

**American Lung Association
Asthma Clinical Research Centers**

**Study of Asthma and Nasal Steroids
(STAN)**

U01 HL089464-01A2 (Dixon) and U01 HL00895101-01A2 (Wise)

**Version 2.0
9 April 2010**

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Abstract

The American Lung Association-Asthma Clinical Research Centers is a network of 18 academic research centers. Results from trials completed by the ALA-ACRC have identified rhinitis and/or sinusitis as a significant co-morbidity in people with asthma that affects asthma symptoms and control. The objective of the proposed clinical trial is to determine if treatment of chronic rhinitis and/or sinusitis improves control of asthma in children and adults. Although chronic rhinitis and/or sinusitis have been associated with poor asthma control and increased health care utilization, the effect of treating these diseases on asthma control is not known.

We propose a six-month randomized, double-blinded, placebo-controlled trial enrolling 380 participants, 190 children and 190 adults, with poorly controlled asthma and chronic rhinitis/sinusitis. We will use sensitive and specific tools, developed by us, to identify chronic rhinitis and/or sinusitis in people with asthma. Participants will be randomized to receive nasal steroid or a matching placebo in addition to their regular asthma treatments. The primary objective of the trial will be to evaluate whether the addition of treatment with nasal steroids improves asthma control. We will perform allergy skin testing on all participants and keep a record of pollen counts at all centers, to determine if allergy is an important factor in the response to nasal steroid in participants.

1. Introduction

1.1 Title

Study of Asthma and Nasal Steroids (STAN)

1.2 Sponsors

The American Lung Association; National Institutes of Health/National Heart Lung Blood Institute R01 HL089464-01A2 (Dixon) and R01 HL00895101-01A2 (Wise), and Schering Plough will provide intranasal mometasone and matching placebo for the trial

1.3 Investigators and Study Centers

Network Chair

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Participating Centers

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Data Coordinating Center

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1.4 Background and Significance

Asthma affects 15 million people in the United States. Poorly controlled asthma is increasingly common and associated with escalating health care costs.¹ In 2003, asthma led to 12 million physician office visits and 1.7 million Emergency Department visits, and so reducing poorly controlled asthma is a key objective of the national "Healthy People 2010" program. The American Lung Association Asthma Clinical Research Centers is a research network committed to performing clinical trials in diverse patient populations with asthma to refine treatment guidelines and have a major impact on the health of asthmatics. We have already completed a number of trials that have impacted asthma treatment guidelines, as highlighted in a recent editorial in the *Annals of Internal Medicine*.²

During recent years a major focus of the network has been the study of sinonasal disease, this is a very important comorbidity in people with asthma. Our own work, and that of others, suggests that over 70% of asthmatics report sinusitis, rhinitis or both.^{3,4} Rhinitis and sinusitis are closely linked. Disease processes considered to be rhinitis clearly affect the sinus mucosa^{5,6,7} and sinusitis is usually preceded, and accompanied, by rhinitis.^{7,8} We have found that approximately 30% of our asthma clinical trial participants report sinusitis,³ and in the preliminary study we performed to prepare for the current application, approximately 1/3 of patients with poorly controlled asthma were found to have chronic sinusitis.

Rhinitis and sinusitis usually precede asthma. An individual with rhinitis has a three-fold increased risk of developing asthma compared to an individual without rhinitis,⁸ and children with rhinitis have a 2.5 fold increased risk of developing cough and recurrent wheezing compared to children without rhinitis.⁹ Because rhinitis precedes asthma, there is current interest in aggressively treating rhinitis as an intervention strategy to prevent the development of asthma in children.¹⁰

Our fundamental interest is to determine if treating chronic sino-nasal disease will improve asthma control. To achieve our goal, we developed a systematic research plan for studying sino-nasal disease. We obtained pilot funding to develop a screening tool for this disease in patients with asthma as a necessary preliminary step to identify participants for a large clinical trial. The primary goal of the current study is to evaluate the effectiveness of nasal steroids to treat chronic rhinitis and sinusitis in children and adults with uncontrolled asthma. We propose a six-month multi-center, placebo-controlled, double-masked, randomized trial to determine if nasal steroids will improve control of asthma in this patient population.

The results of this trial will have an important impact on asthma guidelines. If positive, it will demonstrate that treating chronic sino-nasal disease is an important intervention to improve asthma control. If negative, it will show that this is an irritating co-morbidity that does not affect asthma control.

2 Study Design

This study will be a randomized, double-masked, placebo-controlled trial of the effectiveness of nasal steroids for the treatment of chronic rhinitis and sinusitis on asthma control. Asthmatic patients with chronic rhinitis and sinusitis will be randomized to treatment with 6 months of nasal steroid (mometasone), or matching placebo, in addition to their baseline asthma regimen. Active drug and placebo will be supplied by Schering Plough. Participants will be asked to refrain from taking non-study medications (other than topical decongestants or saline) for their nasal symptoms. They will be trained to exhale all orally inhaled steroids through the mouth, to

avoid any potential benefit of orally inhaled steroids on the nasal mucosa. The primary outcome will be asthma control.

2.1 Study Groups

The study population will be split with 1/2 pediatric population (ages 6-17 years) and 1/2 adult. 190 subjects will be treated for 6 months in each arm of the study (380 total).

Group I – Active Treatment:

- Age ≥12 yrs: Intranasal mometasone, 2 sprays each nostril once a day for 6 months
- Age < 12 yr: Intranasal mometasone 1 spray each nostril once a day for 6 months

Group II – Placebo Treatment:

Placebo Nasal Steroid

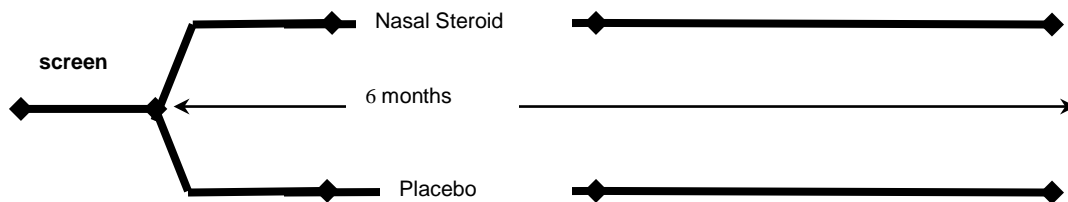
- Age ≥12 yrs: Intranasal placebo, 2 sprays each nostril once a day for 6 months
- Age < 12 yr: Intranasal placebo 1 spray each nostril once a day for 6 months

2.2 Primary Hypothesis

Patients with symptomatic rhinitis and/or sinusitis will have improved asthma control when receiving daily treatment with nasal inhaled corticosteroids.

2.3 Trial Schema

The study is a randomized parallel group double-masked design, stratified by age. Visit 1 (V1) is the screening visit, V2 is the randomization visit. Visits are monthly after the randomization visit (P indicates a phone visit).



V1-V5: Clinic visits
 P1-P3: Phone Visits
 V1, V5: Methacholine testing

Potentially eligible patients will be screened and followed for a 2 to 4 week run-in period. During the run in period the subjects will record daily peak flow and fill in an asthma diary card. Patients will be randomized to one of two study treatments at V2. The allocation ratio is 1:1. A permuted block randomization scheme stratified by clinic and age will be employed. Data collected at baseline and during follow-up will include demographic information, medical history, lung function, asthma and sinus symptoms and asthma and nasal medication usage (via diary cards and interviews).

2.4 Eligibility Criteria

The goal of the trial is to enroll patients who have both inadequately controlled asthma and symptoms of chronic rhinitis and/or sinusitis as determined by their Sino-Nasal Questionnaire (SNQ) score, a score which asks about sinus symptoms over the last 3 months. We will exclude participants with sinus symptoms for less than 8 weeks.

Inclusion Criteria:

1. Physician diagnosed asthma.
2. At least 12% increase in FEV₁ after 2-4 puffs of albuterol or positive methacholine challenge (20% fall in FEV₁ at less than 16 mg/ml methacholine) – either of these can be available from the last 2 years before enrollment.
3. Poorly controlled asthma as documented by a score of 19 or less on the Asthma Control Test (ACT) for participants 12 and older, and a Childhood Asthma Control Test (C-ACT) for 6-11 years. (both V1 and V2).
4. Chronic symptoms of rhinitis and sinusitis as measured by a mean score of greater than or equal to 1 on the Sino-Nasal questionnaire (SNQ) (both V1 and V2).
5. Males and females, age 6 and older.

2.4.1 Exclusion Criteria

1. Co-morbidity that predisposes to complicated rhinosinusitis (e.g. cystic fibrosis, insulin dependent diabetes mellitus, immunodeficiency disorder).
2. Chronic diseases (other than asthma) that in the opinion of the investigator would prevent participation in the trial or put the participant at risk by participation, e.g. chronic diseases of the lung (other than asthma), heart, liver, kidney or nervous system.
3. History of sinus surgery in last 6 months.
4. Systemic/nasal steroids within last 4 weeks.
5. Anti-leukotriene medication within last 2 weeks.
6. History of upper airway symptoms or other acute illness for less than 8 weeks at the time of randomization.
7. Fever > 38.3°C, or patient history of fever in last 10 days (at V2).
8. Greater than 10 pack year smoking history or active smoking within the last 6 months.
9. FEV₁ < 50% predicted (both V1 and V2).
10. Females of childbearing potential that are pregnant or lactating, or unwilling to practice an adequate birth control method (abstinence, combination barrier and spermicide or hormonal).
11. Allergy or intolerance to nasal mometasone.
12. Cataracts, history of glaucoma, or other conditions resulting in increased intraocular pressure.
13. Any investigational drug in the last 6 weeks.
14. Inability to comply with study procedures, including:
 - a. inability or unwillingness to provide informed consent (or assent in the case of a minor).
 - b. inability to take study medication.
 - c. inability to perform baseline measurements.
 - d. completion of less than 10 of the 14 days of screening period diary entry.
 - e. inability to be contacted by phone.
 - f. intention to move out of the area within 6 months.

2.5 Outcomes

2.5.1 Primary Outcome

The primary outcome measure is the Asthma Control Test (ACT) after six months of treatment with nasal inhaled corticosteroids. This instrument has been validated for ages 4-11 in the Childhood Asthma Control Test (C-ACT) and 12 and older in the ACT.^{11,12} It integrates common indicators of asthma control including cough, nocturnal awakenings, frequency of medication use, and frequency of symptoms. The ACT score was chosen as the main outcome measure for several reasons. First, it is a sensitive measure of asthma control, a 3 reflects a clinically meaningful difference in asthma control. Second, the instrument is well validated. Third, the instrument is a short questionnaire with easy to administer questions that are easily understood.

2.5.2 Secondary Outcomes

Episodes of Poor Asthma Control (EPAC): EPAC's will be determined from the daily asthma diaries as well as the interval asthma history obtained at each follow-up visit. They are defined by one or more of the following:

- Decrease of > 30% in morning Peak Expiratory Flow (PEF) (from personal best) for 2 consecutive days (definite yellow zone event), OR
- Addition of oral corticosteroid (e.g., prednisone) to treat asthma symptoms, OR
- Unscheduled contact with a health care provider (ED, physician office, hospital) for asthma symptoms, OR
- Increased use of bronchodilator rescue medication over baseline by 4 or more puffs of metered dose inhaler or 2 or more nebulizer treatments on one day.

Bronchial Hyperreactivity: Airway reactivity will be measured with methacholine challenge testing following ATS guidelines using the dosimeter technique.¹³ Five breaths change of doubling concentrations of methacholine are inhaled starting at 0.03 mg/ml until a 20% or greater fall in FEV1 occurs or a maximum of 16 mg/ml is inhaled. Results are computed as the logarithmic interpolated concentration that causes a 20% fall (PC20) as well as the slope of the dose response relationship. The test will not be performed in participants with an FEV1 < 70% predicted, because of safety considerations.

Sinusitis and rhinitis symptoms: Symptoms will be assessed using standard scoring systems^{14, 15, 16}. The Sinus Symptom Score questionnaire (SS) will be administered at scheduled clinic visits.

Sinusitis and rhinitis quality of life: Quality of life will be assessed using previously validated questionnaires for sinusitis and rhinitis in adults¹⁷ and children.^{18, 19} The Sinonasal Outcome Test (SNOT-22) and the Sinus and Nasal Quality of Life Survey (SN-5) questionnaires will be administered at scheduled clinic visits to assess the effectiveness of our intervention for upper airway disease

2.5.3 Tertiary Outcomes

Participants will also record the following information on the daily diary cards: nocturnal asthma awakenings, asthma treatments, nasal and sinus symptoms, health care use (we will also record medications for sinus disease on these cards) and if a patient thinks they are currently in their allergy season.

The Asthma Symptom Utility Index (ASUI) is a validated 2-week recall questionnaire that addresses issues of asthma control weighted by impact on functional status.²⁰

Asthma specific quality of life is measured with the Marks Asthma Quality of Life Questionnaire (Marks AQLQ) which has been validated for individuals 15 and older. The Children's Health Survey for Asthma (CHSA) will be used to measure quality of life in participants 6-14 years. These questionnaires will be completed at clinic visits.^{21, 22}

Pulmonary function as measured by FEV1 and forced vital capacity (FVC) using American Thoracic Society guidelines²³ pre- and post- bronchodilator at all clinic visits.

Generic health-related quality of life (QOL) is measured using two instruments – the Medical Outcomes Study SF-36 (MOS-36)²⁴ for those 18 years of age and older and the Child Health Questionnaire (CHQ-PF50) for those less than 18 years old. Both are widely used, have been correlated with asthma outcomes²⁵ and will allow a global assessment of treatment effects. Side-effects and toxicity are assessed by questionnaire and open-ended questions at each visit. Reporting procedures for side-effects that may result in temporary discontinuation of study treatment and serious adverse events (SAE) are described in Section 3.2, Side effects of study treatment and Section 4.7 Data and safety monitoring.

Interval History / Health Care use are recorded at each study visit. With participant permission, records of all hospitalizations and, if necessary, deaths are obtained for verification of diagnoses and assessment of safety issues.

Rhinitis/Sinusitis Exacerbations: We will record the frequency of episodes of rhinitis/sinusitis exacerbations as defined by any one of the following criteria:

- Use of additional medication for upper airway symptoms
- Health Care visit for upper airway symptoms
- Patient self-report of episode of acute sinusitis or upper respiratory tract infection

Serum and nasal lavage specimens will be collected to evaluate eotaxins and eosinophilic cationic protein (ecp). These will be measured at a central laboratory located at the University of Vermont under the direction of Dr. Anne Dixon.

Exhaled nitric oxide (eNO) will be measured with a portable NO measuring device, the Insight eNO System (Apieron, Menlo Park, California), at the randomization visit (V2) and final clinic visit (V5). A substudy will be conducted at a few centers, where eNO will be measured using both the Insight system and the NIOX MINO monitor (Aerocrine, New Providence, NJ) to compare outputs between the two instruments for accuracy of the eNO measurements.

2.5.4 Other data

Data on potential confounders and study adherence will also be collected via questionnaires, including:

Questionnaires: administered at baseline to ascertain demographics, general health, medication use, rhinitis or sinusitis severity and duration, asthma symptoms and menstruation (Asthma in Females Questionnaire), smoke exposure (Smoke Exposure in Children

questionnaire), asthma severity and asthma triggers. These data will be used to determine eligibility, characterize the population, and classify asthma subtypes.

Allergy skin testing will use the Multi-Test II (Lincoln Diagnostics, Inc). The Multi-Test II device is a sterile, disposable, multiple test applicator used to administer skin-test substances. This device meets OSHA guidelines for technician protection, and it provides a lower coefficient of variation than similar devices and than a bifurcated small pox needle.

Pollen Counts: Pollen counts at all clinical sites will be recorded using data from National Allergy Bureau pollen counting sites certified by the American Academy of Asthma, Allergy and Immunology.

Closeout Questionnaires will be administered at the last visit to determine global assessments of treatment, adequacy of informed consent procedures, satisfaction with study procedures and personnel, and information about participation in future studies.

2.6 Study Data Collection Schedule

The specific study procedures and approximate time commitment from the participants are shown below:

Screening Visit, Visit 1 (weeks -4 to -2) (5 hours)

- Explanation of study
- Obtain informed consent (and assent when appropriate)
- Baseline eligibility forms
- Brief physical examination
- Spirometry pre and post bronchodilator
- Administer questionnaires: Sino-nasal Questionnaire (SNQ), Asthma Control Questionnaire (ACQ), Asthma Symptom Utility Index (ASUI), Sinus Symptoms Questionnaire (SS), Sinus quality of life (SNOT-20, RQLQ), asthma quality of life (Mini AQLQ or PAQLQ), general quality of life (MOS-36 or CHQ-PF50).
- Asthma action plan
- Distribute baseline diary and portable peak flow meter
- Methacholine challenge test for participants with FEV₁ greater than or equal to 70%
- Pregnancy test (if applicable)

Randomization Visit, Visit 2 (3 hours)

- Review consent and study expectations
- Review diaries
- Asthma action plan
- Interval medical history
- Review eligibility criteria
- Pregnancy test for persons of child-bearing potential
- Administer questionnaires: ACT or C-ACT, , ASUI, SNQ, SS, SNOT-22 or SN-5, RQLQ, Mini AQLQ or PAQLQ, MOS-36 or CHQ-PF50, Asthma in Females, and Smoke Exposure in Children questionnaires
- Exhaled nitric oxide measured
- Allergy skin test
- Spirometry pre and post bronchodilator
- Venous blood sample for DNA, ECP and eotaxins
- Nasal lavage for ECP and eotaxins
- Randomization

- Treatment distribution
- Establish study visit schedule

Interval Clinic Visits, Visits 3 (week 4) and 4 (week 12) (2 hours each)

- Return, review asthma diaries
- Administer rhinitis, sinusitis and asthma questionnaires: Asthma Control Test (ACT or C-ACT), Asthma Symptom Utility Index (ASUI), Sinus Symptoms Questionnaire (SS), Sinus quality of life (SNOT-22, or SN-5), asthma quality of life (Marks AQLQ or CHSA), general quality of life (MOS-36 or CHQ-PF50).
- Adverse event screen
- Interval health history
- Spirometry, pre- and post-bronchodilator
- Adherence counseling
- Treatment distribution

Phone Visits (weeks 8, 16, 20) (15 minutes each)

- Reinforce daily diary completion and PEF monitoring
- Adverse event screening
- Confirm follow up visit date

Final Visit, Visit 5 (week 24) (3 hours)

- Methacholine challenge test for participants with FEV₁ greater than or equal to 70%
- Pregnancy test (if applicable)
- Administer questionnaires (ACT or C-ACT, ASUI, SS, SNOT-22 or SN-5, Marks AQLQ or CHSA, MOS-36 or CHQ-PF50)
- Return, review diaries
- Rhinitis, sinusitis and asthma questionnaires
- Adverse event screen
- Interval health history, Brief physical examination
- Exhaled Nitric Oxide measured
- Spirometry pre- and post- bronchodilator
- Serum specimen and nasal lavage
- Close out questionnaires

Table 1: Study Data Collection Schedule

Visit	V1	V2	V3	P1	V4	P2	P3	V5
Time (weeks)	-4 to -2	0	4	8	12	16	20	24
Consent, eligibility	*							
Pregnancy Testing	*	*						*
Physical exam	*							*
Randomization		*						
Adherence monitoring			*		*			*
Diary instruction, PEFR, action plan	*	*	*	*	*	*	*	*
Return diary cards		*	*		*			*
Baseline questionnaire	*							
Sino-Nasal Questionnaire (SNQ)	*							
Interval asthma & sinus history		*	*	*	*	*	*	*
Asthma Control (ACT or C-ACT, ASUI)	*	*	*		*			*
Sinus symptom questionnaire (SS)	*	*	*		*			*
Sinusitis QOL (SNOT-22 or SN-5)	*	*	*		*			*
Asthma QOL (Marks AQLQ or CHSA)	*	*	*		*			*
General QOL (MOS-36, CHQ-PF50)	*	*	*		*			*
Asthma in Females Questionnaire (FQ)		*						
Smoke Exposure in Children Questionnaire (SQ)		*						
Adverse event screen			*	*	*	*	*	*
Spirometry pre and post	*	*	*		*			*
Methacholine Challenge Test	*							*
Venipuncture		*						*
Allergy Skin Testing		*						
Exhaled Nitric Oxide		*						*
Nasal Lavage		*						*

ACT – Asthma Control Test, C-ACT – Childhood Asthma Control Test, ASUI – Asthma Symptom Utility Index, Marks AQLQ – Marks Asthma Quality of Life Questionnaire, CHSA- Children’s Health survey for Asthma, MOS-36- Medical Outcomes Study Short Form-36, CHQ-PF50- Child Health Questionnaire,

The main outcomes from this study are outlined above. An ancillary study evaluating genetic polymorphisms associations with response to nasal corticosteroids will be conducted by John Lima (PI at NCC). Any other ancillary studies will be first approved by the Steering Committee of the ALA-ACRC.

3 Study Treatments

3.1 Assigned treatments

Participants will be randomly assigned to receive either intranasal mometasone furoate monohydrate or a matching placebo. Active drug and placebo will be provided by Schering Plough. The study drug is packaged in a metered-dose, manual spray unit; each actuation of the pump delivers 50 mcg of mometasone furoate. The dose of mometasone or placebo will be dictated by age, participants age 12 years or older will be instructed to use 2 sprays in each nostril daily for 6 months. Younger participants (ages 6 to 11 years) will be instructed to use one spray in each nostril daily for six months.

3.2 Side effects of study treatments

Nasal mometasone is indicated for the treatment of perennial rhinitis in patients age 2 years and older and for nasal polyposis in patients aged 18 years and older. We will be using this drug to treat perennial rhinitis and chronic sinusitis (which is frequently associated with perennial rhinitis). We will exclude participants with known adverse reactions to nasal steroids. Topical steroids may have the potential to increase intraocular pressure and increase the risk of cataracts. Topical mometasone use for 12 months has not been found to increase intraocular pressure in a trial involving approximately 100 participants, nevertheless, we will exclude participants with a history of glaucoma. There is also a concern that topical steroids may affect the hypothalamo-pituitary-adrenal axis and/or be associated with growth suppression. In a clinical trial of children aged 3 – 9 years, there was no effect on growth velocity or adrenal suppression as assessed by a cosyntropin stimulation test²⁶ when using mometasone at recommended doses. Long term treatment with nasal steroids may increase the risk of epistaxis and/or has been associated with nasal septal perforation. We will examine the nasal mucosa at clinic visits and withdraw any patient with this complication.

Adverse reactions to intranasal steroids will be minimized by monitoring side-effects at clinic visits. If possible side-effects become more than mild, study treatment will be discontinued, and this is recorded as a study outcome event for secondary analyses. If it is considered probable that the side-effects were the result of the treatment, study treatment will not be re-started. If it is considered possible or unlikely that the side-effects are the result of the study treatment, then the treatment will be re-started after the side-effects subside. If the same side-effects recur, the participant will be taken off the study treatment. For severe adverse events thought to be possibly or probably related to study treatment, the treatment will be withdrawn for the duration of the study.

3.3 Randomization

Participants will be randomly assigned with an equal allocation ratio to receive either intranasal mometasone or matching placebo for 6 months. The treatment assignment will be double-masked, neither the participant nor the clinical center investigators will be informed of the treatment group. Randomization will be accomplished with an auditable, documented generation scheme that produces a reproducible order of assignment. Randomization will be stratified by center and age (6 to 17 years and 18 years or older). The randomization scheme will be written and controlled by the Data Coordinating Center (DCC).

Randomization will be carried out at Visit 2, after all eligibility criteria have been checked, the participant has signed consent for the study and baseline assessments are completed. An eligibility form will be entered into the web-based online data system. After the data system verifies eligibility, the participant will be assigned a multi-digit medication ID number. The

participant will only receive study treatment labeled with that ID number throughout the trial. All interactions with the treatment assignment database will be logged. Only the drug distribution center and selected DCC personnel will know the actual treatment assignments.

3.4 Unmasking

Unmasking of the clinic or the participant to the treatment assignment may be required in some situations. If the participant becomes acutely ill and the treating physician requires knowledge of the container contents, the treatment assignment may be revealed. This may be accomplished in one of two ways, with the preference given to the first. 1) When the clinic learns of a request for unmasking from a participant or a participant's physician or a hospital emergency room, a phone call to request unmasking is made to the DCC. The DCC may then contact the participant or the physician directly to reveal the treatment assignment. Thus in some cases partial unmasking may occur, with the clinic staff remaining unaware of the treatment. In other cases the participant's physician may be told of the treatment assignment while both the clinic staff and participant remains masked. 2) If the DCC cannot be contacted in an emergency, clinic personnel may unmask the treatment assignment by opening the sealed treatment assignment envelope in the participant's folder. All instances of unmasking will be recorded and submitted to the Monitoring Board for review.

We anticipate that in most acute illnesses, knowledge of the treatment assignment would not be required for treatment. If necessary, the assigned treatment could be stopped until the emergency passes and re-instituted later.

3.5 Asthma Treatment

If a participant experiences an asthma exacerbation or other signs of significant worsening of asthma, the participant will be referred to their primary asthma care provider for re-evaluation of their asthma medication regimen. If the asthma care provider is not available in a timely fashion, the clinical center physician will evaluate the participant's treatment regimen and make recommendations for the future course. There are no restrictions on rescue medications and clinic personnel will ensure that all participants have a supply of rescue medications at the V2 visit.

3.6 Routine Chronic Rhinosinusitis Treatment

We aim to include any patient with symptomatic chronic rhinitis and sinusitis. Subjects may continue to take anti-histamine type medication if taking this before enrollment, as long as they still have symptomatic upper airway disease at the time of enrollment into this trial. We will encourage participants to refrain from taking any other prescription or non-prescription medication for their sinus symptoms during this trial, but if they need to take medication for symptomatic relief we will suggest they may take topical medications such as a short course of decongestant, nasal saline or artificial tears. We will record all use of antihistamines and nasal medications in diary cards. We will recommend that patients experiencing significantly increasing sinus symptoms be referred for specialist evaluation.

4 Statistical Design and Sample Size

4.1 General Statistical Approach

All analyses will be stratified by age (pediatric and adult). The analysis of the primary outcome, change in ACS score, will incorporate the repeated measures through the use of linear mixed effects models. Power for the trial was calculated using simulations of the estimate of difference between placebo and treatment in the change in ACS from baseline to 6 months based upon a saturated linear mixed effect model. These simulations were performed for the complete data and a simple missing data scenario. Descriptive data summaries of key outcome measures will be performed throughout the study for monitoring safety and data quality. Typically, these summaries include means, ranges and measures of variance by treatment group; box-plots by treatment group; and time series plots of outcome data by treatment group. All major outcome analyses will be performed independently by two analysts to confirm the accuracy of data filters and analytic routines. Analyses are generally done with the current version of SAS. The data filtering routines and analysis programs are catalogued and archived to permit future replication of results.

4.2 Justification of Sample Size

We have calculated the power and sample size using the proposed new primary outcome, change in ACT score at six months. Based upon data from SARCA as well as previous research²⁷, the standard deviation of ACT at a single time point ranged from 3.5 to 5.0. Furthermore, the correlation between baseline and follow-up measurements was approximately 0.5 for both the 6-11 year olds as well as the 12 and older SARCA participants. Therefore, the standard deviation for the change ACT is estimated to be 5.0 based upon the conservative upper bound of the observed cross-sectional standard deviations and the observed correlation. In addition, we allowed for an 11% inflation of the sample size to allow for the expected levels of missing data (6%) and cross over (5%). Calculations were made for the pediatric and adult groups separately and assume a two-sided type 1 error rate. The assumptions for the two populations were the same based upon the initial ACT data from SARCA stratified by age category (6-11, 12+). With the original sample size (190 per age category), we have 90% power to detect a 2.8-point difference in the change in ACT (measured from baseline to 6 months) for individuals in the treatment group as compared to those in the placebo group. A single interim analysis is planned once 50% of the patients have reached the end of follow-up (See initial proposal for O'Brien-Fleming stopping boundaries).

The interim analysis will be performed at the midway point in the trial (Table 2). The actual samples size used in the program is 172 to account for the 10% drop out rate. The calculations are based upon O'Brien-Fleming²⁸ boundaries using the PASS package PASS Software version 6.0 [NCSS, Kaysville, UT, USA].

Table 2: Power calculations for the pediatric and adult cohorts using the O'Brien Fleming boundaries with a single interim analysis.

Sample Size	Time	(Lower Boundary, Upper Boundary)	Inc. Alpha	Total Alpha	Inc Power	Total Power
380	1	(-2.96, 2.96)	0.0031	0.0031	0.1640	0.1640
	2	(-1.97, 1.97)	0.0469	0.0500	0.6358	0.7998

4.3 Primary Hypothesis

Statistical analyses will be Intent-to-Treat (ITT) under the assumption that the missing data process is missing at random (MAR). All randomized individuals will be included in the analysis according to their randomization group. Analyses via the mixed effects, correlated errors model will be premised on ignorable missingness (MAR missing data process and correct mean and covariance structure for observed data). Secondary analyses will explore sensitivity to assumptions.

The primary treatment effect of interest is the effect of treatment on the change in ACT score from baseline to 6 months. Measurements will be taken at baseline, 4 weeks, 12 weeks and 24 weeks (V2-V5). Longitudinal data analysis based upon linear mixed effects model (LME) with robust standard errors will be performed in order to estimate the pattern over time as well as the 6 month difference. In order to properly handle missing data and to use all available information, the model will include all cross-sectional levels. Treatment, visit, site and the interaction between treatment and visit will be included as fixed effects although if the number of individuals at each site is small then a random effect for site may be considered in order to save degrees of freedom. For the primary analysis an 'unstructured' variance-covariance matrix will be used. Contrasts will be used to produce the inferences for the change over six months.

One advantage of the linear mixed effects model is that it can incorporate individuals with missing data and provide valid inference in the presence of ignorable non-response. However, the linear mixed effects models are not robust to mis-specification of the covariance structure. Therefore, emphasis will be placed upon exploring the effects of different variance-covariance (e.g. independent, exchangeable, spatial) structures in order to determine the susceptibility of the estimates to such changes. In addition, all estimates of precision will be based upon robust estimates, which are based upon observed data as opposed to expected or model based estimates, of the information matrix.²⁹ The results of such sensitivity analyses will be used when developing our interpretation of the inference for the primary model based upon an 'unstructured' variance-covariance matrix.

Detailed secondary analyses of the primary outcome will be done to adjust for differences in baseline measures between treatment groups including race, gender, clinic, seasonal allergies and severity of rhinitis or sinusitis at baseline and asthma severity at baseline. In addition to examining the 6 month difference, the overall pattern of outcomes (e.g. mean change, linear or quadratic regression over time) will be assessed. Results from models based upon treatment received will be calculated to assess the potential impact of biases due to lack of compliance. All key analyses of the primary trial results will be replicated independently by different analysts. After completion of reports and manuscripts, the analysis databases and programs used will be archived.

4.4 Subgroup Analysis

Treatment effects will be examined across subgroups by testing for interaction of select subgroup variables with treatment group assignment. These tests usually have low power but are hypothesis generating and may inform interpretation of results. Pertinent subgroups that will be tested for an interaction will include ethnicity, gender, atopy, season, severity and duration of rhinitis or sinusitis, severity of asthma, and asthma medication use. After assumptions are verified, we anticipate analyzing change in ACT score at 6 months and overtime within and across specified subgroups to evaluate generalizability of the treatment

effect within the study cohort. Secondary outcomes, listed below, will be evaluated in a similar manner.

4.5 Secondary and Tertiary Outcomes

Secondary and tertiary outcomes include asthma exacerbation rates, asthma symptoms, and quality of life scores, PEF physiological measures of pulmonary function and biomarkers such as exhaled NO and eotaxins. Secondary outcomes related to sino-nasal disease include exacerbations of upper airway disease, symptom and quality of life scores. In general, analyses for outcomes related to secondary hypotheses will follow the same analytic models proposed for the primary outcome, i.e., overall treatment effect at 6 months and over time with evaluations of confounding and effect modification. Continuous outcomes such as numerical changes in scores or lung function will typically be analyzed using contrasts for change in the measure from baseline to 6 months. Rates of exacerbations will be evaluated using Negative Binomial³⁰ models with robust variance estimates; in our experience standard variance estimates can be especially misleading for comparison of rates. Binomial outcomes such as occurrence of one or more asthma exacerbation, adverse event will be evaluated using logistic regression. The primary analysis will be done by assigned treatment with a secondary as treated analysis for sensitivity.

Table 3: Power Estimates for Selected Secondary Outcomes.

Secondary Outcome	N*	Baseline % Or SD	80% Power	90% Power
			Detectable Difference	
FEV ₁	190	12	5.2	6.0
	380		3.9	4.2
Sinus Symptom Questionnaire	190	13.4	5.8	6.7
	380		4.1	4.7
			Alternative Percentage	
Asthma Exacerbation	190	25%	9%	7%
	380		13%	12%
	190	50%	29%	26%
	380		35%	33%

* Sample size, N, includes a 11% inflation)

Table 3 provides the level of detectable differences for continuous variables and alternative percentages for dichotomous variables for a variety of secondary outcomes at the 80% and 90% power levels with a type 1 two-sided error-rate of 5% for children and adults separately (N=190) and combined (N=380). The estimates are based on the change from baseline to 6 months using a t-test for continuous measurements and a test of proportion for dichotomous variables. The baseline rates and standard deviations are based upon the estimates from the previous ALA-ACRC trials. The sample size includes an 11% inflation for drop out and cross-over.

4.6 Missing Data and Outlier Detection

In other trials with similar designs conducted by the ACRC, we have been able to evaluate outcomes in 95 to 99% of participants and missed visit rates have been 13% or less. We estimate that overall *fewer than 13%* of participants will have missing data on the primary outcomes and covariates of interest. The proportion of missed outcomes and covariates will be tabulated at each visit and will be examined to attempt to identify patterns. As with most longitudinal studies, we would expect some attrition over time with a scattering of missed visits.

Chi-squared and t-tests (or Kruskal-Wallis tests if appropriate) will be used to identify imbalances in the baseline covariates and treatment groups between individuals with and without missing data.

The primary analyses use linear mixed modeling which is robust when the data has ignorable non-response, which implies that the probability of missing data depends only upon the observed data, both covariates and previously observed response variable measurements and falls under the definition of missing at random (MAR). A variety of tools will be used to assess the impact of missing data. These analyses are intended to help evaluate the interpretation of the inference of the primary model upon which the conclusions will be based. Simple techniques such as incorporating pessimistic and optimistic imputations will be included to assess the range of possible estimates. The primary focus of our missing data analysis will be on techniques developed for data that is MAR although a non-MAR (NMAR) technique will also be considered. Although this assumption is probably unrealistic, many MAR techniques are fairly robust, and may in fact provide more accurate estimates for the missing data than non-MAR (NMAR) techniques that require a large number of assumptions, especially when the level of missing data is low.

Sensitivity analyses will be performed using multiple imputation. In essence multiple imputation acknowledges the uncertainty due to missing data, instead of simply ignoring it. Several complete data sets will be generated from predicted distributions for the missing observations given the observed data. The estimates from these generated data sets will be combined using the techniques presented in Rubin and Little.³¹ The uncertainty in the model parameter estimates incorporates the standard errors of the parameter estimates as well as the variability between the parameter estimates from the replicate data sets. The models and parameter estimates needed to derive the imputation distributions are selected by the analyst. This control allows for the exploration of the extreme tails of the distributions. If the inferences obtained are robust to such selections, then the confidence in the results increases. If the results are not robust, then it is possible to define the conditions under which the inference is valid. Under the assumption of MAR, the predictive distribution for the missing outcomes only depends upon the covariates and outcomes up to the time of the missed visit not on the current visit. Therefore, the data can be directly imputed from the models based upon the observed data.²⁹ Under the assumption of NMAR, probability of a missed visit may also depend upon the unobserved outcome and/or covariates at the time of the missed visit. For this phase of analysis, we use logistic regression to model the probability of drop out given the previous and current measurements.³² Since it is not possible to directly estimate the model, a range of values and model constraints will be chosen.²⁹ The graphical techniques presented by Gelman et al will be used to perform model assessment comparing the completed data (complete plus imputed values) with the complete-data inference.³³

To ensure robustness of our primary analyses, potential outliers (e. g., exceedingly large ACS gain or loss) will be identified using stem-and-leaf and box plots and the extreme studentized deviate (ESD) approach.^{34, 35} This approach accounts for sample size (e.g., 3 or 4 standard deviation deviations are expected in large data sets). Decisions will be made to include the data point in the primary analysis or to set the data point aside. Records of unusual data points identified will be examined for correctness.

4.7 Data and Safety Monitoring

NHLBI will appoint a DSMB to review the STAN trial. The Board will include nationally recognized experts in adult and pediatric asthma, clinical trials, and biostatistics.

The DSMB will meet twice a year, usually by teleconference, to review data from STAN and other ongoing ACRC trials. The DSMB is also responsible for review of related issues, such as center performance standards or recruitment incentives. The ALA Scientific Review Group has established criteria for the DSMB to use to evaluate the performance of clinical centers. The DSMB may request more frequent meetings if necessary to fulfill its charge. It may also request additional safety reports on a more frequent basis. After each meeting, the DSMB will make formal recommendations regarding trial continuation and clinical performance. The DSMB recommendations will be submitted to participating center's IRB's.

We propose that the DSMB review one planned interim analysis of the primary outcome measure. O'Brien-Fleming statistical stopping guidelines for efficacy will apply.²⁹ This interim efficacy analysis will occur when approximately 50% of the data are complete or when approximately 190 of the 380 patients have completed the follow-up required for the study.

A special responsibility of the DSMB is to review serious adverse events (SAEs), as defined by deaths, life threatening conditions, hospital admissions, adverse pregnancy outcomes or events requiring permanent discontinuation of the treatment. SAEs are to be reported to the DCC within 72 hours of notice, with follow up reporting until the event has terminated. SAEs will be reported to the Chairman of the DSMB or other designee in a timely fashion for review. This initial review will determine whether there is a recommendation for a change in the protocol or halt to the study until such time as the matter can be considered by a quorum of the DSMB. In addition, the DCC will distribute reports of SAEs from one center to all of the centers for review by the local IRBs.

5 Protection of Human Subjects

5.1 Risks to the Participants

We expect the 18 clinical centers will enroll 380 children and adults ages 6 years and up, of either sex who have poorly controlled asthma. The risks associated with the study treatment were described in section 3.2 of this protocol

Overall, the study has few serious risks. Participants will undergo spirometry at each clinic visit. Occasionally individuals complain of light-headedness during the procedure. The risk of syncope in this study is minimized by having participants sit during the procedure.

Each participant will complete questionnaires of health status and quality of life. There is always the risk that information from a study can be disseminated in ways that can risk the privacy of a person with attendant social and occupational harm. However, this risk is low for a common condition like asthma. Care, however, will be taken to ensure confidentiality. Research records will be held in locked cabinets or secure storage rooms when staff members are not in attendance. All transmission of data to the coordinating center for analysis is by study ID code only. Publication of results will involve aggregate data only so that individual participants cannot be identified. On occasion it may be necessary, for legal reasons, or for good clinical practice, for third parties such as the FDA, IRB, or DSMB members to review

medical records that are identified by name. This is not a common occurrence, and every effort will be made by the investigators to maintain confidentiality during such audits.

Adverse reactions to study treatments will be minimized by monitoring side-effects at clinic visits. If possible side-effects become more than mild, study treatment will be discontinued, and this is recorded as a study outcome event for secondary analyses. If it is considered probable that the side-effects were the result of the treatment, study treatment will not be re-started. If it is considered possible or unlikely that the side-effects are the result of the study treatment, then the treatment will be re-started after the side-effects subside. If the same side-effects recur, the participant will be taken off the study treatment. For severe adverse events thought to be possibly or probably related to study treatment, the treatment will be withdrawn for the duration of the study.

The methacholine challenge test involves the inhalation of an agonist to induce bronchoconstriction and may induce the symptoms of an asthma exacerbation (chest tightness, dyspnea, coughing). The procedure is performed in a closely monitored clinical environment, with availability of bronchodilator. This procedure has been safely used in our previous studies and we will only perform this procedure if the baseline FEV₁ is greater than or equal to 70% predicted. The risks of this procedure are minimized by monitoring spirometry after each increase in the dose of methacholine and stopping the testing when the FEV₁ has fallen by 20%. The risk of serious reaction is minimized by treating the participants with inhaled albuterol, a bronchodilator, at the end of the test if they have more than a 10% decrease in FEV₁ and by not permitting them to leave the testing area until their lung function improves to within their pre-challenge value. Emergency medical equipment, including oxygen, bronchodilators and atropine (a specific antidote) will be readily available. Participants with a baseline FEV₁ less than 70% of predicted will not undergo a methacholine challenge test. Other absolute contraindications to methacholine challenge are any known sensitivity to methacholine or other parasympathomimetics or a history of uncontrolled hypertension (systolic blood pressure of > 200mm Hg, diastolic > 100 mm Hg). Relative contraindications include an inability to perform acceptable quality spirometry, pregnancy, or mothers who are nursing. To minimize the risk of administering methacholine inappropriately, participants will have spirometry on the day of testing. Overall, the risk of methacholine challenge testing is low. In the CAMP study, more than 1000 methacholine challenge studies were done without serious incident in children with asthma.

The drug albuterol can lead to tremor, nervousness, tachycardia, palpitations, and headache. These reactions are transient and rare (< 5%) with the proposed doses used for this study, and if they occur, we will monitor the patient until they return to baseline. High dose albuterol may cause arrhythmias and hypokalemia. However, these reactions are very unlikely with the doses used for this study.

We will draw 10 ml of blood on two occasions at Visit 2 and Visit 5. The main risks of venipuncture are discomfort and bruising. Serum will be used to measure ECP and eotaxins. Packed blood cells will also be used for DNA analysis. Although not proposed in this study, we anticipate submitting in the future an ancillary study exploring genetic determinants of response to nasal glucocorticoids. The risks of DNA analysis are primarily related to the possibility that an outside agency not approved by the participant might obtain and use the information. To minimize this risk, DNA samples will be identified only by a numeric identifier and no genetic analysis will be performed other than that associated with steroid effect, asthma, and airway disease. Any identifying data is kept in a locked cabinet or in a password protected computer

file. Only the Clinic Directors of this study and his/her designee will have access to the numeric code, which identifies participants by name. Genetic information will not be supplied to any outside agency, except as authorized by the participants. Genetic information will be shared with other investigators in the network through study ID codes, and not by name. Genetic results may be presented in publications and meetings, but individual names will not be identified.

Participants in this study will undergo two measurements of exhaled nitric oxide (eNO). The risks of this test are minimal. Collection of exhaled NO requires that the participant, while seated, inhale slowly to total lung capacity and then exhale slowly against a resistance for 10 seconds. Both children and adults are able to perform this maneuver easily and without any complications. To minimize discomfort associated with this procedure, a trained technician is present to both encourage and coach the participant.

5.2 Recruitment and Consent Procedures

Participants will be recruited by each participating clinic by their own methods. These methods may include local American Lung Association campaigns, solicitation in physician offices, clinics, workplaces, schools and public media advertisements. All public advertisements are subject to approval by the local IRB and must indicate that it is a research study. The DCC will help coordinate recruitment among clinics and promote sharing of effective recruitment strategies within the network. The trial will be registered on www.ClinicalTrials.gov.

Potential enrollees and their legal guardian (for pediatric participants) will be approached either in person, by telephone or by mail to establish general eligibility criteria. A general description of the study, including frequently asked questions and a consent form will be provided prior to their initial screening visit. If the potential enrollees are interested in attending a screening visit, they will meet with the study coordinator and the local physician co-investigators to review the study and answer questions. They will be asked to sign consent, and if appropriate provide assent, and undergo the screening procedures at that visit. At the same visit, if they still qualify but need a methacholine test to meet eligibility criteria, that test will be scheduled prior to the randomization visit.

The consent form will be subject to approval by the clinical center IRB. A copy of the consent form will be given to each participant, and the signed original will be kept in the participant's research chart. Individual consent for the methacholine challenge test and genotyping may be required depending upon institutional requirements.

Subjects 6 to 17 years of age may also need to provide assent according to local IRB policies. The legal guardians of participants in this age range must also sign the consent form.

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