

ASTHMA CLINICAL RESEARCH NETWORK

Best Addjustment Strategy for Asthma over Long Term (BASALT)

Study Protocol

Version 25.2

A study to determine if adjustment of asthma therapy based on symptoms or biomarkers of airway inflammation is superior to adjustment of therapy based on consensus guidelines in asthmatics adequately controlled with an inhaled corticosteroid alone

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Asthma Clinical Research Network Protocol
Best Adjustment Strategy for Asthma in Long Term [BASALT]
A Study of Adjusted Asthma Therapy by Biomarker, Guideline, or Symptoms

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I. Rationale, Hypothesis, and Specific Aims

A. Rationale

Asthma is a common respiratory disease characterized by obstruction, hyperresponsiveness, and inflammation of the airways. Current management strategies are based on consensus guidelines and clinical judgment [NHLBI 2002] [GINA 2005]. Moreover, asthma is a temporally variable disease; the variability has many sources, which are both potentially avoidable (cold, exercise), and those which are more difficult to avoid (exposure to allergens, viruses). Some worsenings of asthma have no apparent cause, and are presumed to be related to variations in the (unknown) pathophysiologic mechanisms underlying airway inflammation and hyperresponsiveness. Accordingly, it is common for asthma therapy to require periodic adjustments in the intensity of therapy, increasing it when signs or symptoms of the disease worsen and decreasing it when they improve [GINA 2005] [NHLBI 2002]. However, guidelines for making these adjustments, especially downward adjustments in the intensity of treatment, have not been well established. Some of strategies that have been proposed base the adjustments in therapy on physician assessment of asthma control at regular interval [NHLBI 2002], on laboratory assessment of a “biomarker” of airway inflammation (e.g., bronchial reactivity, exhaled nitric oxide, sputum eosinophils) at regular intervals [Sont 1999] [Smith & Taylor 2005] [Green & Pavord 2002] [Brightling 2005] [Deykin 2005], or on patient assessment of symptom severity on a day-to-day basis [O’Byrne 2005]. The effects of these three approaches on maintaining asthma control and on the cumulative dose of inhaled corticosteroid needed over time have not been compared. We therefore propose to examine two key questions about “adjusted therapy” approaches to the treatment of mild-moderate asthma. The first, and primary question, is whether adjusting ICS treatment either on the basis of the severity of asthma symptoms on a day by day basis [“symptom-based adjusted therapy” (SBA)] or on the basis of the concentration of nitric oxide in exhaled air measured at six weeks intervals [“biomarker-based adjusted therapy” (BBA)] is superior to adjusting therapy according to MD/RN review of pulmonary function, frequency and severity of symptoms, nocturnal awakenings and frequency of rescue use of a β -agonist inhaler at six week intervals, following the NAEPP Guidelines for asthma management [“guidelines-based adjusted therapy, GBA)]. The second question is whether, among patients who by standard Guidelines’ criteria appear to have mild asthma while taking an ICS twice daily, tests of markers of bronchial responsiveness (change in FEV₁) after albuterol, PC₂₀ Methacholine) or of bronchial inflammation (FeNO; Exhaled Breath Condensate [EBC]

pH and cytokines, sputum eosinophil percentage) identify those who will lose asthma control (treatment failure or asthma exacerbation) after reduction in their ICS dose. [Sont 1999] [Deykin 2005] [Pavord 2005] [Smith&Taylor 2005] [Leuppi 2005].

B. Primary Hypothesis

We hypothesize that in patients initially well-controlled on daily low-dose inhaled corticosteroid therapy, symptom-based adjustment [SBA] and/or biomarker-based adjustment [BBA] of inhaled corticosteroid therapy will be superior to standard, guideline-based adjustment [GBA], in maintaining asthma control, as assessed by the time to treatment failure.

C. Null hypothesis

The symptom-based and biomarker based approaches to adjusting ICS therapy do not differ from guideline based adjustment in their effects on asthma control, as measured by the time to treatment failure.

D. Additional hypotheses:

1. That compared to GBA treatment, SBA and/or BBA treatment will result in:
 - Lower cumulative dose of inhaled and oral corticosteroid treatment. This outcome is very important, in that we wish to distinguish the influence of total cumulative, or daily average *dose* of ICS, and the pattern of its use, which might differ by adjustment strategy (either on a per day, or cumulative basis), from the *adjustment strategy* itself.
 - Improved asthma-related quality of life
 - Fewer days lost from work or school
 - Reduced estimated cost of care
 - A greater proportion of visit days with ACQ scores less than 1.25
 - Greater reduction in markers of inflammation (FeNO, exhaled breath condensate pH and cytokines, PC20 methacholine, sputum eosinophils)
 - Reduced drop-out rate
2. That specific phenotypic features on entry (while taking low-dose ICS treatment) correlate with the risk of treatment failure after treatment is shifted from low dose ICS taken twice daily to “adjusted dose” ICS treatment (by any of the three strategies used in this study). The features include:
 - FEV(1) as % predicted.
 - Delta FEV(1) after 4 puffs of Bronchodilator

- Change in pre-bronchodilator FEV1 over 2 weeks after treatment is reduced.
- Bronchial reactivity to Methacholine (PC₂₀ MCh)
- Concentration of nitric oxide in exhaled gas (FeNO)
- Exhaled Breath Condensate pH and cytokines
- Sputum Eosinophils

E. Specific Aims

1. To evaluate the benefits of symptom-based, or biomarker-based therapy adjustment for asthma, compared to guideline-based adjustments on time to treatment failure (primary outcome).
2. To evaluate the benefits of symptom-based, or biomarker-based therapy adjustment for asthma, compared to guideline-based adjustment, on total cumulative dose of ICS, quality of life, days lost from work or school, patient satisfaction with care, and estimated direct and indirect costs of care, and other secondary outcome measures.

F. Exploratory Objectives

1. To compare the predictive value of FEV(1), FEV(1) bronchodilator response change in FEV(1) over two weeks after ICS dose is reduced, PC₂₀ Methacholine, EBC pH and cytokines, sputum eosinophils, and FeNO for treatment failures when ICS treatment is reduced. The rationale for including each of these measures is that these measures are easily performed, and commonly utilized (methacholine challenge, sputum eosinophils, FEV(1) bronchodilator response) have previously shown value in predicting loss of control of asthma as ICS are reduced or withdrawn. Some of these metrics could plausibly be employed in clinical practice.
2. To compare the associations and predictive value of polymorphisms of the glucocorticoid receptor pathway on response to ICS adjustment by GBA, SBA, and BBA. Because steroids are the mainstay of therapy for asthma, and reduce exacerbations and treatment failure, understanding GR pathways has *prima facie* importance for our primary outcome, treatment failure. Were an important polymorphism to emerge from this study as predictive of lack of response to ICS, or for treatment failure, genetic testing could be clinically employed, and could be the target for future prospective investigations.

II. Background and Significance

The NHLBI Guidelines segregate asthma into 4 levels of severity, based on symptoms, pulmonary function, and peak flow variability. These NHLBI Guidelines do not formally adjust for the effects of therapy on these metrics, whereas the GINA Guidelines do take

into consideration the amount and types of therapy, as well as symptoms and pulmonary function in classifying severity [GINA2005]. However, both of the guidelines largely portray asthma severity as a static characteristic. Adjustments to intensify and deintensify therapy are suggested, but the time frame for adjustments is generally months (*i.e.* between clinic visits), rather than more immediately based on the current level of symptoms. In addition, guidelines argue that all patients with “persistent” asthma should receive daily controller therapy, even those with mild disease, and argue further that controller therapy be increased when asthma control worsens. They do not describe specifically how long these increases in therapy should be maintained, and provide only general instruction as to when therapy can be reduced or discontinued. The question as to how long inhaled corticosteroid treatment must be continued once it is started, and when it can be tapered or discontinued is important to patients.

The ACRN IMPACT study evaluated patients with mild persistent asthma in a three arm study. Each subject was provided a symptom based action plan, and was randomized to twice daily treatment with inhaled budesonide, oral zafirlukast, or placebo. No differences in exacerbations, post-bronchodilator FEV₁, maximal achievable lung function, or quality of life were observed. These findings suggest that for patients with mild asthma, symptom-guided adjustments in controller therapy might be as effective as regular daily treatment [Boushey 2005]. Another study of patients with more severe asthma also suggested the possible value of “symptom-based” adjustment in controller treatment [O’Byrne 2005]. This study compared three approaches to treatment: (1) twice daily treatment with moderate-dose budesonide (320 mcg 2x/day) plus “as needed” terbutaline; (2) twice daily low-dose budesonide + formoterol combination therapy (80 mcg+4.5 mcg 2x/day) plus “as needed” terbutaline; and (3) twice daily low-dose budesonide + formoterol plus “as needed” budesonide + formoterol combination treatment. The use of low-dose budesonide-formoterol combination treatment for both maintenance and relief prolonged the time to the first asthma exacerbation, reduced exacerbation rates, and improved asthma symptoms, nocturnal awakenings, and lung function relative to both fixed-dose budesonide treatment regimens. These benefits to symptom-adjusted treatment were achieved at a significantly lower cumulative dose of budesonide than standard, twice-daily moderate dose budesonide treatment.

An alternate approach to adjusting therapy came with the development of a validated, approved methodology for assessing the fractional concentration of nitric oxide is exhaled nitric oxide (FeNO), a putative marker of airway inflammation. A study comparing standard, continued ICS treatment to treatment adjusted by the level of FeNO measured every 1-3 months showed this “biomarker-adjusted treatment” to result in a non-significant reduction in asthma exacerbations and a significant reduction in the cumulative dose of ICS over time [Smith & Taylor 2005].

This initial study of FeNO-adjusted treatment, like the previous studies of basing treatment adjustments on bronchial reactivity [Sont 1999] and on eosinophil numbers in induced sputum [Green&Pavord 2002] did not address the practical difficulties in implementing the approach widely, as in primary care practices, and made no estimate of the economic cost of the benefits achieved. For measurement of bronchial reactivity

to methacholine and sputum eosinophils, the practical difficulties in standardization and implementation and the associated costs would be considerable. This is likely true as well for adjusting treatment based on FeNO. The device for measurement of FeNO is currently priced at >\$40,000 and additional expenses are associated with each measurement made. Consequently, the cost of applying this approach to treatment to the large number of people with mild asthma would be substantial. In contrast, the costs of a symptom-based approach to adjusting controller treatment would be only those of the additional time needed for patient education, and the simpler the approach, the lower these costs would be. Although true that less costly home monitoring devices for FeNO may be on the horizon, the available technology does not support FeNO measurement on a daily or weekly basis as a metric on which to adjust therapy. Accordingly, we have structured BASALT to evaluate FeNO at the time of routine clinic visits, a strategy which could most quickly be implemented in a clinical setting.

Because the FeNO approach to adjustment of ICS therapy would be costly, and would only provide data at the time of a clinical visit (as opposed to symptoms, which provide a real time monitor of disease activity), the benefits of FeNO adjustment would need to be substantial, compared to other strategies, for it to be sensible to recommend its broad based use. There are two potential concerns surrounding the use of FeNO as an adjustment strategy: 1) is not validated as a biomarker of inflammation, and 2) subjects may have symptoms of asthma, but not have FeNO elevated sufficiently to warrant adjustment of their ICS dose. Our protocol addresses these concerns. First, although FeNO may not yet be validated as a biomarker of inflammation, it has been studied prospectively as an adjustment strategy [Smith & Taylor 2005]. In this context, FeNO-based adjustment was associated with comparable asthma control, and reduced ICS use to achieve that control. Secondly, symptoms of asthma will, independent of FeNO-based adjustments, and, if sufficiently severe, will be treated with 14 days of “rescue” open label ICS (per Treatment Failure guidelines).

Considerable new literature and editorial comment highlights the scientific and clinical interest in biomarkers and their potential for implementation in management strategies. Indeed, De Jongste has argued strongly that the field has already advanced to the extent that FeNO ‘inflammometry’ should now be incorporated into clinical management of asthma, as an additional metric of asthma control {De Jongste 2005}. In fact, the limiting factor for broad based implementation of FeNO monitoring that was identified in the editorial was the matter of reimbursement. Deykin {Deykin 2005}, taking a more skeptical view, has suggested that the field of FeNO has advanced sufficiently from the standpoint of technical and scientific considerations that a formal, prospective trial of its use as a metric for steroid dose titration is warranted. Gaston, in reviewing the extant pediatric literature, has suggested that biomarkers may be useful in identifying those children whose inhaled corticosteroids might be safely reduced, and that FeNO has promise in that role. However, the data are at present insufficient to justify a formal recommendation to incorporate FeNO into pediatric asthma management {Gaston 2005}. Collectively, these editorials and the supporting primary literature suggest that there is considerable interest in, and commercial pressure towards, implementation of FeNO measurements into clinical management of asthma. There is a pressing need for

clear data, obtained in prospective, randomized trials free from commercial bias, to address the role, if any, that biomarkers like FeNO may play in asthma management.

Accordingly, we propose here a study comparing three approaches to treatment adjustment. The first, “guidelines-based adjusted” therapy (GBA), is modeled on the NHLBI and GINA guidelines, in which a physician adjusts therapy according to the patient’s symptoms, rescue use of a short-acting β -agonist, nocturnal awakenings, and pulmonary function at visits at six week intervals. The second, “biomarker-based adjusted” therapy (BBA) is modeled on the recent report [Smith&Taylor2005] of adjusting treatment based on FeNO measurement at the same interval. The third strategy, “symptom-based adjusted” therapy (SBA), is modeled on the recent report of benefit from the use of a combination of an inhaled corticosteroid in combination with a β -agonist for relief of symptoms [O’Byrne 2005]. In our protocol, we propose to examine a very simple and generalizable “symptom-based” treatment plan, the use of one puff of an inhaled corticosteroid for every one puff treatment of albuterol taken for relief of symptoms. For the additional expense of bio-marker adjusted therapy to be justifiable, we believe it should have important advantages over standard, guidelines-based therapy, and have powered our study to detect a reduction in the rate of treatment failure from an anticipated 30% with Guidelines-adjusted treatment [Lazarus 2001] [O’Byrne 2005] [Smith & Taylor 2005] to 12% (60% reduction). This reduction is identical to the reduction in exacerbation rate the recent report of FeNO adjusted therapy was powered to detect [Smith & Taylor 2005].

A question invited by the concept of adjusting inhaled corticosteroid therapy, which is classified in the NAEP and GINA guidelines as a “long-term controller treatment,” is whether it is possible to identify some patients who are doing well while taking a low dose of an ICS who will predictably worsen if the treatment is tapered or discontinued. Several studies have demonstrated that among patients whose asthma is well controlled while taking an inhaled corticosteroid, up to 50% develop asthma treatment failures or exacerbations within 6-12 weeks after the treatment is stopped [Lazarus 2001] [Fish 1997] [Lemanske 2001]. Identifying these patients before initiating an adjusted therapy strategy would reduce risk, and we propose in our study to examine some of the phenotypic features suggested as predictors of failure on discontinuing ICS therapy, such as bronchial reactivity to methacholine [Fish 1997] or a marker of airway inflammation such as exhaled nitric oxide [Jones 2001] or exhaled breath condensate (EBC).

The primary outcome, (time to) Treatment Failure (TF), is an established outcome for the ACRN, having been used as a primary or secondary outcome in CIMA, SLIC, SOCS, and SLIMSIT. Treatment failure is a composite outcome reached by meeting physiologic, symptomatic, or behavioral criteria (excessive use of rescue beta-agonists, for example), short of the requirements of a full-blown exacerbation. This lower degree of embarrassment allows the ACRN investigators to intervene sooner, and minimize the risk to the volunteer. Exacerbations represent significant deterioration of asthma control warranting implementation of systemic corticosteroid therapy (as detailed below). “Exacerbations” as defined in BASALT mirror the “major exacerbation” category of

Smith & Taylor [2005] and of the older FACET trial [Pauwels 1999]. In contrast, “Treatment Failure” as defined in BASALT is very similar to “minor exacerbation” in both of those studies. Accordingly, there is both ACRN, and literature precedent for distinguishing TF and Exacerbation as outcomes in BASALT.

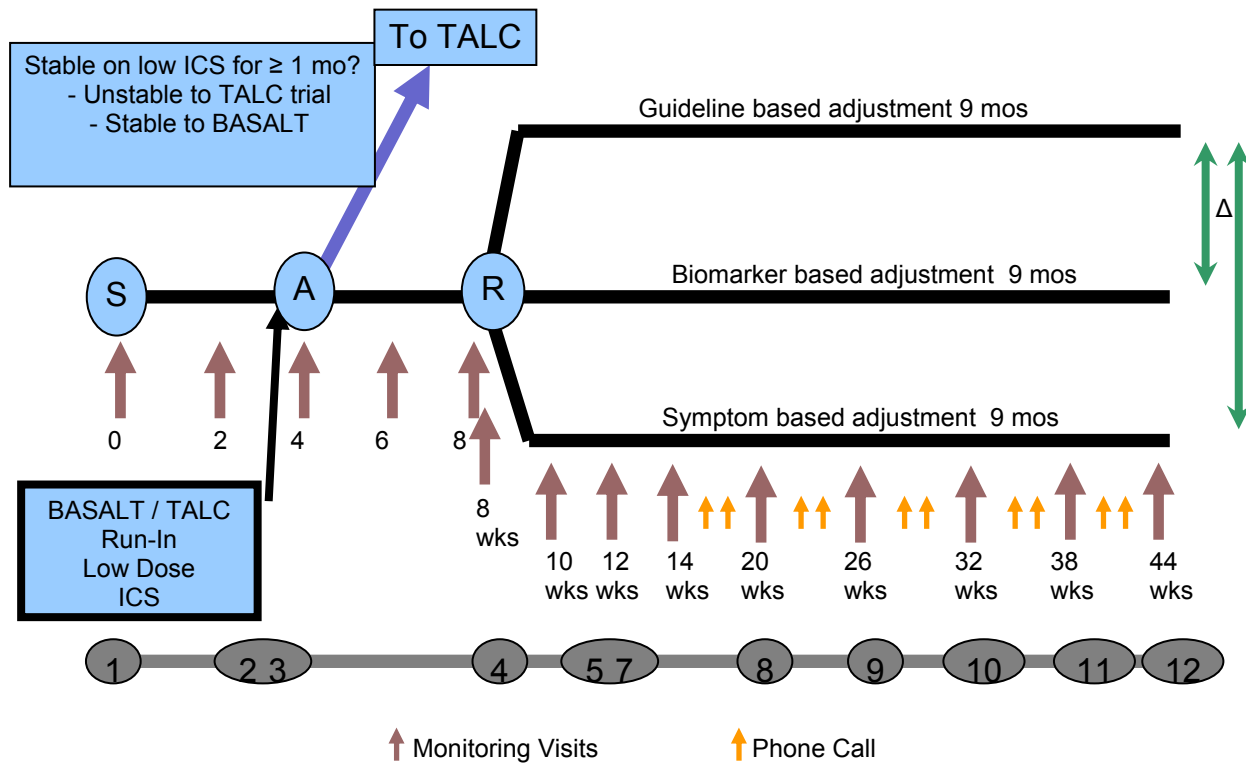
III. Protocol Overview

A. General Design

This study is proposed as a three-arm, parallel group randomized, double-blind, dual-dummy trial, consisting of 6 phases (Screening, Run-in, Study Allocation {BASALT vs. TALC}, BASALT Adherence Testing, Randomization, Intervention) over 12 Visits. BASALT and TALC share a common Screening Visit 1 (S), common 4 week Run-In Period, and Allocation Visit 3. Following allocation to BASALT, subjects undergo 2-4 weeks of monitoring to establish their ability to adhere with the regimen. Visit 4 is the Randomization Visit (R), followed by 36 weeks of intervention to randomized adjustment strategy.

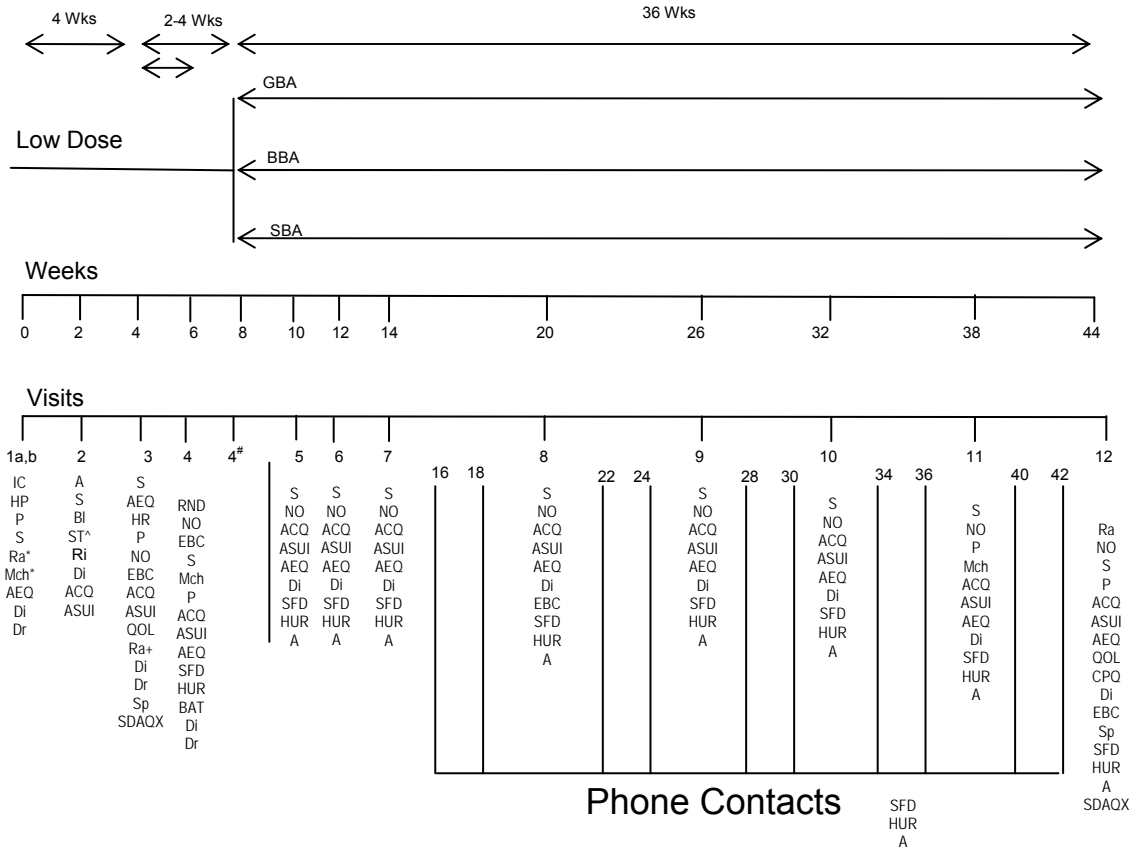
B. Visit Structure

Visit numbers are encircled at the bottom of the diagram. Week numbers from Randomization are shown near the visit arrows. The segment between Screening (S) and Allocation (A) represents a common run-in period shared by BASALT and TALC, using a strategy similar to that of the previous ACRN1 trials SOCS and SLIC. The segment between Allocation and Randomization (R) is the BASALT Adherence Testing phase. The vertical arrows at the right and the Δ indicate the primary hypothesis, and expected differences, that SBA or BBA will prove to be superior to GBA for the primary outcome measure, time to Treatment Failure.



C. Protocol Schema

BASALT Study



*Ra-albuterol reversibility testing and/or *Mch-methacholine bronchoprovocation will be done at the investigator's discretion according to ACRN protocols. Subjects who are eligible for methacholine challenge will undergo this test at Visit 1a¹. If asthma diagnosis is not confirmed, subjects may return for albuterol reversibility testing at Visit 1b at the investigator's discretion. Visits 1a and 1b will occur on different days. Subjects who are ineligible to perform methacholine challenge at Visit 1a will undergo albuterol reversibility testing at that visit. [#]V4 will be done 2 weeks after visit 3. If the subject is not compliant, V4 will be repeated in 2 more weeks (i.e., 4 weeks after visit 3). [^] If the subject cannot undergo skin testing at Visit 2 due to drug washouts or FEV1<60%, skin testing may be done at subsequent visits.

¹ Historical PC20 from an ACRN methacholine challenge performed within 6 months of the Visit 1 date by an ACRN-certified technician may be used to qualify the subject.

Abbreviations used in the protocol include the following: IC-informed consent; HP-medical history, brief physical examination; P-pregnancy test; NO-eNO measurement; EBC-exhaled breath condensate collection; Ra-reversibility testing with 4 puffs of albuterol; Mch-methacholine bronchoprovocation; AEQ-3 question ACRN Asthma Evaluation Questionnaire (Appendix 1); Di-diary dispensing, review; Dr-drug dispensing, adherence; A-specific adherence check and adherence encouragement; BI-blood for IgE level, eosinophils, DNA, etc.; ST-skin tests; Ri-reversibility testing with 4 puffs of ipratropium bromide; ACQ-asthma control questionnaire; ASUI-asthma symptom utility index; HR-resting heart rate as measured by ECG; QOL-asthma-specific quality of life questionnaire (AQLQ); S-spirometry; SP-sputum induction; BAT – BASALT Adherence Testing; RND – randomization; SFD – symptom free day instrument; HUR – healthcare utilization review instrument, CPQ – coordinator/patient questionnaire, SDAQX – sleep and day alertness questionnaire

D. Screening and Study Entry: Criteria for Inclusion and Exclusion

Subjects are consented, and offered participation in BASALT or TALC. Inclusion and Exclusion criteria for the Run-In periods are identical.

1. Inclusion Criteria (Visit 1)

- Male and female subjects, ages 18 and older
- Clinical history consistent with asthma
- FEV(1) > 40% predicted
- Asthma confirmed by either a) or b):
 - a. Beta-agonist reversibility to 4 puffs albuterol \geq 12%
OR
 - b. PC₂₀ FEV(1) methacholine of \leq 8 mg/ml NOT on an inhaled corticosteroid, or \leq 16 mg/ml ON an inhaled corticosteroid
Note: Historical PC20 from an ACRN methacholine challenge performed within 6 months of the Visit 1 date by an ACRN-certified technician may be used to qualify the subject..
- Need for daily controller therapy (i.e., inhaled corticosteroids, leukotriene modifiers, and/or long-acting beta-agonists) based on one or more of the following criteria
 - a. Received prescription for or used asthma controller within the past 12 months OR
 - b. Symptoms more than twice a week and not on asthma controller
- If on inhaled steroids (any drug at any dose not exceeding the equivalent of 1000 mcg fluticasone daily), subject must have been on a stable dose for at least 2 weeks
- Ability to provide informed consent, as evidenced by signing a copy of the consent form approved by the Committee on Human Research of the study institution
- Non-smoker (total lifetime smoking history < 10 pack-years; no smoking for at least 1 year)

2. Exclusion Criteria (Visit 1)

- Use of any drugs listed in Table 1 (Exclusionary medications) during the designated washout period prior to screening visit, or intention to take the drug during the study

Table 1. Drugs to be withheld throughout the study and washout periods prior to Visit 1

Exclusionary Drugs	Washout prior to Visits 1a and 1b
Leukotriene receptor antagonists	≥ 4 weeks
Inhaled steroids, except as provided in study	None
Oral steroids	≥ 6 weeks
Cromolyn/Nedocromil	≥1 weeks
Oral beta-adrenergic agonists	> 1 week
Monoamine oxidase inhibitors	> 4 weeks
Macrolide antibiotics	≥ 4 weeks
Oral Beta-adrenergic blockers	≥ 2 weeks
Inhaled beta-adrenergic agonists (intermediate-acting, e.g., albuterol, terbutaline, metaproterenol, pirbuterol, bitolterol), except as provided in the study	≥ 6 hours
Salmeterol/formoterol	≥ 48 hours
Anticholinergics, except as provided in study	≥ 48 hours for ipratropium; ≥72 hours for tiotropium
Short-acting theophylline (e.g., Slophyllin tablets)	≥ 12 hours
Long-acting theophylline (e.g., Theo-Dur, Slo-bid)	≥ 24 hours
Ultra long-acting theophylline (e.g., Theo-24, Uniphyll)	≥ 48 hours
Anti-IgE therapy	≥ 6 months

Table 2. Drugs allowed during the study with washouts required prior to study visits

Drugs Withheld prior to pulmonary function and/or methacholine challenge, per MOP	Specified time period
Albuterol (study RESCUE drug)	≥ 6 hours
Antihistamines	≥ 48 hours; see ACRN skin testing MOP for required holds prior to Visit 2 skin test
Oral decongestants (pseudoephedrine	≥ 48 hours

and others)	
Nasal decongestants (oxymetazoline (Afrin) and others)	≥ 6 hours
Methylxanthine-containing foods or beverages (e.g., coffee, tea)	≥ 6 hours
Alcohol-containing foods or beverages	≥ 6 hours

- Chronic use of any medications other than study drugs, except:
 - oral contraceptives and other hormonal forms of contraceptives (i.e., DepoProvera-7, Norplant-7)
 - estrogen / progesterone replacement therapy for post-menopausal women
 - vitamins and calcium supplements/osteoporosis medications (e.g. Alendronate, etc.)
 - any nasal inhaled corticosteroid at a stable dose throughout the entire study
 - acetaminophen
 - non-steroidal anti-inflammatory medications (e.g., aspirin, naproxen, ibuprofen, cox2 inhibitors)
 - thyroid replacement medications
 - lipid-lowering medication
 - stable dose medical therapy for well-controlled hypertension and well-controlled diabetes, except those medications specifically excluded in the MOP
 - medium and low potency topical cutaneous steroids
 - nasal saline spray/Nasal Cromolyn/Atrovent Spray
 - topical eye preparations for allergic eye symptoms (e.g. antihistamines, NSAIDs, or antiallergic compounds)
 - diuretics and specific antihypertensives (e.g. calcium channel blockers, clonidine, etc.)
 - acyclovir and all anti-herpetic medications
 - antihistamines (48 hour washout prior to visits; see ACRN skin testing MOP for required washouts prior to Visit 2 skin test)
 - oral decongestants (e.g., pseudoephedrine (Sudafed) and others) (48 hour washout prior to visits)
 - antibiotics for acne (except macrolides)
 - stool softeners and bulk laxatives/hemorrhoid treatment
 - anxiolytics / antianxiety medications -chronic stable dose
 - nasal decongestants (e.g., oxymetazoline (Afrin)) (6 hour washout prior to visits)

- antidepressants (except Monoamine oxidase (MAO) inhibitors)-stable chronic dose
- migraine medications (e.g. Imitrex, etc.)
- non-macrolide antibiotics
- antacids
- select CNS stimulants/appetite suppressants (See MOP)
- H₂ blockers(e.g. ranitidine, cimetidine, famotidine, nizatidine) for GERD
- Proton pump inhibitors (e.g. omeprazole, lansoprazole, esomeprazole) for GERD
- hair growth preparations
- analgesics for acute/chronic pain management with MD discretion
- Lung disease other than asthma, including COPD and chronic bronchitis
- Established or suspected diagnosis of vocal cord dysfunction
- Significant medical illness other than asthma
- History of respiratory tract infection within the previous 4 weeks
- History of a significant exacerbation of asthma in the previous 4 weeks
- History of life-threatening asthma requiring treatment with intubation and mechanical ventilation within the past 5 years
- Hyposensitization therapy other than an established maintenance regimen
- Inability, in the opinion of the investigator or clinical coordinator, to coordinate use of the delivery devices used in the study
- Pregnancy. If potentially able to bear children, not using an acceptable form of birth control (see study MOP).

E. Combined BASALT / TALC Run-In (Visits 1-3)

BASALT and TALC will share a common run-in period of four weeks, during which all subjects will be treated with unblinded low dose inhaled corticosteroids (BDP HFA 80 ug BID {40ug/ puff, 2 puffs bid} or equivalent). At the time of enrollment, subjects will undergo Week 0 procedures. Additional characterization will occur at Weeks 2 and 4.

F. Allocation to BASALT vs TALC (Visit 3)

Following 4 weeks of BDP 80 ug BID (or equivalent) at Visit 3, subjects are allocated to BASALT or TALC.

Criteria Required for Allocation (Visit 3)

- Ability to measure PEF on schedule using electronic peak flow meter (EPFM) and to complete the study diary correctly $\geq 75\%$ of the time during the interval between Visits 2 and 3
- Adherence with study medication dosing $\geq 75\%$ of the time during the interval between Visits 2 and 3
- No asthma exacerbation requiring use of oral corticosteroids, or additional asthma medications (including increased inhaled corticosteroids) during the run-in period.
- $FEV_1 > 40\%$ predicted
- No presence of any exclusionary criteria as listed for Visit 1

Criteria for Allocation to BASALT (Visit 3)

- Pre-bronchodilator $FEV_1 > 70\%$ predicted **AND**
- Score on the ACRN Asthma Evaluation Questionnaire (Appendix 1) of 0 or 1 on each of the 3 questions. (In reviewing your asthma control during the last 2 weeks, you have had: symptoms 5 or less days per week, AND rescue inhaler use 5 or less days per week, AND nocturnal awakenings for asthma once per week or less.)

If either of these two criteria is not met, the subject may be eligible for TALC enrollment.

Criteria for Allocation to TALC (Visit 3)

- No medical contraindications for tiotropium use (narrow angle glaucoma, prostatic hypertrophy, bladder-neck obstruction, renal insufficiency, peanut/soy allergy)
- Failure to meet both allocation criteria for BASALT. That is:
 - (1) Pre-bronchodilator $FEV_1 \leq 70\%$ predicted **OR**
 - (2) Score on the ACRN Asthma Evaluation Questionnaire (Appendix 1) of 2 or 3 on any 1 (or more) of the 3 questions. (In reviewing your asthma control during the last 2 weeks, you have had: symptoms 6 or more days per week, OR rescue inhaler use 6 or more days per week, OR nocturnal awakenings for asthma two nights per week or more.)

G. BASALT Adherence Testing (Visit 4)

Subjects qualifying for enrollment in BASALT will then enter a 2-4 week period of assessment during which three DoserTM equipped inhalers labeled "A", "B", and "C" are provided ("A" contains ICS, and "B" and "C" contain placebo). Also DoserTM equipped albuterol inhaler will be provided. Inhalers A and B will be used 2 puffs BID. Inhaler C will be physically coupled to an albuterol inhaler and subjects will be instructed to use Inhaler C each time he or she activates the rescue albuterol inhaler, regardless of the

reason for albuterol use. The inhalers A, B and C will be color coded, and the subject will be given daily activities cards with specific instructions for taking the each inhaler. All subjects will be informed of the purposes and operation of the “Doser” attached to each inhaler, as a means of monitoring adherence. The subject returns after 2 weeks and must demonstrate at least 75% adherence to this treatment plan. If adequate adherence is demonstrated and the subject is otherwise eligible for randomization in BASALT, he/she will complete Visit 4 (randomization) procedures at that time. If adherence is not adequate, the subject is counseled, re-instructed, and asked to return in 2 weeks for repeat assessment of adherence, and if eligible, will complete Visit 4 procedures at that time. Subjects not able to demonstrate adherence will be terminated from the study.

H. Randomization (Visit 4)

1. Inclusion Criterion for BASALT Randomization:

- Ability of the subject to measure his/her PEF on schedule using the EPFM device and to accurately transcribe the PEF measurements onto his/her diary cards at least 75% of the time during the last two weeks of the run-in.
- 75% compliance with recording peak flow measurements and symptoms in a symptom diary during the last two weeks of the run-in period.
- Ability to take Inhalers A, B, and C at least 75% of scheduled doses. 75% compliance per inhaler is required.
- No treatment failure (includes significant exacerbation) within last 4 weeks.

2. Exclusion Criteria for BASALT Randomization:

- Inability, in the opinion of the investigator or clinical coordinator, to coordinate use of the delivery devices used in the study
- Presence at randomization visit of any of the exclusion criteria stipulated for Visit 1.

The subjects who pass eligibility criteria at V4 will be randomized to one of three controller adjustment strategies in a 1:1:1 ratio:

- 1) guideline based adjustment [GBA],
- 2) biomarker (FeNO) based adjustment [BBA], or
- 3) symptom based adjustment [SBA].

The randomization scheme will be stratified according to center because differences among clinical centers typically yield a large amount of variability. Within each clinical center, randomization will be stratified by FEV1 % predicted at the time of randomization ($\leq 80\%$ vs. $> 80\%$) to ensure balance across treatment arms with

respect to disease severity. This randomization will be performed by the clinic coordinators using the randomization module set up by the DCC, and once randomized, intention-to-treat principles will apply. Following randomization, subjects will be monitored every 2 weeks for three visits, to identify and manage any subjects who may be especially susceptible to deteriorating asthma control on the basis of alterations in ICS dose. Thereafter, subjects will be monitored in clinic every 6 weeks for total intervention duration of 36 weeks.

I. Intervention Period

1. Adjustment Mechanics

Each subject is given 3 blinded inhalers (A, B, and C), plus albuterol. The assignment of the content of A, B, and C is shown in the Randomization Table. Only one of the Maintenance (letter coded) inhalers will contain steroid; the other two are placebo inhalers. Every subject will have unrestricted access to an albuterol MDI to be used for rescue and relief of brief symptoms. Each Maintenance Inhaler is adjusted per the strategies outlined below in the Dosing Table – Inhaler A is adjusted by the ACRN staff, at the time of a Visit, based on measures of lung function and frequency of daytime and nocturnal symptoms (Guidelines) or at the time of a safety visit that will occur within 72 hours after the subject experienced significant exacerbation or treatment failure; Inhaler B is adjusted by the ACRN staff at the time of a Visit based on an exhaled nitric oxide measurement (Biomarker), and Inhaler C is adjusted per symptoms, based on albuterol use – subjects will be instructed to use Inhaler C each time he or she activates the rescue albuterol inhaler, regardless of the reason for albuterol use. In addition, each inhaler C will be physically coupled to an albuterol inhaler; this strategy will provide a further direct, practical method to help our volunteers adhere to the dosing strategy. We anticipate that physical coupling of the devices could be accomplished by placing them in the appropriate bags that can hold two inhalers where each is equipped with the Doser™

2. Initial Conditions

Prior to randomization, Visit 4, each subject will be receiving inhaled steroids equivalent to Step 3 on the dosing table. At the time of randomization, Inhaler A will be adjusted on the basis of the GBA criteria (iii, below); Inhaler B will be adjusted on the basis of the BBA (iv, below). Between Visits 4 and 5, subjects will be instructed to use Inhaler C at a dose of 2 puffs QD (once a day) in the morning, after measuring and recording AM PEFr, in addition to that used PRN regardless of randomization group. Thereafter, they will only use Inhaler C in conjunction with use of the rescue albuterol inhaler. The expectation is that subjects will generally exhibit good asthma control at Randomization, and consequently the Guideline sensitive inhaler (Inhaler A) will generally be adjusted downwards by one step at the time of Randomization. By starting Inhaler C at 2 puffs QD, those subjects randomized to receive placebo in Inhaler A (GBA) or in Inhaler B

(BBA) will not experience an abrupt withdrawal of ICS. The inhalers will be color coded, and the subject will be given daily activities cards with specific instructions for taking the each inhaler.

Inhalers A, B, and C, as well as albuterol inhaler, will be equipped with an electronic dose counters (e.g. Doser®) as a measure of adherence, and to facilitate measurement of secondary endpoints. The decision about adjusting inhalers A and B at each visit will be recorded.

BASALT Randomization Table

Group	Adjustment Strategy	Inhaler A	Inhaler B	Physically Coupled MDIs	
				Inhaler C	Albuterol Unblinded
I	Guideline Based	BDP HFA 40 or 80	Placebo	Placebo	X
II	Biomarker Based	Placebo	BDP HFA 40 or 80	Placebo	X
III	Symptom Based	Placebo	Placebo	BDP HFA 80	X

BASALT Dosing Table

Step	Dose	Frequency
1	None	
2	2p	QD (AM)
3	2p	BID
4	4p	BID
5	8p / 4p double strength	BID

We recognize that the steps are neither linear, nor strictly proportional. According to guidelines, patients receiving 2 puff BID of ICS could have all controller medications stopped. We chose to use an intermediate dose (2 puffs once a day in AM), rather than to discontinue abruptly this controller. There is no satisfactory way to ensure strict dose proportionality as the ICS dose is reduced towards zero. We reasoned that an intermediate step, even if not strictly dose proportional, was a safer strategy than sudden withdrawal, and consistent with common clinical practice. Finally, all arms will have identical dosing tapering.

J. Guideline Based Adjustment [GBA] Strategy

Symptoms over the most recent 2 weeks, and pulmonary function at monitoring visit are reviewed.

Adjustments to Inhaler A are made as follows:

- Prebronchodilator FEV(1) \geq 85% of baseline FEV(1), and symptoms in the previous two weeks consistent with mild intermittent asthma (subject answered 0 for each of the three questions on an Asthma Evaluation Questionnaire (AEQ)) – reduce Inhaler A by one step on the Dosing Table
- FEV(1) \geq 85% of baseline FEV(1), and symptoms in the previous two weeks consistent with mild persistent asthma (subject answered 1 on at least one question and 0s or 1s on the other two questions) – maintain Inhaler A at current level
- Airflow limitation ($<$ 85% of baseline FEV1), or symptoms in the previous two weeks consistent with moderate persistent asthma (subject answered 2 or 3 on at least one question), or one or more TF since last visit and no adjustments were made for that event – increase Inhaler A by one step on the Dosing Table.

If the subject experiences treatment failure, he/she needs to come in to the clinic within 72 hours for an evaluation. At that visit, Inhaler A will be increased by one step on the Dosing Table, unless the subject is already at Step 5, in which case inhaler A will not be further adjusted upwards. If the next regular or another treatment failure visit occurs within the 4 weeks since the inhaler A was adjusted due to subject experiencing treatment failure, the Inhaler A will not be adjusted either up or down at the visit. If the regular or another treatment failure visit occurs at least 4 weeks after the subject's Inhaler A was adjusted due to the treatment failure, Inhaler A will be adjusted as outlined above.

Subjects randomized to GBA will receive inhaled steroids in Inhaler A, and adjustment of Inhaler A will adjust the dose of steroids; for the other two groups, Inhaler A will contain placebo, and adjustment of Inhaler A on the basis of guidelines will not influence inhaled steroid dose.

FEV1 baseline:

- At randomization visit (Visit 4), FEV1 baseline is the FEV1 value measured at Visit 3.
- For the rest of the study (Visits 5 – 12), baseline FEV1 is the value measured at randomization visit (Visit 4).

K. Biomarker Based (FeNO) Adjustment [BBA] Strategy

The fraction of NO in expired breath, performed according to the MOP, is measured at each clinic visit. Adjustments to Inhaler B are made as follows:

- Low ENO (average <22 ppb) – reduce Inhaler B by one step on the Dosing Table
- Midrange ENO (average: 22-35 ppb) – maintain Inhaler B at current level
- High ENO (average >35 ppb) – increase Inhaler B by one step on the Dosing Table

ENO value on which the adjustments will be made is the average of the two reproducible values that were obtained at the visit.

These ranges have been developed by Dr Deykin from detailed analysis of FeNO measurements made in the context of previous ACRN trials (LARGE run-in), and from data in a published trial. Both of these data sets were developed using on-line eNO measurements, and similar equipment.

Subjects randomized to BBA will receive inhaled steroids in Inhaler B, and adjustment of Inhaler B will adjust the dose of steroids; for the other two groups, Inhaler B will contain placebo, and adjustment of Inhaler B on the basis of eNO will not influence inhaled steroid dose.

Controversy remains regarding the interpretation of FeNO in asthma. However, in the context for which we propose to use this measure, namely that of serial measurements in a clinical trial, there is a compelling body of data that support its validity. The responsiveness of FeNO to changes in airway inflammation has been recently reviewed. Factors which amplify airway inflammation are generally associated with increased FeNO, and those which reduce inflammation are associated with decreased FeNO [Kharitonov 2005]. The measurement also has value in asthma in enabling reducing ICS dose, while maintaining asthma control [Smith & Taylor 2005]. Whether FeNO has external validity as a surrogate measure of airway inflammation is an important question, but in the context of BASALT, is moot. We propose to use FeNO as a tool for adjusting ICS dose, a use for which utility has already been demonstrated.

L. Symptom Based Adjustment [SBA] Strategy

Subjects use 2 puffs of albuterol for symptoms, on an as needed basis. All subjects are instructed to use 2 puffs of Inhaler C at the time of albuterol use. Per the Treatment Failure Table, use of more than 16 puffs of albuterol per day for two consecutive days will constitute TF.

Subjects randomized to SBA will receive inhaled steroids in Inhaler C, and use of Inhaler C with rescue albuterol will adjust the dose of steroids; for the other two groups, Inhaler C will contain placebo, and use of Inhaler C will not influence inhaled steroid dose.

M. Visit Structure

Visit	1a ¹	1b ²	2	3	4	5	6	7	8	9	10	11	12
Week	0	0	2	4	6-8	10	12	14	20	26	32	38	44
Window (reg/ext) (Days)			±3/ ±5	±3/ ±5	±3/ ±5	±3/ ±5	±3/ ±5	±3/ ±5	±5/ ±7	±5/ ±7	±5/ ±7	±5/ ±7	±5/ ±7
Study Phase													
Allocation to BASALT				X									
Informed Consent	X												
Randomization					X								
Medical History	X												
Long Physical Exam	X												X
Short Physical Exam				X	X	X	X	X	X	X	X	X	
Blood for IgE/Eosinophils			X										
Blood for genetic analysis (optional)			X										
Pregnancy Test	X			X	X							X	X
Skin Testing			X*										
Heart Rate Assessment (ECG)				X									
ENO				X	X	X	X	X	X	X	X	X	X
EBC				X	X				X				X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	X
Albuterol Reversal (4 puffs)	(X)	X		X									X
Ipratropium Reversal (4 puffs)			X										
Methacholine Challenge	(X)				X							X	
Sputum Induction				X									X
Asthma Evaluation Questionnaire (AEQ)	X			X	X	X	X	X	X	X	X	X	X
ACQ/ASUI Questionnaires			X	X	X	X	X	X	X	X	X	X	X
AQL Questionnaire				X									X
SFD Questionnaire					X	X	X	X	X	X	X	X	X

¹ Subjects who do not have historical PC₂₀ and who have prebronchodilator FEV₁ ≥ 55% of predicted and are eligible to perform a methacholine challenge will undergo the challenge at Visit 1a to determine eligibility; subjects who do not have acceptable historical PC₂₀ and are ineligible to perform the methacholine challenge will undergo albuterol reversibility testing with 4 puffs of albuterol at Visit 1a.

² Subjects who do not meet methacholine PC₂₀ criteria at Visit 1a may return for albuterol reversibility testing (4 puffs) for eligibility assessment at Visit 1b at the study investigator's discretion.

* Subjects who are not eligible for skin testing at V2 due to drug washout or FEV₁ < 60%, may undergo skin testing at subsequent visits.

Healthcare Utilization Review (HUR)					X	X	X	X	X	X	X	X	X	X
Sleep and Daytime Alertness Questionnaire				X										X
Coordinator/Patient Questionnaire(CPQ)														X
ACRN Satisfaction Questionnaire														X
Diary Card Dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diary Card Review			X	X	X	X	X	X	X	X	X	X	X	X
Medication Dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X	
Compliance review (Doser, AM1, etc.)			X	X	X	X	X	X	X	X	X	X	X	X

Intervention Period Phone Contacts Structure Table

Visit	7			8			9			10			11			12
Phone* Call		7a	7b		8a	8b		9a	9b		10a	10b		11a	11b	
Week	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44
Window(reg/ext) (Days)		+3/ +5	+3/ +5		+3/ +5	+3/ +5		+3/ +5	+3/ +5		+3/ +5	+3/ +5		+3/ +5	+3/ +5	
Adherence Encouragement		X	X		X	X		X	X		X	X		X	X	
SFD Questionnaire		X	X		X	X		X	X		X	X		X	X	
HUR Questionnaire		X	X		X	X		X	X		X	X		X	X	

*Data collected during phone calls is also collected at the time of formal visit; see Visit Structure Table above.

N. Rationale for Study Duration

We have chosen a combined 4 week Run-In with TALC so that subjects enrolled at the screening visit can efficiently be allocated to one of two trials, depending on the level of control they exhibit on low dose ICS. We recognize that use of 3 controller inhalers (plus a rescue albuterol inhaler) is logistically difficult, and may exceed the abilities of some subjects to adhere. Accordingly, we have included a 2-4 week period of observation during which adherence will be formally assessed. Only subjects who can demonstrate adherence to the protocol will be enrolled in BASALT. We have selected a 36 week intervention, recognizing that the duration represents a compromise. Favoring longer intervention times would be the increased Treatment Failure signal we would likely observe (expected to increase with time) with a 12 month or longer observation

period, and the ability to observe subjects over the entire annual cycle of environmental-, viral-, and allergen-induced exacerbations of asthma. Favoring shorter intervention times would be reduced cost, improved logistics, and higher retention. Based on data from ACRN1 SOCS and SLIC trials, we estimate that the TF signal will be sufficient to identify differences among treatment strategies (see Statistical Methodologies). Finally, we need to use an intervention long enough to model reasonably a 'long term' dose adjustment strategy; accordingly, a 16 week trial is probably too short. Because the primary outcome is not exacerbation (which would argue for a year long study), but rather is treatment failure, the duration of 36 weeks is justified.

IV. Outcome Variables and Metrics

A. Primary – Treatment Failure

The primary outcome variable for this trial will be time to treatment failure [TF]. See Treatment Failure Table for definitions.

To compare the effects of therapy with the different regimens, the primary outcome variable will be the time to treatment failure during the treatment period. Using survival analysis methods, we will compare treatment failures occurring during treatment with the GBA vs. BBA and GBA vs. SBA. We will also compare BBA vs SBA, although we recognize that our study is not powered to detect differences between them. In addition, we will distinguish between treatment failure due to poor asthma control and withdrawal for any other reasons.

TREATMENT FAILURE TABLE

Subjects are considered to have reached Treatment Failure (TF) if any of the following occurs:

<p>➤ Asthma exacerbation. Unscheduled medical contact for increased asthma symptoms which results in use of oral corticosteroids, increased inhaled corticosteroids, or additional medications for asthma will constitute an exacerbation. Formal definition of exacerbation is detailed below (VI.a.1).</p>
<p>➤ At-home measurements (any of the following three criteria, when not associated with the increased asthma symptoms, satisfies TF criteria):</p> <ol style="list-style-type: none">1. Pre-bronchodilator AM PEF <65% of baseline on 2 consecutive mornings, scheduled measurements.2. Post-bronchodilator PEF <80% of baseline despite 60 minutes of rescue beta-agonist treatment. Post-bronchodilator PEF may be taken at any time of day.3. An increase in PRN albuterol use of > 8 puffs per 24 hours over baseline use for a period of 48 hrs, or >16 puffs/24 hrs for more than 48 hrs.
<p>➤ In-clinic measurements:</p> <ol style="list-style-type: none">1. Pre-bronchodilator FEV(1) values on two consecutive sets of spirometric determinations measured 24-72 hours apart that are <80% of the baseline pre-bronchodilator value (baseline value for BASLT adherence period is the FEV1 value obtained at Visit 3 and baseline for randomization period is the FEV1 value obtained at Visit 4). (Note: all subjects found to have an FEV(1) <80% of baseline at any center visit but who are not considered to meet treatment failure or exacerbation criteria must be seen again within 72 hours to have FEV1 measured).2. Physician judgment for patient safety3. Patient dissatisfaction with asthma control achieved by study regimen.4. Requirement for open-label inhaled corticosteroids or another (non-systemic corticosteroid) new asthma medication (e.g. montelukast) without the addition of systemic corticosteroids.

B. Secondary Outcomes will include:

- Number of episodes of Treatment failure
- Time to first asthma exacerbation
- Number of asthma exacerbations
- Tests of airway caliber and responsiveness (FEV(1) pre and post-bronchodilator inhalation), methacholine PC₂₀
- Tests of airway inflammation (EBC, FeNO, sputum eosinophils)
- Proportion of subjects with exacerbation / Proportion of subjects with treatment failure

- QOL (AQLQ)
- ACQ, and number of visit days that ACQ is <1.25
- Total amount of oral prednisone required during the trial
- Total amount of inhaled steroids required during the trial
- Duration of control until first prednisone burst is warranted
- Number of ED or unscheduled physician/clinic visits (Treatment Failure)
- Hospitalization for asthma (Treatment Failure)
- Treatment outside the protocol (Treatment Failure)
- Calculated costs of treatment
- Adherence monitoring
- Days lost from school or work
- Adverse Events

C. Data to be gathered

1. Physiology
 - Spirometry, BD response
 - Methacholine PC₂₀
2. Biomarkers
 - FeNO
 - EBC
 - Sputum eosinophils
3. Report Based
 - Diary
 - a. Daily symptoms
 - b. AM PEF
 - c. Daily rescue albuterol (and inhaler C) use
 - In clinic instruments
 - a. ACQ / ASUI / AQLQ /
 - b. ACRN Asthma Evaluation Questionnaire
 - c. AE Reporting
 - d. ED visits, hospitalization, unscheduled medical care
 - e. Days lost from work or school
 - f. Adherence monitoring of Inhalers “A” and “B”
 - g. Usage monitoring of Inhaler “C”
 - h. Record of treatment decisions and supporting data

V. Power Analysis and Statistical Methodology

A. Power analysis

This trial is designed as a three-arm trial with two primary comparisons: guideline-based adjustment (GBA) vs. symptom-based adjustment (SBA) and GBA vs. biomarker-based adjustment (BBA). Assuming a 30% treatment failure rate in the GBA group, a sample size of 340-350 randomized subjects (34-35 per center and 113-117 per treatment arm) will provide 87%-88% power to detect a 60% reduction (30% vs. 12%) as in the Smith and Taylor study (Smith&Taylor 2005). This calculation assumes an overall alpha level of 0.05, with $\alpha=0.025$ for each comparison, a 2-sided test, and a post-randomization drop-out rate of 15%.

The original protocol accounted for a 10% post-randomization drop-out rate, but the ACRN Steering Committee observed approximately a 15% post-randomization drop-out rate as the recruitment effort was nearing completion. Therefore, the ACRN Steering Committee requested that the target sample size be increased from 320 to 340 randomized participants to account for this. The ACRN Data and Safety Monitoring Board approved of the request on July 30, 2009.

The study recruitment has been stopped on September 2, 2009. At that time, there were 324 randomized subjects, 27 subjects in the common run-in that is shared with TALC study and 7 in the BASALT run-in. It is possible that more than 16 subjects from the run-ins will be eligible for randomization which would put the total sample size greater than 340. Since the funding is available, additional randomizations will be allowed. With this approach, the total sample size is expected to range between 340 and 350.

The SBA vs. BBA comparison will be secondary but potentially important, especially if either BBA or SBA is found to be superior to GBA treatment. Our study may not have sufficient power to distinguish differences between these two treatments, but should provide at least pilot data permitting estimates of the number needed to determine differences in the effects of these two approaches to adjusted-treatment on treatment failure rates, exacerbation rates, costs of asthma care, quality of life, and other important outcomes.

B. Statistical Analysis Methods

1. Primary Outcome

The primary research aim is to evaluate whether the symptom-based adjustment [SBA] and/or biomarker-based adjustment [BBA] of inhaled corticosteroid therapy will be superior to standard, guideline-based adjustment [GBA], in maintaining asthma control, as assessed by the time to treatment failure. Therefore, to evaluate the primary

hypothesis, we will use survival analysis methods to produce Kaplan-Meier survival estimates and curves for the three treatment groups, and for the SBA vs. GBA and BBA vs. GBA primary comparisons we will evaluate the log-rank test for unadjusted results. In addition as a secondary analysis, we will fit a Cox proportional hazards regression model to compare the treatment groups and incorporate effects of center, center by treatment interaction, and any other baseline covariates which are deemed to be important. Since each subject may experience multiple treatment failures, we will also evaluate a repeated measures proportional hazards regression model which is available in the SUDAAN (SURvey DATA ANalysis) statistical package. In this model we will also evaluate the treatment effect adjusted for important baseline covariates, as well as test the center by treatment interaction.

2. Secondary Outcomes

Secondary outcomes in this trial include physiological variables (am PEF, FEV(1), methacholine PC₂₀), indices of asthma control and quality of life (asthma symptoms, rescue inhaler use, asthma control as assessed by the Asthma Control Questionnaire [ACQ], asthma-specific quality of life [AQLQ], proportion of days that ACQ is <1.25, total amount of oral prednisone required during trial, total amount of inhaled steroids required during trial, duration of control until first prednisone burst is warranted, number of asthma exacerbations), biomarkers of inflammation (exhaled nitric oxide [FeNO], EBC, sputum eosinophils), and pharmacoeconomic measures (ED visit or unscheduled physician visits, hospitalization for asthma, treatment outside the protocol, calculated costs of treatment, adherence monitoring, days lost from school or work) .

Secondary outcomes that are measured on a continuous scale, such as PEF, FEV(1), etc., will be analyzed via analysis of variance which evaluates the treatment comparisons using the change from baseline. Secondary outcomes that are measured as proportions, such as the proportion of visit days that ACQ is <1.25, will be analyzed via a logistic regression model. Event outcomes, such as hospitalizations, ED visits, etc. will be analyzed as (1) time-to-first event using proportional hazards regression, and possibly as (2) count data using Poisson regression. Secondary outcomes that are measured on a continuous scale repeatedly throughout the intervention phase of the trial will be evaluated via repeated measures analysis of covariance models.

C. Missing Data

Because of the possibility of drop-outs and other missed visits, there will be some missing data. The statistical models and analyses that are planned for the primary and secondary outcomes assume that the data are missing-at-random (MAR). Because likelihood-based methods will be applied, MAR data still yield valid estimates. Although not expected, if it appears that the MAR assumption is not reasonable, then non-ignorable statistical analyses, such as pattern-mixture modeling, will be applied.

D. Interim Analyses and Data Monitoring

A formal interim analysis of efficacy data is not planned. The ACRN (II) 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.

VI. Adverse Events

Definition

An adverse event shall be defined as any detrimental change in the subject's condition, whether it is related to an exacerbation of asthma or to another unrelated illness. Adverse events related to asthma exacerbation will be managed according to rescue algorithms outlined below.

Adverse Events Unrelated to Asthma

Adverse events due to concurrent illnesses other than asthma may be grounds for withdrawal from the trial if the illness is considered significant by the investigator or if the subject is no longer able to effectively participate in the study. Subjects 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 also are 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 investigator.

Documentation of an adverse event unrelated to asthma will be recorded on a Clinical Adverse Event Report Form and will include the following information:

- Description of the illness
- Dates of illness
- Treatment of illness (medications, doses, dates)
- Whether hospitalization or emergency treatment was required
- Treatment outcome

Adverse Events Related to Asthma

A. Asthma Exacerbations

During the course of the study, subjects may experience an increase in asthma symptoms. While an increase in asthma symptoms may be brief and self-limited, any increase in symptoms or changes in PEF should be carefully monitored by the subject, the clinic coordinator, and the physician. During the course of the study, symptoms may be of sufficient severity so as to warrant documentation as an asthma exacerbation.

1. Definition

During the common run-in (Weeks 0 through 4):

An asthma exacerbation is defined as the development of an increase in asthma symptoms (e.g. cough, chest tightness, or wheezing) which results in an increase in asthma medications, typically inhaled corticosteroids and/or oral or parenteral corticosteroids or another new asthma medication (e.g. montelukast).

Subjects developing an asthma exacerbation during the initial run-in period will be terminated from study participation and may re-enroll after the exacerbation has fully resolved.

After allocation to BASALT (Weeks 4 through 44):

- An increase in symptoms of cough, phlegm/mucus, chest tightness, wheezing, or shortness of breath in addition to at least one of the following:
 - Fall of pre-bronchodilator FEV1 to < 80% of baseline (defined at V3 and V4)
 - Pre-bronchodilator AM PEF <65% of baseline on 2 consecutive mornings, scheduled measurements
 - Post-bronchodilator PEF <80% of baseline despite 60 minutes of rescue beta-agonist treatment. Post-bronchodilator PEF may be taken at any time of day
 - Increase in PRN albuterol use in excess of 8 puffs per 24 hours over the baseline (baseline defined below) for a 48 hour period
 - Use of >16 puffs of "as-needed" beta-agonist per 24 hours for a period of 48 hours
- Hospitalization for asthma
- Urgent medical care for asthma in an office setting or Emergency Department
- Requirement for systemic corticosteroids (oral, IM, or IV) for the treatment of asthma

Subjects developing significant asthma exacerbation during the BASALT adherence period will need to washout for 4 weeks after the event or if applicable, after the last dose of the treatment was taken before randomization visit may occur.

2. Reference Periods

The reference point for PEF comparisons will be as follows:

During the common run-in period (week 0 to week 4; Visits 1-3):

- Weeks 0-2: Spirometry PEF value (converted to liters/min) associated with the best FEV1 obtained during baseline spirometry at Visit 1.

- Weeks 2 through Week 4: Mean value of AM pre-bronchodilator PEF recorded on symptom diary during the first two weeks of the common run-in (visit 1 through 2)

During the BASALT adherence period (week 4 - week 6 or 8; Visits 3-4):

- Mean value of AM pre-bronchodilator PEF recorded on symptom diary during the interval between the Visits 2 and 3

During double-blind treatment periods (Weeks 6 or 8-44; Visits 4-12):

- Mean value of AM pre-bronchodilator PEF recorded on symptom diary during the last two weeks of the BASALT adherence period (14 days prior to and including the morning of V4, not including V3 or prior data)

Reference points for rescue use (not including exercise preventive puffs):

Baseline use during the common run-in period (week 0 through 4) is not calculated as it is not referenced in the significant asthma exacerbation definition for the common run-in. (using TALC definition)

Baseline use during the BASALT adherence period (week 4 to week 6 or 8):

- Average daily use during the interval between the Visits 2 and 3

Baseline use during double-blind treatment periods (Weeks 8-44):

- Average daily use during the last two weeks of the BASALT adherence period (14 days prior to and including the morning of V4, not including V3 or prior data)

Reference points for FEV1 baseline:

- At randomization visit (Visit 4), FEV1 baseline is the FEV1 value measured at Visit 3.
- For the rest of the study (Visits 5 – 12), baseline FEV1 is the value measured at randomization visit (Visit 4).

3. Recognition

Once an asthma exacerbation has occurred, the subject should contact the clinic coordinator or a study physician. He/she may advise the patient to start treatment with the prednisone tablets that will be dispensed to all subjects at Visit 1 and to come for evaluation within the next 72 hours, or, depending on the apparent urgency of the need for treatment to come to the study site immediately or report to the nearest medical emergency facility as quickly as possible.

Because less significant changes in symptoms and/or PEF may precede more severe alterations in asthma stability, a series of rescue algorithms has been developed to address the various clinical presentations that may occur. Once any of these rescue interventions leads to the administration of systemic corticosteroids, the subject will be considered to have developed an asthma exacerbation. In addition, if in the opinion of the treating physician, systemic corticosteroid therapy is warranted regardless of any antecedent measurements of pulmonary function (PEF, FEV(1), *etc.*), value for symptom score, or frequency of rescue beta-agonist use, the subject will be considered to have developed an asthma exacerbation.

4. Management

Management of Exacerbations

Asthma exacerbations that occur following allocation to BASALT (upon completion of Visit 3) will be managed according to the rescue algorithms described below. During medical management of the exacerbation, other trial medication will be continued, unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. Reinstitution of trial medications will occur when the exacerbation has resolved at the discretion of the investigator. A record of all medications, dosages, and frequency of occurrence will be kept during exacerbations.

Rescue algorithms will employ open label medication, including albuterol.

A significant exacerbation which is identified historically, has resolved entirely, and is more than 1 week in the past need not be treated. Treatment for a significant exacerbation that is intermediate or ongoing will be left to the discretion of the investigator.

Following the significant exacerbation, at the safety evaluation visit, if the subject is in post-randomization period, Inhaler A will be increased by one step on the Dosing Table, unless the subject is already at Step 5 or inhaler A was already adjusted within 4 weeks due to the treatment failure (TF) event, in which cases Inhaler A will not be further adjusted upwards. There are no inhaler adjustments during the BASALT adherence period.

Rescue Algorithms

Once an asthma exacerbation has occurred, the subject should contact the clinic coordinator and/or be evaluated at the study site or the nearest medical emergency facility as quickly as possible.

Rescue algorithms are based on recommendations from the NAEPP Guidelines for the Diagnosis and Management of Asthma. Albuterol, inhaled steroids, and oral prednisone are the principal medications for rescue management. Subjects will be instructed in their use for home management, and supplies of albuterol and prednisone will be provided throughout the study. For severe acute episodes of asthma, treatment will be administered according to the best medical judgment of the treating physician.

1) Home Care

Asthma exacerbations will be recognized by an increase in symptoms and by a corresponding drop in PEF below baseline level. Subjects will be educated to recognize exacerbations as early as possible to facilitate prompt treatment and to lessen morbidity.

- Subjects who recognize exacerbation symptoms will be instructed to use albuterol (RESCUE) inhaler, 2 puffs every 20 minutes up to 60 minutes if needed, and then every 4 hours, or less, if needed. Subjects will be instructed to take 2 puffs from Inhaler C every time 2 puffs from RESCUE inhaler were taken.
- If the PEF does not increase to $\geq 80\%$ baseline level or if symptoms are not improved after the first 60 minutes of albuterol therapy, the subject should contact the investigator or their primary care physician or seek care in the emergency department.
- Failure of albuterol and Inhaler C to control or maintain PEF $\geq 80\%$ of baseline level may necessitate the use of open label corticosteroids (see below).

2) Physician's Office or Emergency Room Treatment

- Subjects will be assessed by history, physical examination, and by physiological monitoring including spirometry or PEF. If the subject's PEF and/or FEV₁ is less than 25% predicted or if the subject shows evidence of altered mental status, cyanosis, labored breathing, or use of accessory muscles, sampling of arterial blood for respiratory gas analysis is indicated, with appropriate action taken depending on the results obtained.
- When treated in the physician's office or the hospital emergency room, subjects should initially be given albuterol by nebulization (0.5 cc of 0.5% solution) every 20 minutes over the first 60 minutes.

- If the PEF increases to $\geq 80\%$ of reference level after the first 60-90 minutes, the subject can be discharged to continue treatment at home. Prednisone may be administered at the discretion of the physician to augment therapy.
- If symptoms persist and PEF remains $<80\%$ of reference level, nebulized albuterol should be continued as often as every hour and further treatment with oral or parenteral corticosteroids should be considered. Monitoring of PEF or spirometry should continue every hour. Within four hours of treatment, a decision should be made regarding subject disposition.
- If PEF increases to $\geq 80\%$ reference level within four hours, the subject can be discharged to continue treatment at home. Home treatment should include an 8-day course of prednisone.
- If PEF remains $>40\%$ but $<80\%$ of reference level, an individualized decision should be made to hospitalize the subject for more aggressive therapy or to continue therapy at home with a course of prednisone and possibly followed by inhaled corticosteroids.
- If PEF is $<40\%$ reference level after repeated albuterol treatments, the subject should be admitted to the hospital unless, in the physician's best judgment, alternative treatment could suffice.

3) Prednisone Treatment

In this protocol, prednisone will be used when, in the judgment of the investigator, acute exacerbations cannot be controlled by albuterol. Indications for prednisone therapy include the following:

- To achieve stable control of symptoms and optimize pulmonary function once asthma exacerbation status is achieved.
- For follow-up management after discharge from the physician's office, emergency room, or hospital for an acute exacerbation.

The dose of prednisone used during an acute exacerbation shall consist of 60 mg as a single oral dose every day for 3 days followed by a 10 mg/day taper over the next 5 days. The decision to initiate or to continue a course of prednisone beyond 8 days is left to the discretion of the physician.

4) Inhaled Corticosteroid Treatment

During common run-in (weeks 0 – 4):

Inhaled corticosteroid dosing for worsened asthma symptoms during the common run-in will be the addition of open-label inhaled corticosteroid at double the dose of ICS, or higher, than that used in the run-in period for two weeks.

After allocation to BASALT (upon completion of V3):

If the investigator at the site determines that subject should be prescribed open-label inhaled corticosteroid, the subject should be put on budesonide at the 800ug BID for 14 days. No other inhaled corticosteroid should be prescribed.

5) Study Center Visits Following Exacerbations

For safety reasons, all subjects will be seen at the clinical center within 72 hours from the day they have been categorized as experiencing an asthma exacerbation or sooner if needed. If budesonide is needed, it will be given to the subject at this visit. Also, Inhaler A adjustment may be done at this extra visit. All medications used to treat exacerbations will be recorded and entered into the study database. Following this "safety" visit, subsequent protocol visits generally will continue in accordance with the visit schedule established at Visit 4.

6) Criteria for Withdrawal from Study Due to Asthma Exacerbation

Subjects developing an asthma exacerbation during the initial BASALT/TALC common run-in period (Visits 1-3) will be terminated from study participation and may re-enroll after the exacerbation has fully resolved.

For safety reasons, after subjects have been allocated to BASALT and have completed V3, they will be terminated from the study if they experience three significant exacerbations requiring oral prednisone OR the use of oral prednisone therapy for more than 30 days.

B. Treatment Failure without Exacerbation

1. Definition

Treatment failure (TF) is achieved if any of the conditions in the Treatment Failure Table occur.

Initiation of the treatment for a TF which is intermediate or ongoing at the time of a monitoring visit be left to the discretion of the investigator. If the treatment will be initiated, it must be done as described below in the management section. A TF which is identified historically, has resolved entirely, and is more than 1 week in the past need not be treated.

2. Management

If the treatment is deemed necessary, a treatment failure that occurs following allocation to BASALT should be managed by open-label budesonide at the 800ug BID for 14 days. Subjects will not have budesonide at home but rather it will be given to the subject during the safety evaluation visit. During medical management of the treatment failure, other trial medication will be continued, unless the treating physician considers it appropriate to suspend such therapy until the event resolves. Reinstitution of trial medications will occur when the TF has resolved at the discretion of the investigator. A record of all medications, dosages, and frequency of occurrence will be kept during TF.

Following the TF, at the safety evaluation visit, budesonide may be given and if the subject is in post-randomization period then inhaler A will be increased by one step on the Dosing Table, unless the subject is already at Step 5 or inhaler A was already adjusted within 4 weeks due to the treatment failure (TF) event, in which cases Inhaler A will not be further adjusted upwards. There are no inhaler adjustments during the BASALT adherence period.

Subjects developing TF during the BASALT adherence period will need to washout for 4 weeks after the event or after the last dose of treatment was taken before randomization visit may occur.

VII. Active Treatment Medications

- a. QVAR 40 and 80 - used during the common run-in, BASALT adherence period and then randomly allocated where each subject will receive 3 inhalers A, B and C; 2 inhalers will always contain placebo and 1 will contain active ICS
- b. As-needed albuterol for relief of acute symptoms
- c. Budesonide, 800ug BID, given to the subject based on the investigator at the site judgment for treatment of significant exacerbation or treatment failure (TF) only.

VIII. Adherence and Monitoring

Adherence testing during the 2-4 weeks prior to randomization will be performed to ensure that the subject can adequately comply with this complex protocol. Following randomization, adherence will be monitored using Doser®-equipped inhaler devices. The Doser monitoring screen will be left uncovered, and the purpose of the Doser device will be made known to the subjects, so that the Doser data screen itself will serve as a positive feedback for adherence. The adherence information will be extracted by the ACRN coordinators, and feedback and counseling will be provided to the subject.

As a secondary source of adherence information, subjects' diary cards will be examined for the number of puffs of each medication recorded for each day. This information will be compared to PEF measurements electronically recorded and date/time stamped from the EPFM device. Because subjects are instructed to perform their morning peak flow maneuver right before taking their study medications, timing of an PEF monitoring can be used as a surrogate for timing of dosing with study medications. Limitations of this mechanism for monitoring adherence are accuracy of the subjects recall and honesty, because the timing or confirmation of dosing cannot be verified directly.

We will call subjects every two weeks (between the 6 week visits; Intervention Period Phone Contact Structure Table) during which adherence with medications will be assessed and encouraged. In addition, we will administer two standardized ACRN instruments: 1) the symptom-free day questionnaire, and 2) the Healthcare Utilization Resource questionnaire (included as appendiceal information). These additional interactions will enable us to calculate pharmacoeconomic outcomes such as cost of a symptom-free day, and the costs of health care utilization.

IX. Risks and Benefits

A. Risks and Risk Minimization Strategies

1. Risks of Exacerbation / Treatment Failure / ICS Withdrawal

The principal risk of the BASALT trial is that of exacerbation of asthma during the course of interventional treatment. This risk is engendered by our formalization of downward adjustment of therapy, as directed by current guidelines (GBA) or the biomarker eNO (BBA), and by incorporation of an arm in which all scheduled anti-inflammatory therapy is delivered "on demand" as prompted by asthma symptoms requiring rescue albuterol. Accordingly, asthma subjects who are well controlled on a low dose of ICS will have that dosage reduced over the course of the trial, and such reduction will, in some subjects, produce deterioration of asthma control.

What is the justification for subjecting our enrollees to this risk? First, there is a small but definable risk of continuous inhaled steroid therapy, perhaps most clearly quantified for its effect on bone mineral metabolism [Israel 2001]. If continuous ICS therapy is shown not to be necessary to maintain acceptable asthma control, then it is appropriate to eliminate the risk of ICS. Secondly, there is a cost of continuous ICS therapy, borne by the health care system. Finally, this protocol seeks to define the optimal *adjustment* strategy – that is, to determine the optimal way to customize asthma therapy for the individual, and match the intensity of therapy to the intensity of disease expression. The ‘risk’ of current static strategies is that they may fail to respond appropriately to the remarkable variability of asthma [Calhoun 2003].

Each arm of the trial has somewhat different qualitative risks. The GBA arm matches current clinical practice, but formalizes downward adjustment of ICS therapy perhaps to a greater degree than the NHLBI or GINA guidelines [GINA 2005] [NHLBI 2002]. The BBA arm employs a biomarker of airway inflammation about which there remains controversy. However, eNO has been used effectively as an adjustment strategy [Smith & Taylor 2002], so there is existing precedent. Finally, the SBA group will have no routine maintenance ICS (after the first two weeks of intervention), and accordingly will have ICS administered only in the context of development of symptoms. Data from the previous ACRN trial of symptom based action plans (IMPACT [Boushey 2005]) has suggested that patients with mild asthma are acceptably managed by this strategy. However, it is not clear whether asthma patients with slightly more moderate disease could be similarly managed using a symptom based approach.

We plan to minimize these risks by careful frequent (q2 wk) monitoring during the first 6 weeks following randomization. During this time during which we anticipate that the dose of ICS will be tapered most rapidly, we will provide the most intensive follow-up. After the first 6 weeks, we will monitor subjects every 6 weeks, a frequency 2-6 times more frequent than what might be the case in the usual practice of clinical medicine.

2. Risks of Inhaled Steroid Administration

It is also true that administering ICS carries risks of both local (dysphonia, thrush) and systemic (altered mineral metabolism, [Israel 2001]) effects. In addition, there are economic implications. We will minimize those risks by educating subjects on the proper use of MDI devices, proper rinsing technique, and monitoring for local effects during clinic visits. We will further minimize these risks by the structure of our adjustment design. High dose ICS exposures will be avoided by the limits placed by the Dosing Table, and by the Treatment Failure criteria, which prevent long term use of a large number of puffs of ICS. More than 16 puffs of ICS per day will not be administered for more than a few days at a time. Finally, we are not enrolling subjects <18 years of age, so we will not be studying this particularly susceptible population.

3. Risks of Fixed Airway Obstruction as a Consequence of Inhaled Steroid Withdrawal

One concern that could be raised about ICS withdrawal is that undertreatment of asthma might lead to the development of fixed airflow limitation. Although it is legitimate to raise the question, we believe that this risk is quite minimal for two reasons. First, there is little evidence that inhaled steroids modify the natural history of asthma, as recently reviewed by Dixon and Irvin [Dixon 2005]. Were ICS clearly associated with reduced loss of lung function over time, the withdrawal of effective therapy might be cause for concern. Those trials that do show immediate benefit of ICS on lung function show such benefit in patients with a short duration of asthma. The average duration of asthma in the ACRN studies exceeds 15 years. Accordingly, with the weight of evidence solidly in the other corner, we view this risk as immeasurable and small. Secondly, our own data from the IMPACT trial [Boushey 2005] suggest that treatment with placebo, in the context of a symptom based action plan (as also incorporated in BASALT), is NOT associated with the development of fixed airflow obstruction. A similar conclusion can be drawn from the outcomes of the Smith&Taylor study [Smith & Taylor 2005], in which fixed airflow limitation did not develop. Finally, it is important to emphasize that BASALT is an adjustment trial, not a steroid withdrawal trial. It is expected that most subjects who qualify for enrollment will NOT be entirely withdrawn from ICS treatment.

B. Benefits and Risk/Benefit

There are no direct benefits to the participants. However, if the trial demonstrates that symptom based management of mild persistent asthma is equivalent in most outcomes to eNO based adjustment, it would suggest that a cost-effective, patient-centered, symptom-driven strategy for ICS adjustment could be more widely implemented. This strategy has inherent attractiveness, in that subjects (and by implication patients) are more empowered to manage their own asthma. Alternatively, if eNO based therapy adjustment is better than GBA, we will have identified a better therapeutic strategy for asthma management. Because the risks are adjudged to be quantitatively small, the risk-benefit ratio is favorable.

X. Expected Results

There are several possible outcomes of this trial that could be foreseen.

GBA = SBA = BBA

Should neither SBA nor BBA be superior to GBA, we learn the minimum above and beyond current practice and consensus. This study is not powered as an equivalence study. However, such a finding would suggest the possibility that a specific adjustment strategy might be unimportant relative to the general asthma care that is common to all three adjustment arms. It might also suggest that clinicians could select among a variety of strategies for individualizing therapy. Further, the simplicity of allowing patients to regulate their asthma therapy on the basis of symptoms, rather than on the basis of guidelines which are cumbersome to implement, would be a very attractive strategy.

SBA, BBA > GBA

This outcome is the scenario for which we powered this study. We anticipate that both SBA and BBA will be associated with a smaller rate of Treatment Failure, the primary outcome, than will be observed in subjects randomized to GBA. Should this outcome obtain, it would be important, because it would suggest that individualized therapy outperforms the more uniformly applied GBA therapy. The robustness of this suggestion will be determined by the number and importance of secondary outcomes that align with, or align against the primary outcome. Another possible implication of this outcome is that intermittent, symptom-based therapy should be used in preference to BBA, due to the lower cost of implementing SBA vs BBA. The costs of implementing SBA are principally those of educating the patient or caregiver. In contrast, the costs of BBA are not inconsequential, due to the expense of purchasing, amortizing, and maintaining equipment to measure FeNO. Finally, we may underestimate the benefit of SBA on quality of life in this trial, because the necessary double dummy design imparts a significant 'hassle factor' which negatively impacts quality of life.

A subset case, with the same general implications as those outlined above, would be that SBA was superior to BBA, with or without superiority to GBA.

BBA > SBA, GBA

Despite our study not being powered to detect superiority of BBA vs SBA, this outcome is possible. If this outcome obtains, it would then raise important issues of cost-effectiveness of BBA. Only if BBA can subsequently be shown to be clearly superior to other adjustment strategies, and the cost-benefit determined in the context of additional studies, might broad-based application of this new technology be warranted in this population.

XI. Recruitment Strategies

Each clinical center involved in the ACRN was chosen based on documentation for patient availability, among other things. It is, however, worthy to note the specific plans of each center.

a. Harvard - Brigham and Women's Hospital, Boston MA

The Boston Center has used a variety of recruitment methods to meet and exceed recruitment goals of previous ACRN studies.

Over the past five years, we have compiled an internal database of approximately 1500 individuals with asthma who are interested in participating in asthma studies. All of these individuals contacted us and expressed interest about asthma studies within the past year, and have been evaluated by our staff for participation in ongoing and future asthma clinical research studies.

The Boston site actively recruits subjects using a variety of external media. All methods are IRB-approved and include postcard mailings to area zip codes, newspaper advertisements, and broadcast e-mails and internet postings

Brigham and Women's Hospital has introduced a new clinical research tool called the BWH Research Patient Database Registry (RPDR) that allows researchers with proper IRB approval to query the hospital's patient database for potential research subjects. We recently queried this system and identified approximately 30,000 patients with a diagnosis of asthma. With permission from their primary care physician, patients may be contacted about current asthma research. We are in the process of developing tools to reach these patients through their physicians. Access to the physician database will further expand our capability to recruit asthmatic patients of differing severities.

b. National Jewish Asthma Research Center, Denver, CO

There are over 400 asthma subjects (not followed in the National Jewish outpatient clinic) that have participated in research studies conducted at the Denver Center. Many of these subjects have been through various medication studies and bronchoscopies with lavage/biopsies. Their FEV(1)s range from 30-110% of predicted.

1. Denver Health Medical Center – Dr. James Fisher, Head of Pulmonary Medicine, is supporting efforts of the Denver Center by helping to recruit from the asthmatic subject population at the Denver Health Medical Center. This is a large county hospital whose subject population comprises mainly Hispanic and African-American people.

2. Denver Veterans Administration Hospital – Dr. Carol Welsh, Pulmonary faculty member, will support this grant. The VA hospital has a large outpatient clinic of patients with asthma, but not chronic obstructive pulmonary disease.

3. Denver Kaiser Permanente HMO – Dr. Timothy Collins is the Director of Pulmonary Medicine and Dr. John Williams is the Director of Allergy at Kaiser. Drs. Collins and Williams have been actively involved in supporting research at National Jewish in the past by referring subjects. Their groups will continue to play an active role in clinical research support.

c. University of Texas Medical Branch, Galveston, TX

The University of Texas site has developed an infrastructure to support all clinical and translational trials (Translational Research Unit for Asthma, Immunology, and Respiratory Diseases [TRU/AIR]. It is directed by Dr William Calhoun, and ably assisted by Drs Andrew Grant and Bill Ameredes. Each of these investigators has more than 13 years experience with clinical and translational trials. The TRU/AIR is headed by Lisa Nemeth, RN, CCTC, who has more than 12 years of experience with multicenter clinical trials. The TRU/AIR includes several technicians, nurses, and a respiratory therapist who serve as Clinical Study Coordinators.

We recruit from the local and regional population using print and electronic media; all advertising and posting materials are approved in advance by the IRB at UTMB. In addition, we recruit from APICS Divisional (Allergy, Pulmonary, Immunology, Critical Care, and Sleep) clinics, which number more than eight ½ day clinics per week. Volunteers who express interest in response to any of the recruiting channels are recorded in a local data base.

Further, Dr James Goodwin, who directs the Sealy Center on Aging, and an NIH funded population study, has agreed to make available his database information on demographically characterized populations of subjects in the Southeast Texas region in support of the ACRN.

The population in our catchment area is about 35% Caucasian, 35% Hispanic/Latino, and 30% African American. Existing population databases have demographic characteristics similar to the population statistics.

d. Washington University, St. Louis, MO

The St. Louis site actively recruits subjects using a variety of external media. All methods are IRB-approved that include newspaper advertisements in the local and minority newspapers, the University newspaper, posting flyers throughout the medical school campus, and the university website called "Volunteer for Health." This is a service the University offers to match interested volunteers with current clinical trials at

the medical school. This service has a website, and anyone can access this with the web address.

Over the past 10 years, Dr. Castro has compiled an internal database of more than 400 individuals with asthma who are interested in participating in asthma studies. All of these individuals have contacted us and have expressed an interest in participating in an asthma study. These individuals have been evaluated by our staff for participation in ongoing and future asthma clinical research studies.

e. University of California, San Diego, CA

Recruitment activities at UCSD Clinical Trials Center is multi-faceted and includes a computerized database with current and previously enrolled subjects, direct advertising, and community outreach programs such as educational lectures on asthma, attendance at health fairs with staff conducting pulmonary screening tests. All activities, flyers and advertisements are approved by the UCSD Human Research Protection Program prior to initiation.

The UCSD Clinical Trials Center database has over 500 asthmatics who have been previously enrolled or expressed an interest in participating in a clinical trial. Interested subjects are entered into the database with fields for demographic, medical, medication, and pulmonary function tests. Quarterly newsletters and flyers are mailed to the subjects with specific information on trials and to maintain accurate contact information of the individuals.

In addition, this application is supported by the Naval Medical Center and Kaiser Permanente Healthcare whose directors (Drs. Warren Lockette and Michael Schatz) are faculty members at UCSD. The Clinical Investigation Department (CID), at Naval Medical Center, San Diego (NMCS D) is directed by Warren Lockette, M.D. and is dedicated to fostering training and research in both basic and patient-oriented research at the Naval Medical Center, San Diego. Dr. Lockette collaborates with the CTC recruitment program to recruit subjects from the active and retired navy community in San Diego for CTC studies. The NMCS D has 700,000 outpatient visits each year and serves as a provider of primary care to 260,000 patients living within an easy commute, i.e. a 40-mile radius of the hospital.

Kaiser Permanente Healthcare: Dr. Schatz is the Director of the Allergy Division of the Kaiser Permanente Healthcare of Southern California, Permanente Medical Group and a faculty member at UCSD. In San Diego alone, they serve over 600,000 members with over 11,000 identified asthmatic subjects. Kaiser-Permanente has a fully operational computerized pharmacy records system, which provides identification of patients using anti-asthma medications. This system will be used to access patients with asthma under the care of primary care physicians and nurses. In addition, because of freeway access to UCSD and traffic, the CTC has been successful in recruiting from southern Los Angeles, Orange and Riverside Counties. Kaiser members living in that region will

also be recruited. Dr. Schatz has previously collaborated with Dr. Wasserman on NIH-sponsored research projects and will continue this active collaboration and contribute to the recruitment for the ACRN protocols.

f. University of California, San Francisco, CA

Study population: The UCSF center's recruitment of asthmatic subjects relies on community advertising and on maintaining a database of subjects who have participated in previous studies, come for a "characterization" visit, or expressed interest in participating. They advertise in the San Francisco Chronicle, the Bay Guardian, and in neighborhood and college newspapers. They also advertise on "Craigslist," a Web-based bulletin board on local radio and television stations. They post fliers on neighborhood and campus bulletin boards, and present our studies to physician groups. Responses to these advertisements are made to a dedicated telephone number. A dedicated recruiter, Lila Glogowsky, responds to each inquiry to obtain basic information about demographics and about asthma severity, duration, and treatment. She schedules apparently qualified subjects for a "characterization visit" in which a coordinator obtains a detailed history and performs spirometry and skin testing.

Subject Characterization: The UCSF center's methods for characterizing subjects conform to national guidelines (e.g. spirometry), to widely accepted custom (e.g. methacholine challenge), or to its own standards as the center developing the method (eg., sputum induction and analysis). They have adopted standardized questionnaires for assessing asthma symptom severity, asthma control, and asthma-related quality of life. They have developed questionnaires on asthma history, patterns of health care utilization, and domestic exposure to allergens.

The recruitment/characterization program is supported by a data-base program ("File-Maker Pro") on a dedicated server. Phenotypic information is now stored on >5,000 potential subjects of a variety of ethnic backgrounds (64% Caucasian, 13% African American, 7% Hispanic, 10% Asian and 6% other).

Subjects at the University of California San Francisco: In addition to community advertising, subjects are recruited, especially those with severe asthma, from clinical programs overseen by UCSF faculty at Moffitt, S.F. Veteran's Administration, S.F. General, and Mt. Zion Hospitals. The faculty is responsive to approaches from colleagues conducting clinical trials and there has been collaboration with the Division of General Internal Medicine to recruit for specific protocols. This Division follows approximately 18,000 patients, of whom 8% (2,683) have a primary or secondary diagnosis of asthma (ICD-9 493.00, 493.01, 493.10, 493.11, 493.20, 493.21). Of these asthmatic patients, 48% are White, 20% Asian/Pacific Islander, 10% Latino, 16% African American, and 1% Native American. Sixty-four percent are female.

g. Columbia University Medical Center, New York, NY

Columbia University Medical Center is the main hospital providing service to the 265,000 residents of Washington Heights/Inwood and to many of the 712,541 people living in Northern Manhattan.

The Asthma Center at Columbia maintains a comprehensive database of all individuals who have responded to our recruitment efforts for asthma studies since 1996. To date, this database consists of over 1,800 asthmatic individuals who have expressed an interest in study participation. Their names have been generated in response to newspaper and radio advertisements, physician referrals, posting and distribution of flyers and community health screening events. All of these subjects have completed phone questionnaires regarding their asthma and medication use; additional information maintained includes age, gender, duration of asthma and demographic details. Approximately 20% of these individuals have been screened at the Columbia University Asthma Center and have had pulmonary function testing performed. Potential study subjects will be identified through screening of this actively updated database and potentially eligible subjects will be contacted in a manner approved by the IRB.

The John Edsall/John Wood Asthma Center at Columbia Presbyterian Medical Center sees approximately 1,200 patient visits per year. Approximately 90% of visits were from patients living or working in Northern Manhattan, approximately 80% are insured by Medicaid. The severity of asthma varies among these patients; approximately 21 % are in the mild category, 63 % are in the moderate category and 16 % are in the severe category, 57% of the patients are atopic as determined by history or skin testing; IgE levels have been measured in the majority. 76% of patients followed at this clinic are female. Approximate demographic makeup of patients is 83% Hispanic, 14 % African American and 3 % other, including Caucasian. Patients included on this database are actively followed in the Asthma Center at Columbia and their asthma is well characterized. These patients have a longstanding relationship with providers in the clinic and have participated in many asthma clinical studies.

Advertisements: We plan to utilize IRB approved newspaper and radio advertisements to inform potential subjects of our studies. We have had success with recruiting subjects through advertisements in newspapers that target ethnic minorities living in Northern Manhattan, the South Bronx and surrounding areas. We will also advertise in media that reaches individuals city-wide. Responses to advertisements will be answered by a dedicated phone line to be manned during business hours and answered by voicemail at other times. A research assistant will respond to each inquiry immediately, using a screening instrument. We plan to regularly post and advertise our studies at the four colleges located in Northern Manhattan. We will also distribute flyers throughout the community on a regular basis, display posters at gathering places such as stores, laundromats, eating establishments and at community centers. Flyers advertising clinical studies will continue to be distributed along with educational materials at all asthma workshops and seminars. We have found these relatively low budget strategies to be highly effective.

Community Awareness of Clinical Trials: Efforts of the Columbia University Asthma Coalition to empower residents of Northern Manhattan by educating them about asthma and the ability to control the disease through lifestyle changes and with controller medications is likely to set the stage for interest in participation in clinical trials. As a result of outreach efforts, we have established contacts with various ethnic community, university, church and business groups and have conducted many community based asthma programs. The close collaboration with community based organizations that we have developed through our Asthma intervention program has resulted in referrals into clinical trials. Our advertisement posters are regularly displayed within these organizations, and staff working at the community based organizations have referred patients to us for research participation, often as a means of allowing uninsured individuals to receive asthma medications and monitoring.

h. University of Wisconsin, Madison, WI

The Allergy Research Program of the University of Wisconsin maintains a file of potential subjects with mild to moderate asthma who are interested in future research participation. These individuals have been screened and/or participated in previous asthma studies. The following information is maintained: birth date, gender, ethnic background, age of asthma diagnosis, childbearing status, atopic status (including results of skin testing if performed previously), concurrent medical history, asthma and non-asthma medications. Approximately 85% of subjects in this database have "mild to moderate" asthma. This database of subjects will be used as the primary source of recruitment for this protocol. If additional subjects are needed, they will be recruited via U.W. Human Subjects committee-approved, newspaper advertising and from the U.W. Allergy Clinic subject population as well as the U.W. Sports Medicine Clinic, U.W. Student Health, V.A. Allergy Clinic, and the Northeast Family Practice Clinic.

i. Wake Forest University Health Sciences Center, Winston-Salem, NC

The Cloverdale Clinical Research Center at Wake Forest University Health Sciences and the Center for Human Genomics maintains a screening database of approximately 1075 subjects with asthma. These are subjects who have called our clinic expressing interest in participating in asthma research studies. Some have been screened for or have participated in past research studies at our site. The following information is maintained on these subjects as it is obtained: gender, age, ethnic background, medical history, asthma history, skin testing results, exhaled breath condensate results, exhaled NO results, methacholine challenge testing results, pulmonary function, sputum induction results, bronchoscopy results, chest x-ray results, and medication usage. Should additional subjects be needed beyond this database of potential subjects, we continuously advertise for potential subjects using television, radio, and newspaper and flyer advertising (all advertising is IRB approved), as well as recruitment from the Wake Forest University Health Sciences Pulmonary and Allergy Clinics through our Primary and Sub-Investigators.

j. Duke University Medical Center, Durham, NC

Duke University recently opened the Duke Asthma, Allergy and Airway Center, a 13,000 square foot facility designed for the evaluation of clinical and research patients with airway disease. We are in the process of creating a HIPPA and IRB-approved database to capture clinical data from patients receiving care at the asthma center. Recruitment efforts focus primarily on Durham but also include Chapel Hill, Research Triangle Park and Raleigh. Durham County has a diverse population that includes 39% African Americans, 11% Hispanics and 3% Asian Americans. Subjects are recruited using print media (advertisements in the local newspapers), radio advertisements and television. The recruitment of African Americans and Hispanics is accomplished through advertisements at community events.

XII. Costs, Liability, and Payment

All tests will be performed without cost to the participating subjects. Since this is a trial using a well-established asthma treatment, liability for subject care costs incurred by subjects during the course of the trial will in most cases be borne by the subject or the insurer. Details of the National Institutes of Health policies concerning this issue can be found in NIH Documents # 5305 and 6352-2, Research Patient Care Costs Supported by NIH Sponsored Agreements, which are in the ACRN Manual of Operations.

Each subject will receive financial compensation within FDA guidelines for participation in an amount determined by the local center. For subjects who drop out, payments will be pro-rated for the length of time they stayed in the study, but payment will not be made until the study would have been completed had the subject not dropped out.

XIII. Data Recording

A. General

Recording of all data including the informed consent, history, physical examination, results of allergy skin testing, vital signs, electrocardiogram, results of pregnancy tests, adverse events, confirmation of medication dispensation, pulmonary function tests, methacholine challenge testing, and quality of life questionnaires will be recorded on forms prepared by the ACRN Data Coordinating Center. Initial data entry will be done at each Clinical Center and forms will be forwarded to the DCC for confirmatory entry. Reports from pulmonary function tests will sent to the DCC. All data will be stored and analyzed at the DCC.

B. Pharmacoeconomic Outcomes

The direct costs of care will be calculated using standard instruments as employed by prior ACRN and CARE network trials. Briefly, medications (both scheduled and unscheduled), clinic visits, spirometric monitoring, FeNO measurements, unscheduled care, and phone contacts will be recorded during the trial. Each intervention will be assigned a value comparable to market value, and the total costs for each arm will be calculated as the sum of the products (valuation x usage) for each component. Total costs, the numerator, will be adjusted for the number of patient-months of follow-up, and multiplied by 12 to estimate annual costs for each strategy. Indirect costs will be estimated by assigning a value of median US income divided by 250 working days per year for each day lost from work due to asthma.

The symptom-free day will be used as an outcome measure for the pharmacoeconomic analysis of BASALT, as recommended by the NAEPP Task Force Report on the Cost Effectiveness, Quality of Care, and Financing of Asthma Care [Sullivan 1996]. Estimates of symptom-free days will be obtained by administration of a five-item Symptom-Free Day Questionnaire at each study visit and study phone contact throughout the study. This tool and approach were effectively utilized in the ACRN1 IMPACT trial. [Boushey 2005]. These 5 questions have been validated in other longitudinal studies for a 14-day subject recall of symptoms. As a complimentary pharmacoeconomic outcome, the validated Multiattribute Asthma Symptom Utility Index [Revicki 1998] will be administered at study visits. This instrument has 4-day reproducibility and allows for calculation of an Asthma Symptom Utility Index score which represents patient preferences for combination of asthma-related symptoms and side effects on a scale from worst possible to best possible state.

Additional pharmacoeconomic endpoints to be compared among the BASALT treatment arms will be the estimated cost of care, derived from the calculations of the costs for daily medications, for asthma exacerbations (costs of all rescue therapies, unscheduled

health care visits, urgent care/ ED visits, days of hospitalization) and costs of school and work absenteeism. Information about these events will be captured by standardized questionnaires and structured interviews at each research center visit and phone contact. These questionnaires and approach were effectively utilized in IMPACT.

Potential side effects associated with the BASALT treatment arms such as hoarseness, sore throat, oropharyngeal candidiasis, elicited through the study visit structured interview and physical examination, will be collected. Medications for study treatment-related adverse events will be assigned a cost value and included in the pharmacoeconomic analysis.

Because of the unique nature of one of the BASALT treatment arms (BBA), we will also calculate the economic implications of monitoring FeNO. The study center costs of purchase and maintenance of the Aerocrine equipment and supplies will be estimated throughout the study. Specific data collection forms at both the study centers and the DCC will be developed to track expenditures. Again, a cost value will be assigned and included in the pharmacoeconomic analysis.

Differences among the treatment arms in overall asthma control will be assessed by the validated Asthma Control Questionnaire [Juniper 1998] that incorporates information about symptom frequency and severity, rescue medication use, and pulmonary test results, and a validated asthma specific quality of life questionnaire [Juniper 1999].

C. Exploratory Pharmacogenetic Outcomes

We propose exploratory pharmacogenetic studies, in concert and parallel with the TALC study, to determine if asthmatics with specific alterations (single nucleotide polymorphisms and/or haplotypes) in the beta-2 adrenergic receptor, and genes in the glucocorticoid pathway will respond positively and negatively to an inhaled corticosteroid and rescue beta-agonists. These studies will be performed at Wake Forest University and Harvard University, in collaboration with the Data Coordinating Center, and will be done with resources provided by investigators at Wake Forest and Harvard, including a collaborative pharmacogenetics grant. DNA sequencing reactions are performed using the ABI dye terminator chemistry as previously described, with sequencing of products using an ABI 3730 XL DNA Analyzer (Applied Biosystems, Inc., Foster City, CA) (Hawkins 2004). Genotyping is performed using the MassARRAY genotyping system (Sequenom Inc., San Diego, CA, USA) (Hawkins 2004).

Gregory Hawkins, PhD, an Associate Professor of Medicine at Wake Forest University School of Medicine has recently been awarded a R21 award to examine genes in the glucocorticoid pathway in asthmatics and controls. Led by his efforts, we have completed preliminary sequencing of steroid complex genes *Hsp90 1*, *Hsp90 1*, *Hsc70*, *Hsp70* (A1A and A1B), *STIP1* (Hop), *Hsp40* and *p23* in 46 severe asthmatics. In addition, we have also been able to sequence two additional genes encoding the immunophilins *FKBP51* and *FKBP52* in 46 severe asthmatics. These two additional

components of the steroid receptor complex are involved in transport of the activated receptor across the nuclear membrane. We have also sequenced the genes for *Hsp70* (A1A and A1B) in a screening panel of consisting of asthmatics and non-asthmatics from Caucasian, African American, and US Hispanic origin. To our knowledge, this is the first comprehensive sequencing of the *Hsp70* genes which defines the uniqueness of these genes.

In our collaboration with Dr. Scott Weiss at Channing Laboratory (Brigham and Women's Hospital and Harvard Medical School), we have used the polymorphisms in the steroid complex genes identified by re-sequencing and additional polymorphisms identified in dbSNP and the HapMap project and tested for association for changes in lung function in adult asthmatics and response to steroid therapy. Fifty nine polymorphisms in *Hsp90 1*, *Hsp90 1*, *Hsc70*, *Hsp70*, *STIP1* (Hop), *Hsp40*, *p23*, *FKBP51*, and *FKBP52* were genotyped in a study of 470 asthmatic adults randomized to once daily Flunisolide or conventional inhaled corticosteroid therapy. The outcome measures included both baseline FEV1 and percent change in FEV1 after 8 weeks of treatment. Significant associations in *STIP1* were found for baseline FEV1 [SNPs rs4980524, p=0.006; rs2236647, p=0.008; rs6591838, p=0.009; and rs2236648, p=0.03]; % change in FEV1 [SNP rs1011219, p<0.001] and change in FEV1 % predicted [SNPs rs6591838, p=0.03; and rs1011219, p=0.008]. Haplotype analysis of *STIP1* indicates a single haplotype associated with % change FEV1 (8 weeks) (p=0.007). An additional 3 window sliding haplotype association tests indicates that polymorphisms rs4980524 and rs6591838, both intronic SNPs, are driving the primary haplotype association results. Additional association was measured for % change in FEV1 for *HSC70* [SNPs rs2276074, p=0.04; and rs2236658, p=0.04]. These data suggests that *STIP1* and *HSC70* may have important roles in predicting and/or regulating lung function.

XIV. Equipment

Manuals of Procedures (MOPs) have been developed and have been in use for performance of all ACRN procedures (spirometry, methacholine challenge, NO collection, etc) including ACRN equipment calibration.

a. Skin Testing

The Multi-Test II provided by 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 smallpox needle.

b. Exhaled Breath Condensate

Equipment from Respiratory Research, Inc.

c. Exhaled Nitric Oxide

NIOX machine provided by Aerocrine, Inc.

d. Spirometry

Spirometry equipment has been provided by QUANTUM Research, Inc. The spirometry equipment has been customized for ACRN.

e. Peak Expiratory Flow

AM1 device by Viasysi will be used. The AM1 device will provide daily measurements of peak flow and FEV(1) and also provide compliance checks.

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XVI. Appendix Material

Appendix 1 – ACRN Asthma Evaluation Questionnaire

ASTHMA CLINICAL RESEARCH NETWORK

ASTHMA EVALUATION QUESTIONNAIRE

Please consider your last two weeks of asthma control in answering these questions. Check the box next to the response that best describes your asthma symptoms.

1. In the past two weeks, how often have you experienced asthma symptoms?

- 0 Less than or equal to 2 days a week
- 1 3 to 5 days per week
- 2 6 or more days per week, but not continual
- 3 Continual (multiple times every day)

2. In the past two weeks, how often have you used your rescue beta-agonist medicine (e.g., albuterol (Proventil, Ventolin)), aside from preventive use prior to exercise?

- 0 Less than or equal to 2 days per week
- 1 3 to 5 days per week
- 2 6 days per week
- 3 At least once per day (daily)

3. In the past two weeks, how often have you awakened at night due to asthma symptoms?

- 0 No awakenings or awakened 1 night during the 2 weeks
- 1 1 night per week
- 2 2 or 3 nights per week
- 3 4 or more nights per week