined as the number of unscheduled medical visits divided by the length of follow-up time in days. We will report rate differences between the two treatment groups at day 15 and day 43 along with 95%CIs.

Covariates of interest are based on previous studies and epidemiological plausibility. The covariates listed below are for model consideration though they are not limited.

Main exposure: treatment group

Baseline measurement: PEFr, cACT, PROSE, asthma severity level such as severity status (mild, moderate or severe), control status (well-controlled or not well-controlled), and age, gender, race, daytime and nighttime asthma scores, nighttime awakening, BMI/BMI percentile

Other covariates may include days from immunization, community pollen levels near to the time of cclIV4 or IIV4 vaccination, exposure to second-hand smoke, and the frequency of smog alert/ozone alert days over the study interval in the communities where the children reside.

## **9 PRIVACY/CONFIDENTIALITY ISSUES**

Subject confidentiality is strictly held in trust by the site principal investigators, other study personnel, the sponsor, and their agents. Subjects 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 subject'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 subject; or (4) study results which may be published. If a written contract for the conduct of this study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

## 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 for at least 2 years after study completion, but potentially longer based on local institutional requirements.

### 10.1 Data collection and management

The amount of data that will be collected for the proposed feasibility study will be limited in quantity, but a large, multisite study based on this feasibility study would be substantial and would 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 reaction forms, and short customized questionnaires to collect information from study subjects. This system will be used by Vanderbilt, Cincinnati and Duke for data management. All electronic linkages will fulfill regulations for protection of human subjects and requirements to minimize the risk of breach of confidentiality. After initial set-up, the work load required for electronic data collection will be substantially reduced (description of REDCap resources below).<sup>22</sup> The Vanderbilt, Cincinnati and Duke investigators have previously used the REDCAP system for collection and analysis of large quantities of data. Participants' parents/guardians will be given the option to fill out their reactogenicity diary either directly in the REDCap system or on paper. Participants who choose the paper form will receive a phone call on day 3-6, 7-9, 14-17, 27-31, and 44-47 post-vaccination to collect the information recorded on their memory aid, which will then be entered by study personnel onto REDCap. All study-related documents containing protected health information, e.g. enrollment logs, case report forms, memory aids completed by study participants, will be maintained in secure research offices at Vanderbilt, Cincinnati and Duke, respectively, which are accessible to research staff only.

#### **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.<sup>22</sup> REDCap was designed around the concept of giving research teams an easy method to specify project needs and rapidly develop secure, web-based applications for collection, management and sharing of research data. REDCap accomplishes these key functions through use of a single study metadata table referenced by presentation-level operational modules. Based on this abstracted programming model, databases are developed in an efficient manner with little resource investment beyond the creation of a single data dictionary. The concept of metadata-driven application development is well established, and the critical factor for successful data collection lies in creating a simple workflow methodology allowing research teams to autonomously develop study-related metadata in an efficient manner. Of particular interest for this project, a subcomponent of REDCap, the REDCap Survey is designed for studies where data are collected directly from the research participant. This will be used with the web-based reaction forms that will be completed by the study subjects' parents/guardians. Both products include secure institutional data hosting and include 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, sample collection date, and laboratory results in an automated database family, to perform data cleaning and data quality assurance efficiently, and to design an analytical dataset for the analysis of the project data.

### **Double data entry**

Double data entry for each record is a means of ensuring quality data collection by later comparing the records. We will create two identical REDCap databases to store our data, each site can designate two data entry persons to enter each database. Or if there is only one data entry person, then at least 7 days lagging time between entering same participants' info into these two databases will be required to reduce/remove memory residual, in other words, same participants' info can't be entered into both databases within 7 days. For example, participants 1-10 and 11-20 can be entered into database 1 and 2 this week respectively, and next week they can be switched and entered into the other database respectively. From previous experience, seven days waiting period is long enough to minimize memory residual effect.

Both the leading site and the collaborating sites will use REDCap to collect subjects' information and all sites will do double data entry. CDC can use REDCap as a means of monitoring the study. Data will be entered into REDCap in a timely manner by experienced data entry personnel. Periodic data enrollment audits will be conducted through the recruitment period to ensure that we are not missing appropriate children and help monitor study progress. Comparisons of double data entry will be conducted and a list of discrepancies between two databases will be generated for each site on a regular basis.

### **Data cleaning and data quality assurance**

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

### **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 (Kathryn Edwards and Andrew Sokolow) will oversee the overall study and direct activities at Vanderbilt University. Duke University (Emmanuel (Chip) Walter and Amy Stallings) will contribute subjects and direct activities at Duke, and Mary Staat and Carolyn Kercksmar will contribute subjects and direct activities at Cincinnati. CDC personnel will collaborate with both 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/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 subjects into this trial, the approved protocol and informed consent form will be reviewed and approved by the appropriate IRB.

### 11.3 Informed Consent Process

#### Informed Consent

The site principal investigator will choose subjects in accordance with the eligibility criteria detailed in Section 3. Before any study procedures are performed, subjects must sign an informed consent form that complies 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, subjects' parent(s)/legal guardian(s) will receive a comprehensive explanation of the proposed study procedures and study interventions/products, 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. Subjects' parent(s)/legal guardian(s) will also receive a detailed explanation of the proposed use and disclosure of their protected health information. Subjects' parent(s)/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.

Informed consent forms describing in detail the study interventions/products, study procedures, risks and possible benefits are given to subjects. Informed consent forms will be IRB-approved and subjects 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 subjects and their parent(s)/legal guardian(s) and answer any questions that may arise. The subject's parent(s)/legal guardian(s) must sign the informed consent form, and written documentation of the informed consent process is required prior to starting any study procedures/interventions being done specifically for the trial, including administering study product. Subjects will be given a copy of all informed consent forms that they sign.



By signing the informed consent form, parents/guardians give permission on behalf of their children and agree to complete all evaluations required by the trial, unless the subject withdraws voluntarily, or is withdrawn or terminated from the trial for any reason.

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

**Informed Consent/Assent Process**

Assent will be obtained from all children following local IRB policies and standard practices for obtaining and documenting assent.

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## APPENDIX

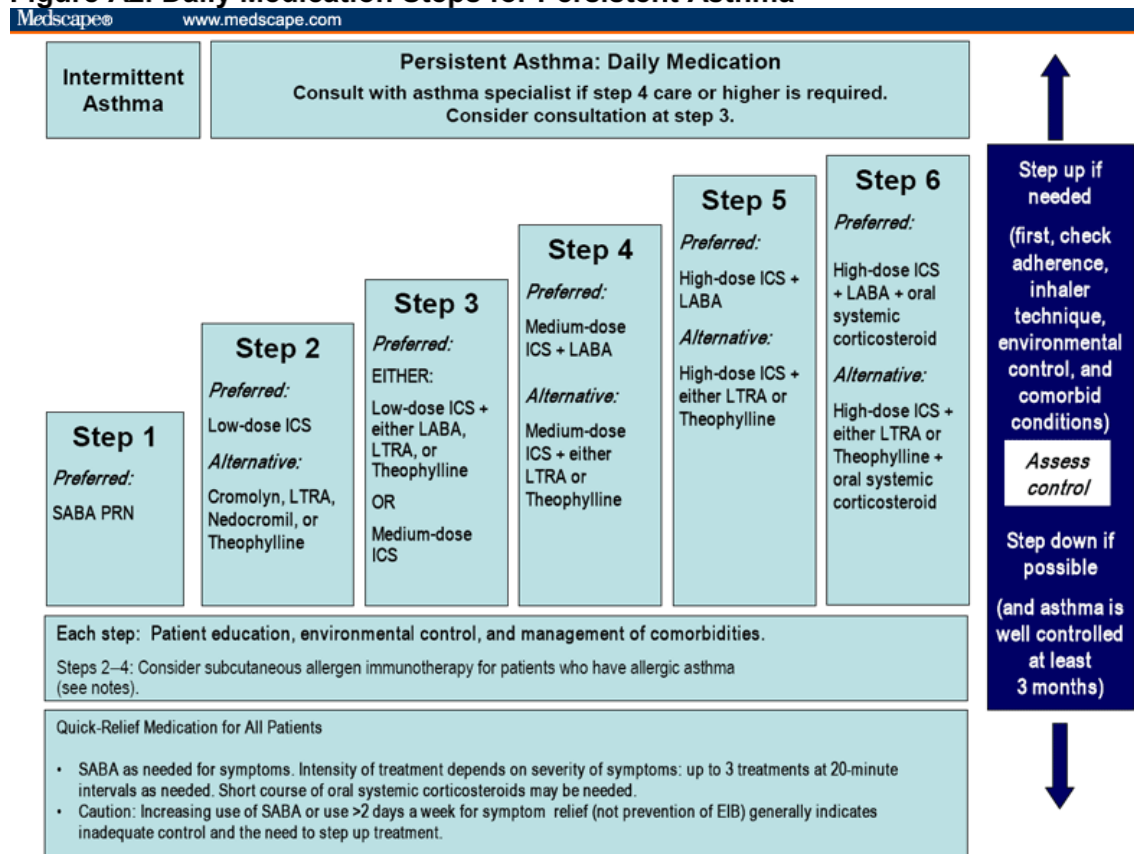
Figure A1. Asthma Control Chart for Children 5-11 years of age<sup>17</sup>

# Asthma Control Chart

FIGURE 3-5b. ASSESSING ASTHMA CONTROL IN CHILDREN 5–11 YEARS OF AGE

Components of Control		Classification of Asthma Control (Children 5–11 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function			
	• FEV <sub>1</sub> or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	• FEV <sub>1</sub> /FVC	>80%	75–80%	<75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term followup.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

Key: EIB, exercise-induced bronchospasm; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

**Figure A2. Daily Medication Steps for Persistent Asthma<sup>17</sup>**

**Key:** Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta<sub>2</sub>-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta<sub>2</sub>-agonist

#### Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

Figure A3. Estimated Comparative Daily Dosages for Inhaled Corticosteroids<sup>23</sup>

## 4.9 Estimated Comparative Daily Dosages for Inhaled Corticosteroids

FIGURE 18. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS									
Drug	Low Daily Dose			Medium Daily Dose			High Daily Dose		
	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults	Child 0–4 Years of Age	Child 5–11 Years of Age	≥12 Years of Age and Adults
<b>Beclomethasone HFA</b> 40 or 80 mcg/puff	NA	80–160 mcg	80–240 mcg	NA	>160–320 mcg	>240–480 mcg	NA	>320 mcg	>480 mcg
<b>Budesonide DPI</b> 90, 180, or 200 mcg/inhalation	NA	180–400 mcg	180–600 mcg	NA	>400–800 mcg	>600–1,200 mcg	NA	>800 mcg	>1,200 mcg
<b>Budesonide Inhaled</b> Inhalation suspension for nebulization	0.25–0.5 mg	0.5 mg	NA	>0.5–1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
<b>Flunisolide</b> 250 mcg/puff	NA	500–750 mcg	500–1,000 mcg	NA	1,000–1,250 mcg	>1,000–2,000 mcg	NA	>1,250 mcg	>2,000 mcg
<b>Flunisolide HFA</b> 80 mcg/puff	NA	160 mcg	320 mcg	NA	320 mcg	>320–640 mcg	NA	≥640 mcg	>640 mcg
<b>Fluticasone HFA/MDI:</b> 44, 110, or 220 mcg/puff	176 mcg	88–176 mcg	88–264 mcg	>176–352 mcg	>176–352 mcg	>264–440 mcg	>352 mcg	>352 mcg	>440 mcg
<b>DPI:</b> 50, 100, or 250 mcg/inhalation	NA	100–200 mcg	100–300 mcg	NA	>200–400 mcg	>300–500 mcg	NA	>400 mcg	>500 mcg
<b>Mometasone DPI</b> 200 mcg/inhalation	NA	NA	200 mcg	NA	NA	400 mcg	NA	NA	>400 mcg
<b>Triamcinolone acetonide</b> 75 mcg/puff	NA	300–600 mcg	300–750 mcg	NA	>600–900 mcg	>750–1,500 mcg	NA	>900 mcg	>1,500 mcg

Key: DPI, dry power inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group)

**Therapeutic Issues:**

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. Once control of asthma is achieved, the dose should be carefully titrated to the minimum dose required to maintain control.
- Preparations are not interchangeable on a mcg or per puff basis. This figure presents estimated comparable daily doses. See EPR—3 Full Report 2007 for full discussion.
- Some doses may be outside package labeling, especially in the high-dose range. Budesonide nebulizer suspension is the only inhaled corticosteroid (ICS) with FDA-approved labeling for children <4 years of age.
- For children <4 years of age: The safety and efficacy of ICSs in children <1 year has not been established. Children <4 years of age generally require delivery of ICS (budesonide and fluticasone HFA) through a face mask that should fit snugly over nose and mouth and avoid nebulizing in the eyes. Wash face after each treatment to prevent local corticosteroid side effects. For budesonide, the dose may be administered 1–3 times daily. Budesonide suspension is compatible with albuterol, ipratropium, and levalbuterol nebulizer solutions in the same nebulizer. Use only jet nebulizers, as ultrasonic nebulizers are ineffective for suspensions. For fluticasone HFA, the dose should be divided 2 times daily; the low dose for children <4 years of age is higher than for children 5–11 years of age due to lower dose delivered with face mask and data on efficacy in young children.

**Potential Adverse Effects of Inhaled Corticosteroids:**

- Cough, dysphonia, oral thrush (candidiasis).
- Spacer or valved holding chamber with non-breath-actuated MDIs and mouthwashing and spitting after inhalation decrease local side effects.
- A number of the ICSs, including fluticasone, budesonide, and mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported.
- In high doses, systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising). In low-to-medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established.

**Table A1. Feasibility Benchmarks**

Item	Goal
Enrollment	70% of those who are approached and eligible provide consent and are enrolled in the study
Reason for non-enrollment	90% of those approached and eligible who decline to enroll will be asked for reason for refusal
Education provided at first visit is understandable	Before leaving the clinic, all parents or guardians will demonstrate: <ul style="list-style-type: none"> <li>• proper use and care of the digital peak flow meter</li> <li>• proper use and care of oral digital thermometer</li> <li>• proper use of study ruler to assess erythema and induration</li> <li>• proper use of paper and/or electronic data entry forms</li> </ul>
Memory Aid Data Completion through Day 15	At least 80% of the patients will complete the memory aid for 11 of the 15 day monitoring period
Memory Aid Data Completion Day 16 through day 43	At least 70% of the patients will complete the memory aids for Day 16 through 43
Peak Flow measurements (early study)	At least 75% of subjects will perform and document all home digital peak flow measurements (per protocol) for on at least 11 of the 15 day monitoring period.
Peak flow measurement (late study)	At least 70% of subjects will perform and document the digital peak flow for Day 42.
Nighttime awakenings (done in am)	At least 70% of subjects will document nighttime awakenings for at for on at least 11 of the 15-day monitoring period.
Day 4 (-1 to +2) call	At least 80% of study subjects will respond to Day 4 call and provide requested data (ACT and Prose are administered on the call)
Day 8 ( $\pm 2$ ) call	At least 80% of study subjects will respond to Day 8 call and provide requested data. (ACT and Prose are administered on the call)
Day 15 (-1 to +2) call	At least 80% of study subjects will respond to Day 15 call and provide requested data. (ACT and Prose are administered on the call)
Day 29 ( $\pm 2$ ) call	At least 70% of study subjects will respond to Day 29 call and provide requested data.
Day 44 (+3) call	At least 70% of study subjects will respond to Day 44 call and provide requested data. (ACT and Prose are administered on the call)
Parental Satisfaction survey	At least 70% of parents will complete the Parent/Guardian satisfaction survey



## Schedule of Events

Table A2.

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	7-9	14-17	27-31	44-47
Type of Visit	Clinic	Call/email	Call/email/clinic <sup>a</sup>	Call/email	Call/email	Call/email
Obtain Informed Consent	X					
Obtain Assent (if applicable per site's IRB requirement)	X					
Review Eligibility Criteria	X					
Document Prior Year Flu Vaccination	X					
Review Medical History	X					
Review Asthma History	X					
Assess asthma clinical symptoms <sup>b</sup> (PROSE)	X	X	X	X		X
Assess asthma control <sup>c</sup> (cACT)	X	X	X	X		X
Asthma severity classification <sup>d</sup>	X					
Concomitant Medications <sup>e</sup>	X	X	X	X	X	X
Oral temperature	X					
Height, Weight, BMI	X					
Peak Flow Measurement <sup>f</sup>	X	X	X	X		X
Document zip code	X					
Enrollment/Randomization <sup>g</sup>	X					
Study Vaccination	X					
Post vaccination evaluation period (20 minutes)	X					
Distribute Memory Aid/ Materials	X					
AE collection/Memory Aid Review	X	X	X	X		
SAE/Medical Services Utilization <sup>h</sup>	X	X	X	X	X	X
Parent/guardian satisfaction survey						X

<sup>b</sup> Asthma clinical symptoms assessed using the PROSE questionnaire.<sup>c</sup> Asthma control assessed using the "Childhood Asthma Control Test (cACT)."<sup>d</sup> See section 3.3 in the protocol, for categories of asthma severity.<sup>e</sup> All current medications taken within 28 days prior to signing the informed consent form and through Day 43 (Visit 6).<sup>f</sup> The highest of 3 peak flow measurements will be recorded.<sup>g</sup> Subjects will be randomized 1:1 to cclIV4 or IIV4; stratified by two groups of disease severity: 1) mild persistent or 2) moderate or severe persistent.<sup>h</sup> Medical services utilization to include visits to doctor, urgent care, emergency room, hospitalization.