STep-up Yellow Zone **I**nhaled **C**orticosteroid**S** to Prevent Exacerbations

(**STICS**)

Protocol Working Group:

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On behalf of the AsthmaNet Steering Committee

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TABLE OF CONTENTS

Abbreviations

Abbreviation	Term
ACRN	Asthma Clinical Research Network
AE	adverse event
AIMS	Acute Intermittent Management Strategies
BADGER	Best ADd on therapy Giving Effective Responses
BASALT	Best Adjustment Strategy for Asthma in the Long Term
CARE	Childhood Asthma Research and Education network
c-ACT	Childhood Asthma Control Test
DCC	data coordinating center
EPR	Expert Panel Report
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
ICAC	Inner City Asthma Consortium
ICF	informed consent form
ICS	inhaled corticosteroid
IMPACT	IMProving Asthma Control Trial
IOS	Impulse oscillometry
LABA	long acting beta agonist
MCG	microgram
MIST	Maintenance and Intermittent inhaled corticoSteroids in wheezing Toddlers
NAEPP	National Asthma Education and Prevention Program
NIH	National Institutes of Health
NHLBI	National Heart, Lung, and Blood Institute
PACT	Pediatric Asthma Controller Trial
PEFR	Peak Expiratory Flow Rate
PRO	patient reported outcome
PFT	pulmonary function test
SABA	short acting beta agonist
SAE	serious adverse event
TREXA	Treating EXacerbations of Asthma

PROTOCOL SUMMARY:

The objective of this study is to determine whether, in children receiving low-dose ICS, quintupling the dose of inhaled corticosteroids in the “yellow zone” based upon a symptom-based action plan reduces the rate of severe asthma exacerbations treated with oral corticosteroids. The study design is a double-blind, parallel-group trial, including a total of 250 participants, ages 5-11 years, who meet NAEPP criteria for step 2 asthma treatment and have a history of at least 1 asthma exacerbation treated with oral corticosteroids in the prior year. Participants will undergo a 4-week run-in on low-dose ICS to assess adherence and adequate control (c-ACT>19). After randomization, participants will be treated for 48 weeks with open-label fluticasone 44 mcg 2 puffs twice daily. During the 48-week treatment period, participants will receive blinded therapy for 7 days each time they enter the “yellow zone”. Yellow zone therapy will be fluticasone 44 or 220 mcg 2 puffs twice daily.

The primary outcome is the rate of asthma exacerbations treated with oral corticosteroids.

The estimated total study duration is approximately 24 months, which includes a 12-month recruitment/enrollment period for the 9 centers and associated participating sites, and a one-year study period (4-week run-in plus 48-week treatment period).

I. BACKGROUND

Asthma exacerbations are a major cause of morbidity in children with asthma and current therapeutic strategies are only of limited efficacy in exacerbation prevention. The NHLBI EPR-3 guidelines recommend that patients be provided with a written asthma action plan for home management. However, there is limited evidence to guide clinicians in the selection and implementation of "yellow zone" strategies within these guideline recommendations that are of proven benefit in exacerbation prevention (*i.e.* preventing the patient from entering into the "red zone")(1). While frequently utilized in clinical practice, doubling the dose of ICS has not been shown to reduce prednisone-requiring exacerbations(1). Quadrupling the dose has demonstrated potential efficacy in adult patients, but this step-up short term intervention strategy(2) has not been studied in children(3). *This protocol is designed to determine whether step-up short-term ICS as a "yellow zone" strategy can prevent severe asthma exacerbations in children. It will address a critical gap in guideline-based care of children with asthma.*

A. ASTHMA POPULATION

EPR-3 divides asthma assessment and treatment recommendations into 3 age groups: 0-4 years, 5-11 years, and 12 year and above. Children in the 0-4 year age group most often have episodic disease triggered by viral respiratory tract illnesses and tend to be completely well between episodes(4). During the early school years (5-11 years), children tend to develop more persistent asthma symptoms, but asthma exacerbations remain a critical component of disease. Data from the Childhood Asthma Management Program (CAMP) clearly highlight that exacerbation frequency is much greater in this age group than in individuals 12 years and above(5). In addition to the significant morbidity and cost associated with exacerbations of asthma, there is growing evidence that exacerbations may lead to progressive loss of lung function(6, 7).

Low-dose ICS monotherapy and low-dose ICS + LABA combination therapy have been shown to reduce exacerbations and improve asthma control in children in this age group; however, many children have exacerbations despite these therapies (8-10). Currently, the best predictor identified for the development of subsequent exacerbations is a prior history of exacerbations, and indeed, the rate of exacerbations in the PACT(9) and BADGER(10) trials in children with a history of exacerbations at study entry was ~0.9 exacerbations/year despite daily step 2 or step 3 controller therapy. Low-doses of intermittent rescue ICS added to daily ICS have not proven beneficial for exacerbation prevention in this age group(11). Budesonide/Formoterol as a single inhaler for both maintenance and reliever therapy has been shown to further reduce exacerbation risk in this age group(12); however, this approach is not FDA approved. Finally, omalizumab (anti-IgE) as add-on therapy has also been shown to reduce severe exacerbations in this age group(13, 14), but high cost and lack of FDA approval for use in patients <12 years of age currently limits its practical use in this age group. Thus, clinicians are in need of additional strategies for the treatment of children who have exacerbations despite daily low-dose ICS or low-dose ICS + LABA therapy.

B. INTERVENTION

The intervention to be tested in this trial is quintupling the dose of ICS (fluticasone) at the onset of yellow-zone symptoms in patients treated with fluticasone 44 mcg 2 puffs twice daily. The intervention will be continued for 7 days each time the participant enters the yellow zone. This strategy will be compared in a blinded fashion to maintaining the participants' low-dose ICS during the yellow zone.

C. RATIONALE FOR THE STUDY

The concept of stepping-up asthma therapy has recently been considered in at least three contexts (Figure 1).(2) First, if lack of control is persistent over long periods of time (e.g., 2-3 weeks or longer), an increase in the overall medication regimen will be prescribed by moving up one or two steps as defined in the EPR-3 or GINA asthma guideline recommendations. This particular intervention has been termed "***step-up long-term (SLT)***". This step-up in overall therapy is usually continued for 3-6 months to evaluate the ability and consistency of the new regimen to maintain adequate asthma control. At this point, consideration could be given to stepping down one absolute level with the stipulation that reevaluation should occur within the next 1-2 months to determine the consistency of control that this step-down regimen is able to maintain over time. An example of a clinical trial in children that evaluated this step-up long-term approach was the BADGER trial performed by the Childhood Asthma Research and Education (CARE) Network.(10)

STEP-UP LONG-TERM **(SLT)**	STEP-UP SHORT-TERM **(SST)**	STEP-UP INTERMITTENT **(SUI)**
increase in therapy for uncontrolled asthma (weeks)	increase in therapy for brief loss of control (days)	increase in therapy for variable symptoms (day-to-day)
persistent loss of control	brief loss of control (upper respiratory tract infections, pet exposure)	mild symptoms
step-down therapy when control achieved after 3-6 months	step-down therapy when control achieved after 3-10 days	intermittent use

Figure 1

A second approach to step-up therapy may occur in relationship to an anticipated brief loss of control (days) or actual brief loss of control, such as at the onset of a viral respiratory tract illness(15) or as a consequence of an acute short term exposure (e.g., a furred pet) that has been known to induce a temporary loss of acceptable asthma control.(16) In most cases, this will entail a step-up in therapy consisting of more frequent short acting beta agonist (SABA) use and, potentially, an increase from baseline in the dose of inhaled corticosteroids (ICS) aimed at preventing a more significant exacerbation requiring oral corticosteroid treatment. This step-up in therapy is usually discontinued in 3-10 days once asthma control has been satisfactorily achieved; at this point, a step-down to the baseline medication regimen is instituted. This particular intervention strategy has been termed "***step-up short-term (SST)***".(2) The SST strategy most closely represents what many clinicians label "yellow zone" treatment. Examples of clinical trials that have evaluated this type of therapeutic approach include the IMPACT(17) trial in adults conducted by the Asthma Clinical Research Network (ACRN) and the AIMS(18) and MIST(19) trials in preschool children conducted by the CARE network.

Finally, for treating symptoms related to the variability of asthma on a day-to-day basis, ICS used concomitantly and intermittently with a short acting beta agonist (SABA) or a long acting beta agonist (LABA) has been evaluated. While this type of therapy has been studied in clinical trials and approved for use in many parts of the world, it is currently not approved in the United States. This particular intervention strategy has been termed "***step-up intermittent (SUI).***" Interestingly, this approach has been used in clinical trials involving both LABAs(20, 21) and SABAs, with the SABA trials being performed by both CARE (TREXA(11)) and ACRN (BASALT(22)) NHLBI-funded networks, and others(23, 24). When applied in the 5-11 year age group in the TREXA study, the step-up intermittent strategy added to daily therapy with low-dose ICS did not provide added benefit in children with mild asthma.

In reviewing the data regarding these various step-up approaches that has been generated by CARE and ACRN, as well as other groups around the world, it became apparent that one very important concept has not been directly addressed by the protocols that have been conducted thus far. In the EPR-3 guidelines, the importance of the use of written asthma treatment plans is stressed. These treatment plans use the terms "green zone", "yellow zone", and "red zone", with the yellow zone being defined as some type of step-up in treatment that will hopefully reestablish asthma control and prevent the patient from entering the red zone, which in most cases involves some type of oral or parenteral corticosteroid intervention.

Interestingly, guidelines as to what determines when a patient is entering or is in the yellow zone are never precisely defined due to lack of evidence to base precise recommendations upon. The examples that are used in the sample asthma action plan use peak expiratory flow rate (PEFR) values as one criterion, and symptoms consisting of wheezing, coughing and shortness of breath as another. As such, these plans have been labeled PEFR-based or symptom-based, respectively. In 2007, the expert panel felt that studies did not clearly show that a peak flow monitoring-based action plan was better than a symptom monitoring-based plan in improving outcomes, but that it did show similar benefits. The committee felt that the plan should direct the patient to adjust medications in response to particular signs, symptoms, and peak flow measurements and should state when to seek medical help. The clinician should tailor the plan to the needs of individual patients. EPR-3 further states that the nature of the plan, whether it is based on symptoms or based on peak flow, is not the important issue; rather, it is having a plan in place versus not having one at all.

Paradoxically, although action plans are a firm recommendation by the expert panel for asthma management, guidance to clinicians as to the specifics of how these plans should be formulated are not provided. For example, what level of symptom severity, rescue albuterol use, activity limitations etc. would warrant a step-up (short term or intermittent) in therapy into the yellow zone? While quantitative cut points for PEFR that would constitute being in the yellow zone are suggested (50-80% of the patient's personal best), similar threshold guidelines for quantifying symptom severity are never specifically provided. Moreover, once a given threshold is reached, what therapeutic intervention should be recommended once the patient enters into the yellow zone? Higher than usual doses of inhaled corticosteroids? A burst of oral corticosteroids? Other or additional strategies? These gaps in the asthma guidelines, and a need to provide more evidence-based

recommendations for yellow zone therapy were the major impetus for the design and development of the current protocol.

II. OBJECTIVES & RESEARCH HYPOTHESES

A. PRIMARY

Primary Objective

The primary objective of this study is to determine whether in children receiving low-dose ICS therapy, quintupling the dose of inhaled corticosteroids in the “yellow zone” (at the onset of symptoms previously associated with upper respiratory illnesses and subsequent asthma exacerbations) reduces the rate of severe asthma exacerbations treated with oral corticosteroids.

Primary Research Hypothesis

The primary research hypothesis is that in children receiving low-dose ICS, quintupling the dose of inhaled corticosteroids in the yellow zone will reduce the rate of severe asthma exacerbations treated with oral corticosteroids.

B. SECONDARY

Secondary Objectives

The secondary research objectives of this study include determining whether, in children receiving low-dose ICS, quintupling the dose of inhaled corticosteroids in the “yellow zone” leads to reductions in symptoms [assessed by area under the curve (AUC) for total daily symptoms(18) and the asthma index(25)] time to first asthma exacerbation, and rate of treatment failures. Additionally, we aim to assess overall corticosteroid exposure, and the potential for growth effects of increased ICS exposure.

Secondary Research Hypotheses

The secondary research hypothesis is that quintupling the dose of inhaled corticosteroids in the yellow zone will lead to reductions in symptoms [assessed by AUC for total daily symptoms and the asthma index] more rapidly than continuing on the same inhaled corticosteroid dose. We also hypothesize that quintupling the ICS dose in the yellow zone will lead to greater time to first asthma exacerbation and a lower rate of treatment failures. Further, we hypothesize that this intervention will reduce overall corticosteroid exposure, and will not lead to significant reductions in growth velocity over 1 year.

C. EXPLORATORY OBJECTIVES

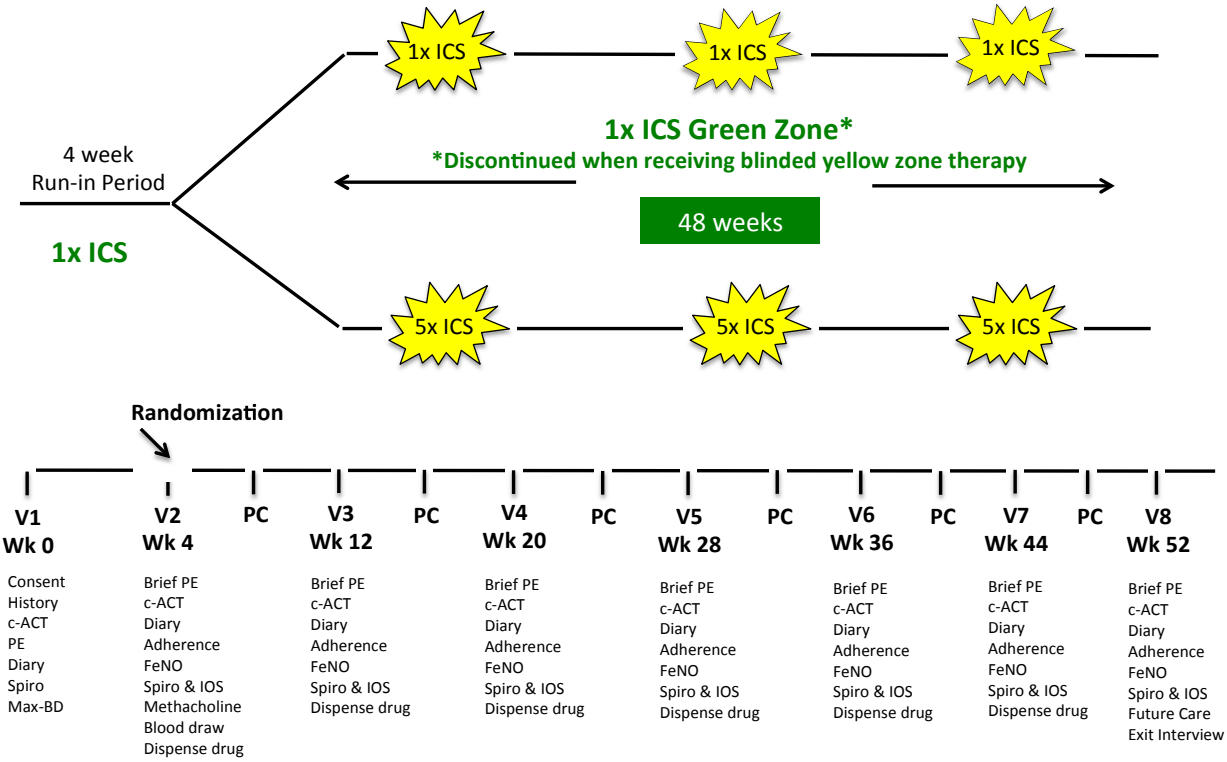
Exploratory research objectives include comparing the timing of yellow zone initiation using a symptom-based action plan (STICS gold standard, appendix C) vs. a peak-flow based action plan by obtaining blinded peak flows throughout the duration of the STICS trial.

Further, we will identify predictors of asthma exacerbations in this exacerbation-prone population and identify predictors of response to the study intervention and assess the cost-effectiveness of the yellow zone strategies.

III. STUDY DESIGN

A. SUMMARY OF STUDY DESIGN

This study is a double-blind, parallel group study with a 4-week run-in period to establish adequate control (c-ACT >19) and adherence followed by a 48-week treatment period. After randomization, participants will be treated for 48 weeks with open-label fluticasone 44 mcg 2 puffs twice daily. During the 48-week treatment period, participants will receive blinded therapy for 7 days each time they enter the "yellow zone". Yellow zone therapy will be fluticasone 44 or 220 mcg 2 puffs twice daily.



B. RATIONALE FOR THE STUDY DESIGN

The STICS trial is designed to address an important clinical question: should clinicians recommend quintupling the dose of a patient's ICS therapy at the onset of yellow zone symptoms in order to prevent progression to the red zone? As illustrated in Figure 2, the timing of the initiation of the yellow zone intervention likely should be at the point at which symptoms are just beginning to escalate in terms of them not responding in the usual way to rescue therapy (i.e., relief onset, duration, or need for repetition). Alternatively, some other change in asthma control measures could be considered to define this yellow zone threshold. This timing for beginning yellow zone therapy is likely a critical factor in altering subsequent outcomes. Indeed, a number of trials that have been unable to show efficacy with inhaled corticosteroid interventions have been criticized for the escalation in therapy being started too late.(26) However, starting an intervention too early may lead to overtreatment and potentially unnecessary side effects of medication.

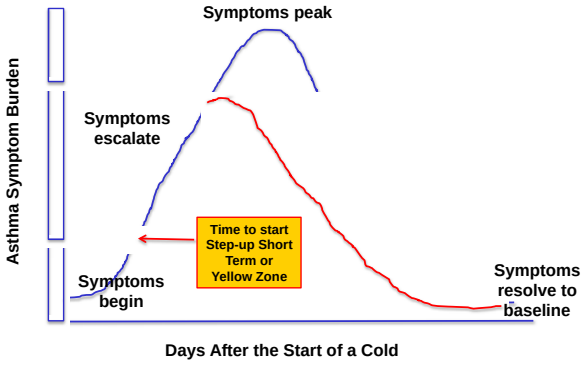


Figure 2

Studies performed by both the ACRN and CARE networks have explored some of these threshold definitions. In adults, the ACRN developed a symptom based action plan that was used in the IMPACT study as part of a step-up short-term yellow zone strategy. The participant was considered to be in the yellow zone when one of the following thresholds were met: awakening from asthma three or more times in a two-week period or on two consecutive nights; using albuterol for relief of symptoms four or more times/day for two or more consecutive days; albuterol relieved symptoms for less than four hours after each treatment over a 12-hour period; using albuterol for relief of symptoms daily for seven days, and this use exceeded two times the weekly use of albuterol during the baseline period; or exercise induced unusual breathlessness.(17) If any of these criteria were met, the participant was instructed to use open-label budesonide, 800 mcg twice daily for 10 days.

In children, the CARE network steering committee spent almost a year trying to develop a set of uniform criteria that could be used by parents of all preschool children enrolled in the AIMS trial to define when the treatment intervention (step-up short term or yellow zone medication) should be initiated. Interviews with parents eventually led the committee to realize that the threshold for initiation of the intervention needed to be individualized for each participant.(27) Thus, in preschool children, the criteria for beginning the yellow zone therapy differed among participants. Once these criteria were met, the children received scheduled albuterol, oral montelukast, or high dose nebulized budesonide (1 mg twice

daily). None of these three interventions reduced the use of oral prednisone (i.e., preventing escalation into the red zone). However, a subset of children with a positive modified asthma predictive index (mAPI)(28) (at high risk of subsequent asthma development) did experience a significant reduction in symptom burden when treated intermittently with high-dose ICS therapy during respiratory tract illness. The same criteria for yellow zone therapy were utilized in the CARE Network MIST trial which showed that intermittent high-dose budesonide was associated with a similar rate of severe exacerbations, when compared to daily, low-dose budesonide, used over the course of 1 year in preschool children with a positive mAPI(19). Another preschool study demonstrated some interesting results. The study examined the efficacy and safety of preemptive treatment with *very* high-dose fluticasone (750 mcg twice daily or placebo) in reducing the severity of recurrent virus-induced wheezing in children 1 to 6 years of age(29). Treatment was started at the onset of an upper respiratory tract infection and continued for a maximum of 10 days. The primary outcome was rescue oral corticosteroid use. Over a median period of 40 weeks, 8% of upper respiratory tract infections in the fluticasone group led to treatment with rescue systemic corticosteroids, as compared with 18% in the placebo group (odds ratio, 0.49; 95% confidence interval [CI], 0.30 to 0.83). Importantly, treatment with this very high dose of fluticasone was associated with a smaller gain in height and weight. The authors concluded that, given the potential for overuse by initiation at the very first sign of a respiratory tract illness, this preventive approach should not be adopted in clinical practice until long-term adverse effects could be further clarified.

Although the data generated in the above studies provide insight into timing of yellow zone strategies, it is important to point out that the age range for participants to be enrolled in the STICS protocol was not included in either of these three study populations. Additionally, these studies involved patients with intermittent or *very* mild persistent asthma. Nonetheless, based on these results and published studies, the steering committee developed the following criteria for defining the threshold for entering the yellow zone in the STICS protocol:

- Rescue albuterol 2x (4 puffs) in 6 hours OR
- Rescue albuterol 3x (6 puffs) in 24 hours OR
- 1 night-time awakening due to asthma that leads to albuterol use

The specific medication and dose used to attenuate further symptom escalation is also likely an important element in achieving successful prevention of exacerbations. In this regard, a number of strategies have been evaluated in both children and adults. Although very frequently utilized in clinical practice, doubling the dose of ICS in both adults(30-32) and children(33) has not been shown to be effective. However, it should be noted that these studies all had relatively small sample sizes and often delayed the yellow zone intervention until quite significant symptoms and/or reductions in PEFR were present(26). In contrast, preliminary data generated a number of years ago suggested that quadrupling the dose of an ICS for 7 days, starting at the first appearance of worsening symptoms, may prevent exacerbations requiring oral systemic corticosteroids.(34) These intriguing data were subsequently further evaluated in a trial specifically designed to ascertain the value of quadrupling the dose of ICS in reducing the need for subsequent oral corticosteroid

administration. The primary outcome of this trial was progression of yellow zone symptoms to the point of being sufficient enough to warrant oral corticosteroid treatment.(3) Overall, the primary outcome was not significant. However, in a post hoc analysis of the data, reductions in prednisone use were significantly noted in those participants who initiated step-up therapy per protocol. The authors concluded that, although the primary outcome did not reach statistical significance, quadrupling the dose of inhaled corticosteroid when asthma control starts to deteriorate appears to reduce acute exacerbations of asthma and is deserving of further investigation. Further, in this study, the quadrupling of ICS dose occurred after significant symptoms had developed, and it therefore could be suggested that earlier institution of quadrupled ICS dosing may be more likely to prevent exacerbations successfully. Finally, this study included adults across a spectrum of asthma severity, but whether the participants' baseline ICS dose or concomitant treatment with a LABA altered response to therapy was not reported.

In summary, the current literature indicates that doubling the dose of ICS is not an effective strategy for attenuating and/or abrogating progression from the yellow zone into red zone therapy. However, in adult patients, quadrupling the dose may achieve these outcomes. *Since the data in children to address this particular form of intervention are nonexistent, the steering committee felt it extremely relevant to design a trial in school-aged children (5-11 years of age) that would provide evidence to guide therapy in this regard.* Based upon ICS dose preparations available, we have chosen a protocol in which step-up short term or "yellow zone" therapy consists of quintupling the dose of the participant's "green zone" or baseline therapy. This gap in our evidence base is important in children treated with either low-dose ICS or low-dose ICS + LABA therapy, but due to the potential for interaction by baseline therapy, we will include only children treated with low-dose ICS in the STICS trial.

C. OUTCOME MEASURES

Primary outcome

The primary outcome is the rate of severe exacerbations treated with oral corticosteroids (prednisone). Oral prednisone will be administered for the treatment of impending episodes of severe asthma when bronchodilator therapy is inadequate(35). The decision concerning the initiation or continuation of a course of oral prednisone will be at the physician's discretion, based upon criteria previously published by the ICAC.(13) Prednisone should be prescribed if:

- The participant used more than 3 nebulizer treatments with albuterol or comparable beta-agonist bronchodilator or 6 puffs of albuterol (3 treatments of 2 puffs each) in the prior 4 hours for relief of asthma symptoms OR
- The participant used 12 or more puffs of albuterol in the last 24 hours for relief of asthma symptoms OR
- The participant awakened due to cough, shortness of breath, chest tightness, or wheezing AND needed to use albuterol at least 2 of the previous 3 nights OR
- The participant used 8 or more puffs of albuterol per day during 2 of the previous 3 days

for relief of asthma symptoms.

Secondary outcomes

Specific secondary outcomes of particular interest to be obtained in this study include additional outcomes in domains of impairment and risk. These secondary outcomes include the following:

1. Time to first exacerbation treated with oral corticosteroids
2. Treatment failures
3. Area under the curve (AUC) symptom scores(18) during the yellow zone episodes, including those that progress to red zone therapy
4. Asthma Index(25) during the yellow zone episodes, including those that progress to red zone therapy
5. Albuterol rescue inhaler use (# of puffs) during yellow zone episodes
6. Unscheduled emergency department (ED) or urgent care visits for asthma
7. Hospitalizations for asthma
8. Linear growth
9. Total corticosteroid exposure (ICS + OCS)

Exploratory analyses

1. To identify predictors of exacerbations treated with oral corticosteroids
   a. Number of exacerbations in prior year
   b. Atopic characteristics (total IgE, allergen-specific *in vitro* IgE [number of positive IgE tests, sum of IgE values, specific allergen sensitivity patterns, mono vs polysensitization])
   c. IOS [R5-R20 and AX] at randomization (subset)
   d. FEV_1 at randomization
   e. FeNO at randomization
   f. Maximum bronchodilator reversibility at V1
   g. Methacholine responsiveness at randomization
   h. Atopic dermatitis
   i. Race/ethnicity
   j. Body-mass index (BMI)
   k. Gender
   l. Nasal samples during yellow zone episodes
      i. HRV species (A vs. B vs. C)
      ii. Virus positive vs. Virus negative episode
      iii. Bacteria positive vs. Bacteria negative episode

2. To identify predictors of response to yellow zone therapy [same as in #1]
3. To compare yellow zone episode identification by symptom-based action plan [gold standard in STICS, appendix C] vs. a peak flow-based action plan [blinded peak flows]

4. To compare rates of unscheduled emergency department (ED) or urgent care visits for asthma and hospitalizations between treatment groups
5. To assess cost-effectiveness of the yellow zone strategies

D. STUDY POPULATION AND CONTROL GROUP

This study will enroll children 5-11 years of age who meet criteria for treatment with long-term, step 2 asthma controller therapy, as defined by the NAEPP EPR-3 guidelines. They must have had at least 1 asthma exacerbation treated with oral corticosteroids in the year prior to study enrollment. To ensure adequate representation, we will enroll at least 30% ethnic and racial minorities.

E. PLAN FOR PATIENT SAFETY

Study specific risks

Risks and benefits of study procedures

Venipuncture*:* Blood samples will be obtained by venipuncture of an antecubital vein to determine *in vitro* IgE levels, peripheral blood eosinophils, and for DNA extraction for future genotyping studies.

Risks: The risks of venipuncture are minimal. The possible risks include bruising and/or infection at the site of the venipuncture and vasovagal episodes experienced by the blood donors. Pressure will be applied to the venipuncture site to prevent bruising. Aseptic technique will be used to prevent infection. Blood will be obtained while the participants are in a seated position and medical and nursing personnel will be available at the study sites to treat and manage vasovagal episodes.

Benefits: The DNA isolated for future genotyping studies will provide important insight into potential genetic modifiers of responses to therapy.
The potential benefits justify the potential risks.

Questionnaires.

Risks: Answering questionnaires and daily diaries about asthma is of minimal risk. If participants feel uncomfortable they are welcome to discuss the questions with the study coordinator.

Benefits: There are no direct benefits to the participant.
The potential benefits justify the potential risks.

Pulmonary function testing (spirometry and impulse oscillometry)

Risks: Spirometry will be performed to determine the participants' pulmonary function. The

risks of spirometry are minimal. The possible risks include precipitation of bronchospasm and light-headedness from repeated blowing attempts. Medical and nursing personnel and medications will be available at the study sites to treat and manage bronchospasm. Inhalation of a SABA (albuterol) will be used to assess maximum reversibility. The possible risks of inhaled beta-2 adrenergic agonists include tachycardia and hand tremors. These side effects are non-life threatening and are short-lived. Impulse oscillometry (IOS) will also be performed in a subset of participants. There are no significant risks associated with IOS.

Benefits: Spirometry with assessment of maximum reversibility to a SABA and IOS will be utilized to characterize the participants and to determine whether they are potential biomarkers to predict asthma exacerbations or response to therapy.
The potential benefits justify the potential risks.

***Methacholine inhalation challenge*:**

Risks: The major risk of methacholine challenge is the induction of severe bronchoconstriction. As a precaution, participants will not undergo methacholine challenge if their FEV_1 is less than 70% of predicted. Methacholine challenges have been performed with high levels of safety in children in both the Childhood Asthma Management Program (CAMP) and the Childhood Asthma Research & Education (CARE) Network. Medical and nursing personnel, medications and equipment will be available at the study sites to treat and manage any bronchoconstriction episodes.

Benefits: Methacholine challenge will be utilized to characterize the participants and to determine whether it is a potential biomarker to predict asthma exacerbations or response to therapy.
The potential benefits justify the potential risks.

Exhaled nitric oxide: This measures the amount of nitric oxide in the exhaled breath and is thought to increase when the lungs are irritated or inflamed.

Risks: There are no known risks associated with this procedure.

Benefits: Participants may benefit from knowing the amount of inflammation in their airways as measured by FeNO.
The potential benefits justify the potential risks.

Nasal blow for virus detection: Respiratory viruses are the most common trigger of asthma exacerbations. Collecting samples at home during yellow zone episodes using methods included in prior AsthmaNet studies (April/Ocelot & Infant/Avica) will allow us to assess the pathogens involved in the yellow zone episodes and asthma exacerbations.

Risks: There is a small chance of lavage fluid going down the throat leading to an uncomfortable feeling.

Benefits: Nasal sampling will allow investigators to identify pathogens involved in exacerbation episodes and determine whether illnesses caused by particular pathogens are

more or less responsive to quintupling the ICS dose.
The potential benefits justify the potential risks.

Risks and benefits of study drugs
Fluticasone

Risks: Daily low-dose inhaled corticosteroids have been associated with a small, but statistically significant reduction in growth velocity.(36) High-doses of inhaled corticosteroids used for prolonged periods of time have been associated with additional side effects, including hoarseness, sore throat, and thrush, adrenal gland suppression, weight gain, bruising of the skin, and diabetes. These side effects are not anticipated in STICS because of the 7-day yellow-zone treatment period and the maximum of 6 yellow zone courses per participant in the trial. We will monitor growth throughout the trial (see secondary outcomes).

Benefits: The efficacy of fluticasone at low dosages has been well established in both adults and children(9, 37) In a meta-analysis of 71 randomized trials (14,602 adults and children) comparing fluticasone to budesonide or beclomethasone, at a dose ratio of 1:2, significant improvements in lung function (FEV_1, FEF_{25-75}) and morning peak expiratory flow were noted in the fluticasone-treated group(38). Low-dose ICS is the current preferred therapy for step 2 treatment of asthma in children 5-11 years of age(1). Quadrupling the dose of ICS in the yellow zone may reduce oral steroid requiring exacerbations in adults(3). This study is designed to determine whether quintupling the dose of ICS in the yellow zone, an approach currently utilized in clinical practice, is efficacious in children 5-11 years of age. The design of the intervention, quadrupling versus quintupling the dose, is based upon currently available ICS inhaler dose escalation choices available in the United States.

The potential benefits justify the potential risks.

Routine safety monitoring

Fluticasone

Physical exams including assessment for oral candidiasis and measurement of linear growth will be performed at each study visit.

Data Safety Monitoring Board

A pre-specified stopping rule is not necessary for this trial, and a formal interim analysis of efficacy data is not planned. The AsthmaNet Data and Safety Monitoring Board (DSMB), however, will be monitoring all of the safety data throughout the course of the trial and will be notified within 72 hours of any serious adverse events (SAEs) that occur.

F. ETHICAL ISSUES
Participation of children

Asthmatic participants ages 5-11 years of age will be included in this study. An IND will be required for the use of fluticasone MDI in this age group.

Participation of females

The target recruitment goal is at least 40% females, as approximately 60% of children in this age group with asthma are males.

Participation of minority groups

The target recruitment goal will be to enroll 30% minorities. Asthma affects African Americans more frequently and more severely than other ethnic groups. Some subsets of Hispanics (e.g., Puerto Ricans) have particularly frequent and severe asthma, while others (e.g., Mexican-Americans) do not. In the present study, we will classify race and ethnicity separately, in line with HHS guidelines, and allow individual participants to identify their racial category. The reporting of such data will allow for numbers of individuals who indicate more than one racial category insofar as it does not interfere with individual participant confidentiality. Based on the demographics of our clinical research sites and our experience in other AsthmaNet studies, which up to this time have enrolled approximately 50% minorities, it is highly likely we will be able to meet our race/ethnicity targets. If individual AsthmaNet centers are unable to meet minority targets from initial recruitment efforts, they will redirect their recruitment strategies to use local newspaper and radio advertising that have more focused minority demographics. Other efforts that have been successfully used for minority recruitment include the targeting of clinics, work sites, schools, churches, and civic groups with high minority representation.

G. STUDY ORGANIZATION

Participating sites

Nine AsthmaNet Clinical Center partnerships (and their associated satellites) will participate in the STICS trial. Each partnership has recruitment and retention plans in place to maximize enrollment. These nine partnerships include:

1. Brigham & Women's Hospital (Dr. Elliott Israel, PI), and Boston Children's Hospital (Dr. Wanda Phipatanakul, PI), Boston, MA

2. Chicago Metropolitan Asthma Consortium, Chicago, IL (Drs. Lewis Smith, Jacqueline Pongracic, Julian Solway, Jerry Krishnan, PIs)

3. National Jewish Health, Denver, CO (Drs. E. Rand Sutherland and Stanley Szefler, PIs) and University of New Mexico in Albuquerque (Drs. W Kelly and H Haidarian-Raissy)

4. University of Wisconsin, Madison, WI (Drs. Chris Sorkness and Robert Lemanske, PIs)

5. University of Pittsburgh, Pittsburgh, PA (Drs. Sally Wenzel and Fernando Holguin, PIs)

6. Washington University, St. Louis, MO (Drs. Mario Castro and Leonard Bacharier, PIs)

7. University of California, San Francisco, CA (Drs. Homer Boushey and Michael Cabana, PIs)

8. Duke University, Durham, NC (Dr. Monica Kraft, PI) and University of Arizona, Tucson, AZ (Dr. Fernando Martinez, PI)

9. Wake Forest University, Winston Salem, NC (Dr. Stephen Peters, PI) and Emory University, Atlanta, Georgia (Dr. Anne Fitzpatrick, PI)

Steering Committee

The AsthmaNet Steering Committee is comprised of representatives from the nine clinical centers. All centers have participated in the decision to design and conduct this protocol. Any protocol amendments or administrative changes require Steering Committee approval as well as that of NHLBI (based upon recommendation from the Protocol Review Committee) and DSMB as appropriate.

Vendors

GlaxoSmithKline has preliminarily agreed to provide fluticasone and albuterol for the STICS trial.

Role of National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) of the NIH provides funding for AsthmaNet clinical trials as well as the network sites and DCC. Program Officers from NHLBI serve as members of the Steering Committee for oversight of the interests and priorities of the NIH as well as applicable regulations.

H. COMPLIANCE

This study will be conducted in Compliance with The Common Rule. Prior to the initiation of the study, study sites have current Office of Human Research Subjects Protection (OHRP) approved Federal Wide Assurance (FWA) and provide certification that an Institutional Review Board (IRB) registered under the specific Assurance has reviewed and approved the study. All investigators have documented completion of training on the protection of human research subjects. As the design, conduct, or reporting of this study is under a cooperative agreement with the NIH, investigators are required to be free from bias by any conflicting financial interest.

IV. METHODS AND MATERIALS

A. STUDY POPULATION

Recruitment and selection of patients

This study will enroll children ages 5-11 years of age who meet criteria for treatment with long-term, Step 2 or 3 asthma controller therapy, as defined by the NAEPP EPR-3 guidelines.(1) To ensure adequate representation, we will enroll at least 30% racial minorities.

Inclusion criteria

1. Males and females, ages 5-11 years
2. All ethnicities/races eligible
3. Physician-diagnosed asthma (at visit 1)
4. At least 1 exacerbation treated with systemic (oral or injectable) corticosteroids in the past 12 months
5. Able to perform reproducible spirometry
6. Current treatment with step 2 controller therapy [low-dose ICS, leukotriene receptor antagonist (LTRA)] OR current treatment with step 3 controller therapy [low-dose ICS + LABA, low-dose ICS + LTRA, or medium dose ICS] with a c-ACT score of >19 at enrollment, no more than 2 prednisone treated exacerbations in the past 6 months, prebronchodilator FEV_1 ≥ 80% predicted and willing to step down therapy OR controller naïve and qualifying for step 2 controller therapy per EPR3 guidelines [asthma symptoms or SABA use > 2 days per week or night-time awakenings due to asthma > 2 nights per month]
7. Prebronchodilator FEV_1 ≥ 60% predicted at V1
8. Ability to provide screening and baseline information at visits 1 and 2
9. Ability and willingness to provide informed assent (age determined by local IRBs) and for parents to provide informed consent (ages 5-11 years) at visit 1
10. For females of childbearing potential: not pregnant, non-lactating, and agree to practice an adequate birth control method (abstinence, combination barrier and spermicide, or hormonal) for the duration of the study (at visit 1)
11. History of clinical varicella or varicella vaccine

Exclusion criteria (at enrollment)

1. Corticosteroid treatment for any condition within the following defined intervals prior to enrollment.
   a. Oral – Use within 2-week period of the screening visit
   b. Injectable – Use within 2-week period of the screening visit
   c. Nasal corticosteroids may be used at any time during this trial at the discretion of the study investigator or primary care physician
2. Current or prior use of medications known to significantly interact with corticosteroid disposition (within a 2-week period of Visit 1), including but not limited to carbamazepine, erythromycin, phenobarbital, phenytoin, rifampin, and ketoconazole
3. Presence of chronic or active lung disease other than asthma
4. Significant medical illness other than asthma, including thyroid disease, diabetes mellitus, Cushing's disease, Addison's disease, hepatic disease, or concurrent medical problems that could require oral corticosteroids during the study

5. A history of cataracts, glaucoma, or any other medical disorder associated with an adverse effect to corticosteroids
6. History of a life-threatening asthma exacerbation requiring intubation, mechanical ventilation, or resulting in a hypoxic seizure
7. More than 5 prednisone treated exacerbations in the past 12 months
8. More than 1 hospitalizations lasting >24 hours for asthma in the past 12 months
9. Prematurity <35 weeks EGA
10. Significant failure to thrive (< 2nd percentile)
11. History of adverse reactions to ICS preparations or any of their ingredients
12. Receiving hyposensitization therapy other than an established maintenance regimen (On maintenance regimen for ≥ 3 months)
13. Pregnancy or lactation
14. If of child bearing potential, failure to practice abstinence or use of an acceptable birth control method
15. Inability to perform study procedures
16. Participation presently or in the past month in another investigational drug trial
17. Evidence that the family may be unreliable or nonadherent, or may move from the clinical center area before trial completion

Exclusion criteria (at randomization)

1. Inadequate adherence (< 75% of the electronic diary records completed, or < 75% of the expected medication doses taken)
2. Asthma exacerbation requiring systemic corticosteroids (may be re-enrolled at a later time if the subject was not hospitalized)
3. c-ACT < 20 at V2
4. Prebronchodilator FEV_1 < 80% predicted at V2 (May be re-enrolled at a later date if inclusion criteria are still met)
5. Exclusion criteria assessed at V1 are no longer met

B. STUDY INTERVENTION

Description and frequency of drug/ modification

For the purpose of this study, each participant will receive three study inhalers (*green zone* = fluticasone 44 mcg, *yellow zone* = fluticasone 44 mcg or 220 mcg, SABA). The *green zone* inhaler will contain fluticasone 44 mcg (not blinded) to be used as a daily controller (twice daily) throughout the trial, ***but stopped when the participant is in the yellow zone***. The *yellow zone* inhaler will contain fluticasone 44 mcg or 220 mcg. This medication will be double-blind and used twice daily for 7 days in place of the green zone inhaler when the patient meets yellow zone criteria. This yellow zone inhaler will be used for 7 days for each yellow zone course, and yellow zone courses must be separated by at least 7 days. The third inhaler will contain SABA and will not be blinded (90 mcg/inhalation of albuterol sulfate) and used as needed throughout the study.

Prednisone. All participants will have access to prednisone (2 mg/kg/day for 2 days [maximum 60 mg/day], followed by 1 mg/kg/day for 2 days [maximum 30 mg/day]) for treatment of an exacerbation.

Promoting medication delivery

Demonstrating medication delivery techniques at each study visit will maximize delivery of the medications. To minimize the variability in the dose, the patient's medication technique will be reviewed at each study visit. Objective feedback will be given to each participant to improve performance. Participants will be instructed in proper valve holding chamber cleaning techniques, including air-drying. Instructional tools, memory aids, and electronic diary prompts will also be administered to participants to ensure proper medication delivery, safety monitoring, and adherence. Additionally, we will review the asthma action plan at each study visit. Further, to help avoid confusion between green and yellow zone medications, we will color-code (green or yellow) the outside of the inhalers to match the action plan.

Rescue therapy

Participants will use open-label SABA as needed for symptoms throughout the study, regardless of treatment assignment. All participants will be managed with rescue algorithms and/or short courses of prednisone for asthma exacerbations in a manner consistent with the NAEPP guidelines(1) and previous CARE Network & Inner City Asthma Consortium (ICAC) protocols(10, 11, 13). If a participant experiences two exacerbations requiring oral corticosteroids in 6 months or three exacerbations requiring oral corticosteroids in 12 months, they will be terminated from the study. For the purpose of this study, two courses of systemic corticosteroids must be separated by more than one week to count as two separate exacerbations.

C. PERMITTED CONCOMITANT MEDICATIONS and INTERVENTIONS

Medications used to treat asthma must remain constant after the screening visit and through completion of the study, with modifications permitted as needed when medically indicated. A list of the medications that cannot be taken and the period of exclusion are listed in the Appendix.

In addition to the prohibitions in Table 1 of the Appendix, on the day of study visits after the screening visit, SABAs may not be used for at least 6 hours prior to the visit. After the screening visit, use of SABA within 6 hours should result in rescheduling of the visit, unless no other appointments are available. (After the screening visit and prior to randomization, the visit should be cancelled and if it cannot be rescheduled the patient must be excluded from the study.) At the screening visit, the most recent use of SABAs and LABAs should be noted, but spirometry may still be performed.

D. STUDY ASSESSMENTS

Description of assessments

Overall, there are five types of scheduled study visits or contacts as follows. These visits are illustrated in the study diagram shown previously:

1. Screening (V1)

2. Randomization visit (V2)

3. Clinic visits to assess safety and efficacy (V3-V7)

4. Treatment telephone calls between study visits

5. Yellow zone phone calls

6. Exacerbation (Red zone) phone calls

7. Exacerbation (Red zone) clinic visit (optional)

8. Study close-out visit (V8), 48 weeks after the randomization visit

Order of assessments

Ideally all visits for a given patient should be scheduled at the same time of day. The order of assessments may be flexible with the following exceptions:

- Patient reported outcomes (PROs) should be completed before other assessments begin.
- FeNO must be performed before spirometry
- IOS (at selected sites)
- Spirometry should be completed after FeNO and IOS, *and* following any PROs if there are any.

Visit structure

Enrollment/Screening (V1), Study Week 0

1. Informed consent obtained

2. Eligibility determined based upon inclusion and exclusion criteria; Childhood Asthma Control Test (c-ACT) is administered

3. Medical history obtained

4. Complete physical examination including height and weight performed (see Appendix C)

5. Spirometry with maximum reversibility

6. An Action Plan provided and explained, to include standard education about wheezing, use of the action plan, avoidance of allergens and irritants

7. Dispense open-label medications (SABA [albuterol], ICS, prednisone)

8. Dispense spacer

9. Dispense electronic diary and instruct in proper use, including peak flow measurement and establishing personal best value

10. Provide education for appropriate medication and spacer use

11. Review current long-term asthma controller medication use and discontinue if appropriate, or dispense open-label study medication if criteria are met

12. Urine pregnancy test for females who have had 1st menses

Randomization Visit (V2) Study Week 4 (± 5 day window)

1. Electronic diary records reviewed and evaluated for adherence - participants must demonstrate at least 75% adherence to electronic diary

2. Inclusion and exclusion criteria reviewed

3. Asthma symptoms and medical history, including healthcare utilization reviewed

4. c-ACT administered

5. Brief physical exam including height and weight performed

6. Exhaled nitric oxide measurement (FeNO) performed

7. IOS performed (at selected sites)

8. Spirometry

9. Methacholine challenge

10. Blood sample drawn for *in vitro* IgE testing, total IgE, peripheral blood eosinophils; DNA banked for later genetic testing

11. Action plan administered and reviewed

12. Nasal sample will be collected

13. Education provided for appropriate medication and spacer use

14. Green zone open label ICS provided and blinded yellow zone medication provided

15. Observe peak flow procedure

16. Urine pregnancy test for females who have had 1st menses

Clinic visits (V3-V7) to assess safety & efficacy:
Weeks 12, 20, 28, 36, 44 (± 5 day window)

1. Electronic diary records reviewed and evaluated for adherence
2. Asthma symptoms and medical history, including healthcare utilization reviewed
3. c-ACT administered
4. Brief physical exam including height and weight performed
5. Exhaled nitric oxide (FeNO) performed
6. IOS performed (at selected sites)
7. Spirometry
8. Action plan reviewed
9. Education provided for appropriate medication, peak flow and spacer use
10. Green zone open label ICS provided and blinded yellow zone medication provided

Phone calls for safety: weeks 8, 16, 24, 32, 40, 48 ± 5 day window)

1. Respiratory symptoms, albuterol use, healthcare utilization since previous visit assessed
2. c-ACT administered
3. Medical follow-up for symptoms or prior healthcare utilization if this has not already been done encouraged
4. Electronic diary completion confirmed
5. Study procedures, action plan, and medication adherence reviewed

Study close-out visit, (V8 – Study Week 52, ± 5 day window)

1. Electronic diary records reviewed
2. Asthma symptoms and medical history, including healthcare utilization reviewed
3. Brief physical exam including height and weight performed
4. Questionnaires administered (c-ACT)
5. Exhaled nitric oxide (FeNO) performed
6. IOS performed (at selected sites)
7. Spirometry
8. Exit interview performed (critique of study experience; permission to be contacted for future studies)
9. Action plan reviewed
10. Treatment recommendations given

Yellow Zone Phone Calls

Participant care-givers will be asked to notify the study site within 72 hours of initiating the yellow zone medication. During this call, the participant's clinical status will be assessed and their action plan will be reviewed, including criteria for initiating red zone therapy. Additionally, participant care-givers will be asked to notify the study site if the participant continues to meet yellow zone criteria at the end of the 7 day yellow zone treatment period. In these cases, the participant's clinical status will be assessed by the coordinator and discussed with the study clinician. *The clinician will then decide whether to start prednisone by phone or have the participant be evaluated at the study site, where a decision would be made on whether to start prednisone, start an antibiotic (for sinusitis), or otherwise treat as medically indicated.*

Exacerbation (Red Zone) Phone Call (5 days after exacerbation onset ± 2 day window)

This phone call will be initiated by the study coordinator for every participant who experiences an exacerbation treated with prednisone between regularly-scheduled study visits. This will be performed for safety purposes. If the participant is not improving on prednisone therapy, a follow-up phone call or study visit will be scheduled.

Exacerbation (Red zone) Clinic Visit (optional)

This visit will be performed if the participant experiences an exacerbation between scheduled study visits and needs to be seen at the clinical site. If this visit is necessary, the following will be performed:

1. Electronic diary records reviewed

2. Asthma symptoms and medical history, including healthcare utilization reviewed

3. Spirometry

4. Long physical exam

5. Treatment recommendations given

Description of Procedures

Spirometry and Methacholine provocation testing. All participants will undergo spirometry at each clinic visit. Spirometric studies are performed in accordance with ATS recommendations (American Thoracic Society, 1987) and AsthmaNet manuals of procedure (MOP). All participants will undergo methacholine bronchoprovocation at visit 2 in accordance with ATS recommendations (American Thoracic Society, 1999) and AsthmaNet MOP. A positive response is considered a drop in the FEV_1 from post-diluent FEV_1 ≥20%.

Bronchodilator reversibility phenotype. Participants will undergo spirometry with bronchodilator reversibility testing and maximal bronchodilation as defined by the maximal achievable FEV_1 after 4 puffs albuterol at visit 1. Participants will withhold medications as per the AsthmaNet MOP.

Asthma symptoms and control. Asthma symptoms will be assessed by diary recall of asthma-control days (ACD), days recorded in the daily diary without any asthma symptoms or rescue albuterol use, at all visits. *Asthma control* will be assessed by the childhood Asthma Control Test (c-ACT)(39) at V1, randomization, regular visits and phone calls.

Fraction of exhaled Nitric Oxide (FeNO). Levels of exhaled nitric oxide (FeNO) are elevated in people with asthma. In addition, FeNO may be involved in airway inflammation. The FeNO collection procedures should precede any pulmonary function testing procedures at a given visit. FeNO will be performed at visits 2-8 using the Aerocrine NIOX MINO device.

Impulse Oscillometry (IOS). IOS will be performed at a subset of study sites. Recent data suggests that IOS measurement may predict loss of asthma control in children(40).

E. STATISTICAL METHODS

Sample size determination

The primary hypothesis for STICS will be evaluated by comparing the estimated exacerbation rates (expressed as number per year) in the two treatment groups. A total sample size of 250 randomized participants will provide 90% power to detect a 40% difference in exacerbation rates, while allowing for up to 15% drop-out. This is based on the assumption that the larger exacerbation rate of the two treatments is at least 0.9 exacerbations per year.

Method of randomization and blinding

Randomization

Children between the ages of 5 and 11 years who satisfy all eligibility criteria during the run-in period will be randomized to one of two treatment arms, 1xICS or 5xICS during yellow zone episodes, with clinical center serving as a stratifying factor. Each of the nine clinical centers and their associated satellite sites is expected to randomize 28 participants. However, enrollment will not be constrained to require exactly 28 participants per clinical center.

Blinding

To minimize the bias due to possible knowledge of the sequence assignment, the study will be double-blinded. Thus, the investigators and the participants will not know which treatments are being received.

Assessment of treatment group comparability

The run-in period is considered the baseline evaluation period. The initial statistical analysis will focus on summarizing the baseline characteristics of the study participants. Descriptive statistics (means and standard deviations, or medians and inter-quartile ranges) will be calculated for continuous baseline measures such as current age and asthma symptom severity. Frequency tables will be generated for categorical baseline measures such as sex and prior medication history.

Efficacy analyses

Primary analysis

The primary outcome is the rate of exacerbations per year. It is important to note that the primary clinical question is whether the *strategy* of identifying yellow zones and then using either 5xICS or 1xICS during the yellow zone makes any difference on the rate of exacerbations over the course of the study. The question is not whether treatment with either 1xICS or 5xICS during any particular yellow zone treatment makes a difference on the likelihood of an exacerbation occurring during that particular yellow zone. That is, a patient who has no exacerbations and no yellow zone courses during the study is equivalent to a patient who has no exacerbations and 5 yellow zone courses during the study.

Ideally, all participants would complete 48 weeks of follow-up and the exacerbation rate could be adequately estimated by modeling the number of observed exacerbations with the Poisson distribution and calculating the rate as the estimated mean number of exacerbations divided by the number of years of follow-up, which is just under 1.0 (48 weeks/52 weeks). However, estimates based on that model will be biased unless all participants complete the full 48 weeks of follow-up, which is unlikely under the STICS study design. When there is unequal follow-up time, better estimates can be obtained by including an ‘offset’ in the model, which is typically defined as the logarithm of the observed follow-up

time. Estimates from models incorporating follow-up time as an offset are generally unbiased as long as the follow-up time is independent of the outcome frequency.

In STICS, however, follow-up time is not necessarily independent of exacerbation frequency. Apart from the typical truncation of follow-up time due to early drop-out common in clinical trials, two additional aspects of STICS will likely contribute to truncated follow-up. As described below in section V.H., study participants will be withdrawn for safety reasons after the 6th yellow zone course. In addition, study participants will be withdrawn after the 2nd exacerbation, if it occurs within the first 6 months, or after the 3rd exacerbation, if the 2nd didn't occur within the first 6 months. The second mechanism for early termination, based on exacerbations, induces dependence between follow-up time and exacerbation frequency. The primary analysis will utilize maximum likelihood estimation based on the log-linear regression model for outcomes following the negative binomial distribution. This model is a generalization of the Poisson-based model that can be adapted to incorporate follow-up times that are not independent of outcome frequency, as well as zero-count inflation and over-dispersion, which can be used to account for population heterogeneity.

Analyses of secondary outcomes

Additional secondary analyses will examine the effect of study treatment on other outcomes. For outcome variables that are also measured as counts, such as number of unscheduled visits for acute wheezing episodes and number of days missed from daycare or parental work, a similar log-linear model maximum likelihood analysis will be applied. Repeated measures ANOVA models will be applied for outcomes that are measured on a roughly continuous scale, such as area under the curve symptom scores, Asthma Index, albuterol use during the yellow zone episode, and linear growth. For continuous outcomes that are do not exhibit an approximately normal distribution, appropriate transformations will be applied prior to ANOVA. Outcome variables that are measured as time-to-event, such as time to first exacerbation and will be analyzed within the framework of proportional hazards regression. This can be done incorporating treatment assignment as a fixed covariate, as opposed to a time-dependent covariate, which will result in a comparison of treatment strategies.

Exploratory analyses

Exploratory analyses will examine possible effects of participant baseline characteristics the primary outcome. Multivariable regression analyses, under the model framework described above, will be applied. Characteristics to be explored include history of exacerbations in prior year, atopic characteristics, spirometric measures such as FEV_1, maximum bronchodilator reversibility, IOS, methacholine responsiveness, F_ENO, atopic dermatitis, race/ethnicity, body-mass index and gender.

Economic analyses will also be undertaken and will reflect the societal perspective for the yellow zone high-dose ICS approach for treatment of grade-school aged with persistent asthma. There are several limitations for these analyses in this trial. Most important are the potential lack of generalizability due to population selection and the fact that the protocol mandates closer monitoring of patients than would be expected in general practice. However, major advantages of economic analysis in the randomized, controlled clinical trials are that detailed assessments of prospectively defined resource utilization can be obtained

and that treatment selection bias or confounding is eliminated by randomization. Cost of treatment medication as well as rescue medications and prednisone used to treat exacerbations requiring systemic corticosteroids will be evaluated as wholesale costs. Costs of unscheduled physician or ED visits or other costs related to diagnosing and treating anticipated adverse events will be standardized across clinical centers. The goal of the cost-effectiveness analysis will be to estimate the incremental cost-effectiveness ratio for study treatment. Standard methods for cost-effectiveness analysis in clinical trials will be used. Bootstrapping will be used to quantify the uncertainty of the ratio, and cost-effectiveness acceptability curves will be produced in order to determine the probability that the intervention in cost-effectives under a range of willingness-to-pay scenarios.

Interim analyses

The 250 children participating in STICS will be enrolled over a 12-month period and each participant will be followed for up to one year. The study will be monitored by the AsthmaNet Data and Safety Monitoring Board (DSMB). The DSMB will receive reports of serious adverse events as they occur throughout the course of the trial and will meet semi-annually to review non-serious adverse event data and quality control reports. No formal interim analyses for futility/efficacy are planned because the length of follow-up is approximately the same length as the recruitment so that enrollment will be completed well before there is sufficient information to allow an efficient interim efficacy analysis. A feasibility analysis will be performed after 50% of the participants have completed at least 6 months of follow-up. The purpose of this analysis will be to check whether the assumptions regarding loss to follow-up, rate of yellow zone treatment initiation, and rate of treatment failure are being borne out. If the assumptions are not borne out, additional power analyses will be conducted to examine study feasibility. The two treatment arms will be combined for this analysis. Based on these results, the DSMB may recommend changes to the study design.

F. DATA MANAGEMENT

Data collection

Recording of all data including informed consent and assent, history, physical examination, adverse events, confirmation of medication dispensation, and initial data entry will be done at each Clinical Center and forms will be forwarded to the Data Coordinating Center (DCC) for confirmatory entry. Results from all tests and compliance will be transmitted electronically to the DCC where all data will be stored and analyzed.

The DCC will be responsible for generating the data collection forms based on input from the clinical centers. Once the data collection forms have been completed and reviewed, the Clinic Coordinator will log into the AsthmaNet Network web site and enter the data within 14 days of the patient visit. The advantage of this distributed data entry system is that the Clinic Coordinators will review the data a second time as they are entering it, which serves as another level of quality control. However, the Clinic Coordinators will not be able to query their own data. The data base management system will have range checks and validity

checks programmed into it for a second level of quality control. Forms will then be forwarded to the DCC for the second data entry and filing, which will be performed within 7 days of receipt.

Data integration

Each Clinical Center will have a computer configuration that includes a PC, a printer, and a modem. This will give each clinical center the capability of logging directly into the AsthmaNet web site with the modem as a back-up if the connection is not possible. Though this set-up is installed primarily to allow for distributed data entry into a centralized and secure database at the AsthmaNet web site, menu options will also include sending electronic mail, downloading study documents such as forms and reports, and viewing a calendar of AsthmaNet events. A sophisticated security system will limit access to qualified personnel and prevent corruption of the study database.

Data integrity and quality assurance

The DCC will be responsible for identifying problem data and resolving inconsistencies. Once the quality control procedures are complete, new study data will be integrated into the primary study database.

Data disclosure

AsthmaNet policies for the submission of data and forms to NHLBI for public use will be followed.

Data retention

Sites are required to follow the applicable guidelines of state and local regulations for keeping source data and case report forms.

Anticipated Results

We anticipate that quintupling the dose of ICS in the yellow zone will reduce the rate of severe exacerbations treated with oral corticosteroids in patients treated with daily low-dose ICS. We will additionally attempt to identify predictors of response to this intervention in order to provide more personalized approaches to therapy.

V. SAFETY

A. REPORTING PERIOD

Participants are at risk of developing adverse events during study enrollment. The safety reporting period begins with the first study specific procedure and ends with completion of study participation with the exception of SAEs potentially attributed to study

drug/interventions. Throughout the reporting period all adverse events (AEs) related to study mandated procedures must be reported. Other AEs (not related to study procedures), which occur prior to study drug administration should not be reported (as AEs but may be reported as medical history). All serious adverse events (SAEs) from the first study specific procedure through study completion must be reported. Any SAE thought to be related to the study intervention or a study mandated procedure should be reported if the onset is within 30 days of study completion.

B. ADVERSE EVENTS

An adverse event is an unfavorable occurrence in a study participant that begins or worsens during the study (from the time of informed consent through study completion). The reporting of an *adverse event* does not imply a causal relationship between the event and study participation. Determination of the relationship between the event and study drug or a study mandated procedure must be made by the Investigator using the guidance provided in Section V.E.

Eliciting adverse events should be spontaneous or in response to an open-ended question, such as “How are you?” or “Have you noticed any changes in your health since your last visit?” Directed questions may be used to follow up spontaneous reporting of events for clinically relevant details. All spontaneously reported adverse events (in the judgment of the investigator) should be recorded.

Scheduled outpatient procedures or hospitalizations for non-urgent interventions (e.g., cataract surgery or knee replacement surgery) should be reported in treatments/interventions. For example, cataracts should be included in the patient’s medical history prior to beginning treatment. The treatment (surgery) can be added with the indication of cataracts when appropriate. If there were worsening of vision in a patient with a history of cataracts during the study, that should be reported as an AE (as it represents worsening of a baseline condition) and the procedure can be reported in the treatment.
The following conventions should be used for reporting AEs:

- If a specific diagnosis is unclear at the time of reporting, descriptive terms should be used. For example, a patient with cough and a headache may later be diagnosed with influenza. Initially “cough” and “headache” may be reported and later changed to “influenza” after the diagnosis is evident.
- Multiple symptoms or signs related to the same event should be reported as a single event, unless complications of the same event are considered medically relevant and not adequately captured in an existing AE. For example, the single AE ” influenza” should be reported rather than headache, cough, sore throat and myalgia if these symptoms are considered related to the infection. However, if the same patient develops renal failure due to severe dehydration with influenza, the renal failure should be reported as another AE.
- The onset of the AE is the date of the first symptom or sign as noted by the patient or a care provider. For example, a patient may have a cough for several days followed by fever and shortness of breath before the diagnosis of pneumonia is made. The AE

should be reported as “pneumonia”, with the onset being the date of the first symptom or sign (cough, in this case).

- Worsening of pre-existing conditions should be reported with a description of the change in status. For example, “worsening allergic rhinitis” may be reported in a patient with a medical history that includes allergic rhinitis while reporting in “allergic rhinitis” in such an individual is not informative.
- Lab or other test results outside the normal range should be reported as AEs if there are associated signs or symptoms or further evaluation or more frequent monitoring is required. Isolated lab findings may be reported as such (e.g., hypokalemia) if no diagnosis is apparent while lab abnormalities associated with a reported AE should not be reported unless they are of independent significance. For example, leukocytosis in a patient with a diagnosis of pneumonia should not be reported whereas leukocytosis (to >60,000 cells/ml^3) in a patient with pneumonia and potential hematologic malignancy should be reported.

Adverse events are reported by the study team and may provide a diagnosis rather than the patient’s own words. Every effort should be made to report the patient’s description of an event, however clinical accuracy is paramount. For example, reporting “chest pain” with no treatment for the event on the case report form because the patient used the word “chest pain” but the physician ascribed the chest discomfort to gastroesophageal reflux for which the patient was already receiving treatment provides information that cannot be interpreted clinically.

Adverse events due to concurrent illnesses other than asthma may be grounds for withdrawal if the illness is considered significant by the study investigator or if the participant is no longer able to effectively participate in the study. Participants experiencing minor intercurrent illnesses may continue in the study provided that the nature, severity, and duration of the illness are recorded and that any unscheduled medications required to treat the illness are also recorded. Examples of minor intercurrent illnesses include acute rhinitis, sinusitis, upper respiratory infections, urinary tract infections, and gastroenteritis. Medications are allowed for treatment of these conditions in accordance with the judgment of the responsible study physician.

C. SERIOUS ADVERSE EVENTS

An AE is serious if the event has had or may have any of the following outcomes:

- Death
    - Any events that are life threatening, or would have resulted in death in the absence of an intervention, must be reported as SAEs in addition to events that result in death.

- Hospitalization
    - Any events that occur during hospitalization and prolong the duration of the hospital stay should be reported as SAEs in addition to the SAE reported with the initial hospitalization.

  - Events that are managed in an emergency room without resulting in hospital admission should be evaluated for other criteria for an SAE (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event) and reported as appropriate.

- Disability or permanent damage
  - Any events that interfere with an individual's ability to perform their usual functions or maintain their quality of life should be reported as SAEs.

- Congenital anomaly or birth defect

- Required an intervention to prevent disability or permanent damage

- Medically important events
  - Events that do not meet any of the listed criteria for an SAE but are nevertheless medically significant should be reported as SAEs. A seizure or syncope may not require hospitalization or be life threatening but should be reported as SAE due to its medical significance.

SAEs that are both unexpected (see Safety Plan section III.E above) and possibly related (see Section V.E. below) to study drug/intervention must be reported to the DCC expeditiously as described below.

D. GRADING SEVERITY OF ADVERSE EVENTS

The severity of AEs should be determined according to the following scale:

Severity	**Characterized by:**
Mild	Event imposes no limitations on individual's ability to perform usual activities
Moderate	Event interferes with ability to perform usual activities
Severe	Event prevents the individual from performing usual activities

It should be noted that severity and seriousness of AEs are separate assessments.

E. DETERMINING RELATEDNESS

The investigator must determine if an AE is "possibly related" or "not related" to the study drug or a study mandated procedure. Determinations should be based on the biologic plausibility, the temporal relationship, and the presence or absence of an alternative explanation for an AE. Events thought to be related to study drug with a high degree of certainty (e.g., temporal correlation between the administration of the drug and the onset of

the AE with resolution after withholding treatment and recurrence following a challenge) should be reported as possibly related. In the context of an alternative explanation (e.g., recent introduction of a concomitant medication known to be associated with the event, with resolution of the event after discontinuing the concomitant medication and continuing study drug), AEs should be reported as not related. In general, most events without an alternative explanation should be reported as “possibly related”.

F. REPORTING REQUIREMENTS

As with all study data, AEs should be reported in a timely fashion. Specific expedited safety reporting requirements are applicable as follows:

- Any SAE which is both suspected of being related to study drug or a study mandated procedure and is unexpected must be reported to the DCC within 7 calendar days.

- Any AE which is both suspected of being related to study drug or a study mandated procedure and suggests a level of risk to study participants that was previously unrecognized or unknown must be reported to the DCC within 30 calendar days.

- Pregnancy requires expedited reporting within 7 calendar days

G. REQUIRED FOLLOW UP OF ADVERSE EVENTS

All adverse events must be followed (and documented on case report forms) until one of the following criteria is met:

- Resolution

- A documented plan for further evaluation and management, including the overseeing care provider, is provided.

- The event is considered and documented to be stable and adequately managed, though ongoing.

H. ADVERSE EVENTS RELATED TO ASTHMA

Asthma exacerbations

Safety net procedures, including visits and frequent telephone contacts, are in place to identify participants who experience an asthma exacerbation during the study.

Asthma exacerbations are severe episodes of acute worsening of asthma symptoms, defined by meeting one or more of the following:

1. Oral/injectable corticosteroid due to asthma

2. Need for emergency treatment at a medical facility that is related to, or complicated by, the participant's asthma and which results in systemic corticosteroid treatment or hospitalization for an acute asthma exacerbation

These episodes can be identified during routine phone follow up or study visits, or can be brought to the attention of the sites by the participants' action plans.

Between in-person study visits (as described above), participants will be contacted by telephone at weeks 8, 16, 24, 32, 40 and 48 by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, to answer any questions that may arise, and to assure that their asthma is under adequate control, as assessed by the participant and through completion of a c-ACT. The coordinator will attempt to determine whether the participant is showing signs of asthma exacerbation using criteria identified below.

Adjustments of Trial Medications and Rescue Algorithms during Asthma Exacerbations

Participants who develop an exacerbation during the run-in period (pre-randomization) will be terminated from study enrollment and managed as clinically-indicated, with treatment based on clinical standard and initiated by/in accordance with the participant's usual asthma care provider. Once the asthma exacerbation has resolved for at least four weeks, the participant may be rescreened for entry into the study once.

For participants who meet criteria for an exacerbation during the post-randomization phases of the study, prednisone will be prescribed at a pre-specified burst at 2 mg/kg/day for 2 days [maximum 60 mg/day], followed by 1 mg/kg/day for 2 days [maximum 30 mg/day].

For those participants experiencing worsening control as demonstrated by the above criteria, the coordinator will contact the study physician to determine if additional treatment, a clinic visit or follow up phone call is required.

Prednisone Treatment

Oral prednisone will be administered for the treatment of impending episodes of severe asthma when bronchodilator therapy is inadequate(35). The decision concerning the initiation or continuation of a course of oral prednisone will be at the physician's discretion, based upon criteria previously published by the ICAC.(13) Prednisone should be prescribed if:

- The participant used more than 3 nebulizer treatments with albuterol or comparable beta-agonist bronchodilator or 6 puffs of albuterol (3 treatments of 2 puffs each) in the prior 4 hours for relief of asthma symptoms OR
- The participant used 12 or more puffs of albuterol in the last 24 hours for relief of asthma symptoms OR
- The participant awakened due to cough, shortness of breath, chest tightness, or

wheezing AND needed to use albuterol at least 2 of the previous 3 nights OR

- The participant used 8 or more puffs of albuterol per day during 2 of the previous 3 days for relief of asthma symptoms.

The recommended prednisone dose for acute exacerbations is 2 mg/kg/day (maximum 60 mg) as a single morning dose for two days followed by 1 mg/kg/day (maximum 30 mg) as a single morning dose for two days. All administered doses should be rounded down to the nearest 5 mg.

In order to limit variability in prednisone prescribing habits across multiple clinicians in the various AsthmaNet partnerships,(41) all providers will be educated regarding the above criteria for prednisone use. They will additionally be provided with a wallet-sized card for easy reference. The DCC will track the reasons for prednisone administration, particularly clinician discretion outside of the above criteria. The DCC will report to the steering committee if excess variability is occurring among sites, and an open discussion regarding these discrepancies will be utilized. This process has successfully been implemented in the NIAID Inner City Asthma Consortium (ICAC).

Asthma Rescue Plan Algorithm

Rescue Algorithm for Acute Loss of Asthma Control

The approach to rescue medications will be based on the consensus report presented in the National Heart, Lung and Blood Institute Guidelines(1). Each patient will be given specific guidelines for decision-making and institution of rescue management (action plan). Two medications, albuterol and/or oral prednisone, will be employed when increasing symptoms require treatment. For a severe acute asthma exacerbation, patients will be medicated according to the best medical judgment of the treating physician (see above).

Home care:

Caretakers and patients will be educated to recognize the signs and symptoms of an asthma exacerbation early so that prompt rescue treatment may be instituted and morbidity decreased. The onset of an asthma exacerbation will be recognized by symptoms such as coughing, dyspnea, chest tightness and/or wheezing that **either** become more severe despite the yellow zone plan being initiated previously, **or** they are severe enough on baseline therapy based on the following criteria.

The threshold for defining entry into the red zone (i.e., exacerbation) will be determined based on the adequacy of the participant's response to albuterol to treat these asthma symptoms. Patients who experience symptoms of cough, dyspnea, chest tightness, and/or wheeze, will initiate use of albuterol (2 puffs) by MDI every 20 minutes for up to 1 hour and then every 4 hours if necessary. If the patient's symptoms persist after 3 treatments, the study center should be contacted. If the patient requires albuterol every 4 hours for 24 hours for persistent symptoms, the study center should be contacted. At the time of study center contact, a clinic visit may be necessary. The initiation of oral prednisone therapy will be based on specific guidelines and on physician discretion.

If symptoms are severe, the child has retractions, evidence of cyanosis based on saturations on room air of < 90% based on pulse oximetry, has evidence of increased work of breathing, shortness of breath and/or "air hunger", the patient **must seek immediate medical care** and should contact the study center.

Physician's office or emergency room:

In the primary physician's office or emergency room, the patient with an acute asthma exacerbation will be treated with nebulized albuterol or high dose MDI albuterol (6-8 puffs every 20 minutes x three or more often if needed). The dose of albuterol for the doctor-supervised situation is 0.10 – 0.15 mg/kg up to 5 mg per treatment. Albuterol can be delivered by nebulizer driven with oxygen, and treatments will be given every 20 minutes for up to 3 treatments. If after 3 treatments, the child is not stable as described below, the physician may use additional albuterol treatments or other medications as is in his/her best clinical judgment. The child will be assessed for general level of activity, color, pulse rate, use of accessory muscles and airflow obstruction determined by auscultation, and FEV1 and/or PEF before and after each bronchodilator treatment. Measurement of oxygenation with a pulse oximeter may also be indicated for complete patient assessment during the acute exacerbation. The following assessments will also be made.

- If the patient has a favorable response to initial albuterol nebulizer treatment (FEV1 at least 80% predicted and/or PEF at least 80% post-randomization reference value), the patient will be observed for 1 hour prior to being discharged home with instructions to continue albuterol every 4 hours as needed and to report any decline in PEF and/or symptom fluctuation promptly.
- If the patient does not improve (FEV1 less than 80% predicted or PEF less that 80% post-randomization reference value) after the initial albuterol nebulizer treatment, nebulized albuterol therapy will be continued for at least 2 more trials (for a total of 3 times in 1 hour). If the patient's clinical symptoms are stabilized and FEV1 or PEF is between 50-80% of predicted or post-randomization reference value, the patient will be discharged home to continue use of albuterol (2 puffs every 4 hours) and to start a four-day course of oral prednisone.
- If the patient's FEV1 is less than 50% of predicted or PEF is less than 50% of post-randomization reference value after 3 treatments with nebulized albuterol in 1 hour, the physician may use his/her best medical judgment to treat the patient. Such clinical judgment may include the need for hospitalization and inpatient monitoring.

Criteria for Study Withdrawal

If a participant experiences 6 yellow zone courses in 12 months, they will be withdrawn from the study. Additionally, if a participant experiences 2 severe exacerbations treated with oral corticosteroids in 6 months or 3 within 12 months, they will be deemed a *treatment failure* and withdrawn from the study. Finally, if a participant is hospitalized for an asthma exacerbation >24 hours, they will be withdrawn from the study.

I. UNBLINDING

Unblinding to determine treatment group assignment in the event of medical necessity will be performed by center PI in consultation with study PI and the DCC PI.

VI. STUDY COMPLETION

Study completion is defined by enrollment, randomization, receipt of study drug/intervention and follow up through Visit 8.

A. STUDY TREATMENT DISCONTINUATION

Study treatment discontinuation occurs if the patient, Investigator, or Sponsor stop treatment prior to the last scheduled dose per protocol. Study treatment discontinuation does not necessarily result in early termination; a patient may continue study participation without receiving treatment if at least one dose/intervention has been received.

B. EARLY TERMINATION

Early termination occurs if the participant, Investigator, or the Sponsor does not permit the participant to complete the last scheduled study visit or assessment. By definition, early termination during the treatment period of the study will result in study treatment discontinuation.

VII. STUDY SITES

A. SITE RESPONSIBILITIES

A single Principal Investigator must be designated and is responsible for study conduct at each site.

B. INFORMED CONSENT

The process of informed consent should be led by an individual qualified to understand and present the potential benefits and risks of a research study to potential participants. Ideally, someone who is not directly involved in the patient's usual clinical care should lead informed consent. The informed consent process must be completed before any study procedures can be performed for the purpose of this protocol. Verbal assent and written assent will be obtained based on age determined by local IRBs.

C. INSTITUTIONAL REVIEW BOARD

Each institution conducting research must have a federal wide assurance and an IRB registered with the Office of Human Research Subjects' Protection prior to study

participation. Individual IRB's policies regarding reporting practices and communication must be adhered to throughout the conduct of the study.

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IX. APPENDICES

APPENDIX A: TABLE OF VISIT STRUCTURE

Visit	V1	V2	T1	V3	T2	V4	T3	V5	T4	V6	T5	V7	T6	V8	V_{EXAC}
Visit type	Enroll	Random-ization	Phone f/u	Clinic f/u	Phone f/u	Clinic f/u	Phone f/u	Clinic f/u	Phone f/u	Clinic f/u	Phone f/u	Clinic f/u	Phone f/u	Exit visit	Exacer-bation
Study Week	0	4	8	12	16										PRN
Window (days, reg/ext)		±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	±3/±5	
Informed consent	X				20	24	28	32	36	40	44	48	52		
Full medical history	X														
Long physical exam	X														X
Partial physical exam				X				X		X		X		X	
Height/Weight	X	X		X				X		X		X		X	
Exhaled nitric oxide (FeNO)				X				X		X		X		X	
Spirometry	X	X		X	X			X		X		X		X	X
Impulse oscillometry (IOS)				X	X			X		X		X		X	
Max-BD assessment	X				X										
Methacholine challenge		X			X										
Case report forms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Action plan dispensed	X	X													
Action plan reviewed	X	X		X				X		X		X		X	X
Electronic diary dispensed	X														
E-diary reviewed		X		X				X		X		X		X	X
Blood draw		X			X										
Urine pregnancy test	X	X													
Nasal blow		X			X										
Dispense home nasal blow kit				X				X		X		X			
Dispense open-label study medications	X	X		X				X		X		X			
Dispense study medications	X			X	X			X		X		X			
Review medication technique	X	X		X	X			X		X		X			
Collect study medications	X				X									X	
Discuss future care														X	
Exit interview					X									X	

APPENDIX B: TABLE OF EXCLUDED CONCOMITANT MEDICATIONS

Table 1. Excluded concomitant medications

Medication	Period when medication may not be taken or modified
Immunomodulatory medications	5 half-lives of the medication prior to screening visit – 3 month washout for Xolair
Coumadin	2 weeks prior to screening
Immunotherapy	Stable dose and frequency for at least 90 days prior to the study and intended to remain stable throughout the study
Theophylline	48 hrs prior to screening
Beta blockers	48 hrs prior to screening
Anti-psychotic medications	1 month prior to screening
Cancer chemotherapies	Ever
Chronic antibiotics	2 weeks prior to screening
Montelukast/zafirlukast	48 hrs prior to screening
Daily NSAIDs	48 hrs prior to screening

APPENDIX C: STICS ACTION PLAN PATIENT HANDOUT

STICS ACTION PLAN

When your child first awakes:

1. **Have your child take his/her daily morning medications.**
   - Administer 2 puffs from the **GREEN OR YELLOW** Inhaler with spacer. Rinse his/her mouth.

Before your child goes to bed:

1. **Have your child take his/her daily evening medications.**
   - Administer 2 puffs from the **GREEN OR YELLOW** Inhaler with spacer. Rinse his/her mouth.
2. **Complete the spirotel® session (5 PM to 12 AM).**
   - Answer each question.
   - Your child will be required to perform 3 peak flow measurements.

Starting the Yellow Zone:

Do NOT wait for your spirotel® device to tell you to start the using the YELLOW inhaler. Start as soon as your child meets any of the criteria below.

If your child has any of the following, Yellow Zone should be started:
- **Nighttime awakening** with asthma symptoms requiring albuterol use
- **6 or more puffs of albuterol** taken for asthma symptoms **in 24 hours**
- **4 puffs of albuterol** taken for asthma symptoms **in a 6 hour period**

Starting Prednisone:

Do NOT Start Prednisone on your own. Contact the Study Team.

Contact the study team immediately if your child:
- uses 6 or more puffs of albuterol taken for asthma symptoms **in a 4 hour period**
- uses 12 or more puffs of albuterol taken for asthma symptoms **in a 24 hour period**
- awakens at night due to asthma symptoms requiring albuterol **for 2 consecutive days**
- uses 8 or more puffs of albuterol taken for asthma symptoms in a 24 hour period **for 2 consecutive days**

Bring to your child's next study visit:

- Your child's spirotel® device
- **All** your child's study medications and spacers
- The handout folder
- Any nasal samples collected if your child had a cold

APPENDIX D: PROCEDURES FOR MEASURING HEIGHT

Equipment and Standardization

A Harpenden stadiometer, either wall-mounted (Holtain Model #602VR) or portable (Holtain Model #603), will be used for height measurements. Measurements will be in centimeters.

The stadiometer will be calibrated daily. The wall-mounted stadiometer is calibrated by measuring the height of the metal calibration bar that was included with your stadiometer and recording the exact length on the stadiometer. The portable stadiometer is calibrated by lowering the platform to its lowest position and setting the counter to the number listed on the inner cover of the stadiometer.

The stadiometer is designed so that if something breaks, it will be the counter. At least one extra counter should be available at all times. The stadiometer platform should be moved slowly; moving it too fast could cause it to break.

Height Measurement Procedure

Height will be measured in all children. The child should be barefoot or wearing thin socks for the height measurement. Follow the steps below to obtain standing height:

1. Raise the platform of the stadiometer well above the child's head.
2. Have the child stand erect, with his/her back against the stadiometer.
3. In positioning the child for measurement, start at the child's feet and go upward.
4. The heels should touch the back of the stadiometer, with the ankles and feet touching each other.
5. The knees should be straight and locked.
6. The heels, buttocks and shoulders should be against the stadiometer.
7. The arms should hang freely by the sides of the trunk with the palms facing the thighs.
8. The operator may need to push in on the child's abdomen slightly to minimize lordosis.
9. The child should look straight ahead and not raise his/her chin.
10. The middle of the ear and the corner of the eye should be in a straight line.
11. When standing properly, the child should take a deep breath, hold it, and maintain a fully erect position for the measurement.
12. To make the measurement, lower the platform to the child's head; the operator should be at eye level with the child's head.
13. Record the height in centimeters.

14. The platform is lifted and the child steps away from the stadiometer.
15. Repeat these steps twice to obtain 2 additional measurements.
16. Repeat measurements until you have 3 measurements such that the maximum difference between any 2 measurements is 3 mm or less.

Since using the above protocol will minimize the diurnal variation in height, there will not be any restriction on the time of day of the measurement, but the time of the measurement will be noted on the data collection form.

Girls should be instructed to not have their hair “high” since hair has to be flattened during the measurements. Younger children may need two operators (one can be a parent), with the second operator helping to hold the child's feet flat on the ground since some children tend to stand on their toes.