BELT
Blacks and Exacerbations on LABA vs. Tiotropium

Study Protocol

Version 4.0

February 08, 2012

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PROTOCOL SIGNATURE PAGE

BELT STUDY PROTOCOL

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, 45 CFR 46, to GCP as described in ICH guideline E6 and to hospital Institutional Review Boards.

_____________________________
Clinical Site

_____________________________    _____________________
Principal Investigator Signature    Date

_____________________________
Principal Investigator
Printed Name
Protocol Summary

Title: BELT: Blacks and Exacerbations on LABA vs. Tiotropium

Design: A multi-center prospective, randomized, parallel group, open-label trial.

Purpose: This study is designed to compare the effectiveness of long-acting beta agonists (LABA)/inhaled corticosteroids (ICS) vs. tiotropium/ICS in delaying the time to exacerbation in Black patients with asthma.

Brief Description: This study will enroll patients with a clinical history consistent with asthma, who are receiving ICS/LABA combination therapy, or ICS monotherapy. Subjects will be randomized to either LABA/ICS or TIO/ICS and be monitored for asthma exacerbations and changes in asthma symptoms. Subjects will be followed for 1 year from randomization.

Enrollment: Maximum of 1500 patients

Clinical Sites: 15 to 25 sites in the United States

Timeline
- Initial enrollment (actual): March 30, 2011
- Last enrollment (expected): December 31, 2012
- Last anticipated follow-up contact: June 30, 2013, thus allowing for varying follow-up duration of 6 months – 18 months

Patient Population: Adults over the age of 18 with clinical history consistent with asthma who are receiving ICS/LABA combination therapy or ICS monotherapy who are able to provide informed consent and undergo pulmonary function tests.

Primary Endpoints: Time to asthma exacerbation, defined as an event of worsening asthma requiring oral or parenteral corticosteroids, such as an unscheduled physician visit, ER visit, hospitalization, or physician judgment of clinical asthma status.

Secondary Endpoints:
1. Patient-reported outcomes
   - Asthma Quality of Life
   - Asthma Control
   - Asthma Symptom Utility Index
   - Symptom Free Days
2. Spirometry (FEV1)
3. Rescue Medication Use
4. Moderate Asthma Deterioration
Study Investigators

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I. Introduction

Asthma is a chronic respiratory disease that affects over 22 million people in the United States. Asthma produces 500,000 hospital admissions and accounts for 10.1 million days of lost work in adults annually. *Asthma has been designated a priority condition of the Effective Health Care Program.*

Blacks bear a disproportionate burden of asthma morbidity and mortality. In its 2005 report on ethnic disparities in health care, AHRQ identified hospital admissions for asthma as the second largest disparity in quality of health care for Blacks vs. Caucasians.

Long-acting beta-agonists (LABAs) produce extended increases in airway caliber among patients with asthma via action at the beta2-adrenergic receptor (ADRB2). Adding a LABA to an inhaled corticosteroid controller medication (ICS), can decrease asthma symptoms for many individuals and appears to decrease asthma exacerbations. LABA/ICS has become the most commonly prescribed ICS containing medication.

Drugs acting at ADRB2, including LABAs, have been associated with rare loss of long-term asthma control and increased serious adverse outcomes including death and respiratory failure, even when used with ICS. The risk appears four to five-fold greater in Blacks than non-Black patients with asthma.

Consensus guidelines recommend LABAs be added to ICS in those not completely controlled on ICS alone. These recommendations are based on weighing data on the *benefit demonstrated in the general population* vs. the rare risk of serious adverse outcomes and balancing the apparent benefits vs. the risks of LABAs (Kramer 2009). However, it appears that LABA/ICS may be significantly less effective in Blacks than Caucasians. Comparison of studies with LABA/ICS in Blacks vs. studies where Blacks were a small minority suggests that Blacks may have much less benefit than other racial groups. Additionally, recent data (Wechsler 2009) suggest that a polymorphism at the 16th position of the ADRB2 gene identifies a group of Blacks (those homozygous for arginine (Arg16Arg)) in whom the response of adding a LABA to an ICS is further diminished. This polymorphism is present in ~20% of US Blacks.

I.A. Research Questions and Study Aims

These facts leave us with the following gaps in knowledge needed to individualize our therapeutic recommendations for a minority group disproportionately affected by asthma.

1. In Blacks, what are the benefits of adding a LABA to an ICS? Are these benefits superior to the effects to be gained by using an alternative non-LABA medication? Is the response to LABAs in Blacks reduced to the level that the benefit does not outweigh the risk of rare but serious adverse events?

2. Do genetic polymorphisms identify a subgroup of Blacks who experience even further reduced benefit from LABA/ICS?

To answer these questions we propose the following Specific Aims:

1. To determine, in a practice-based, real-world, randomized, prospective, parallel group, longitudinal comparative effectiveness trial with clinically important outcomes, whether in self-identified Black patients with asthma, treatment with
LABA/ICS is superior to use of a non-β-adrenergic bronchodilator (tiotropium) combined with ICS (Tio/ICS).

2. To determine, in the context of this trial, whether in the 20% of self-identified Black patients with asthma bearing Arg16Arg of ADRB2, treatment with LABA/ICS is superior to use of a non-β-adrenergic bronchodilator combined with ICS.

To accomplish this goal the American Academy of Family Physicians National Research Network and the Olmsted Medical Center will recruit and manage practices with large minority groups for this real-world comparative effectiveness study. We have consulted with patient groups, minority physicians, and writers of the guidelines to assure the applicability of our study. The study is powered to the outcome of asthma exacerbations a real world outcome that is important to the patient. Secondary outcomes will include important patient outcomes using validated instruments that measure asthma control, quality of life, and symptom utility indices. Lung function and asthma-symptom free days will be assessed as well. Results will also be examined in a genotype-stratified manner to assess the effect of ADRB2 genotype in response to LABA/ICS vs. Tio/ICS. Deep sequencing of the ADRB2 locus will be undertaken to identify rare variants associated with lack of response.

The results of this study will provide the information necessary to make evidence-based, individualized, recommendations concerning treatment algorithms and potential alternative treatment recommendations for the 3.5 million Blacks with asthma. The performance of this study in real life primary care settings will hasten the translation of these findings into day-to-day practice for this minority population that experiences a disproportionate burden of asthma and has been underrepresented in previous asthma studies.

I.B. Background

I.B.1. Asthma is a High Priority Medical Condition

Asthma is a chronic respiratory disease that affects over 22 million people in the United States (NHRQ 2007). Approximately 34.1 million Americans have been diagnosed with asthma by a health professional during their lifetime (ALA 2007). The prevalence of asthma increased 75% from 1980 to 1994 and it estimated that the number of people with a diagnosis of asthma will grow by 100 million by 2025 (WHO, 2007). One third of patients with asthma are children under 18 and 2.5 million people over age 65 have asthma. More than 40% of the latter reported that they had an asthma attack or episode (Moorman 2007). More than 13.5 million adults reported an asthma attack during a year (Lethbridge 2002).

Asthma has been designated a priority condition of the Effective Health Care Program. It produces a significant amount of morbidity. Asthma produces 500,000 hospital admissions and accounts for 10.1 million days of lost work in adults annually (Akinbami 2006). It accounts for ¼ of all emergency room visits in the United States. The total cost of asthma was estimated at 14.7 billion dollars of direct costs and 19.7 billion dollars of total costs in 2004 (ALA 2007). Prescription drugs account for more than $6 billion of asthma expenditures (ALA 2007). In 2005, asthma was responsible for 3,384 deaths in the United States (Kung 2008).

I.B.2. Asthma Morbidity is Increased in Blacks

Blacks bear a disproportionate burden of the morbidity of asthma as compared to Caucasians. As reported by the Center for Disease Control, they experience more urgent care visits, higher
rates of hospitalizations, and higher death rates (Akinbami 2006). The asthma attack prevalence rate of Blacks is reported to be 19.2% higher than the rate of Caucasians with even higher rates of hospitalizations and emergency room visits (Eisner 2001; Adams 2000; Griswold 2005; El-Ekiaby 2006). Hospitalization rates for asthma are almost 2.5 times greater in Blacks than in Caucasians (Akinbami 2006). Even more alarmingly, the death rate is 165% higher in Blacks than it is in Caucasians (Akinbami 2006).

In its 2005 report on ethnic disparities in health care, AHRQ identified hospital admissions for asthma as the second largest disparity in quality of health care for Blacks vs. Caucasians (with new cases of AIDS being the largest) (AHRQ 2005). While some of the increased burden of asthma in Blacks may be related to differences in socioeconomic status and/or access to health care, the disparity in morbidity exceeds disparities in prevalence (Gold, 1993; Roberts 2002). Further, in a cross-sectional study of asthma in an integrated middle class population, asthma prevalence was twice as high for Blacks and as compared to Caucasians suggesting that biologic factors might be playing a role in these disparities (Nelson 1997). Thus, Blacks are an underrepresented minority population that is asymmetrically affected by the burden of this high profile disease.

I.B.3. **BLACKS with Asthma and Increased Risk with LABAs**

The disproportionate effect of asthma in Blacks also appears to extend to untoward effects of medications used to manage asthma. Long-acting β-agonists (LABAs) combined with inhaled corticosteroids (ICS) are the most rapidly growing form of asthma therapy in the USA. They have become among the most widely prescribed asthma controller medications and now represent more than 50% of all prescriptions for an ICS containing treatment (Wijesinghe 2008). While studies have suggested that the combination of a LABA and an inhaled corticosteroid (LABA/ICS), on average, improves asthma control, other studies have suggested that LABA use may be associated with increased incidence of severe, life threatening respiratory events (Castle 1993; Nelson 2006). The latter study, known as SMART, suggested that Blacks may be a population particularly at risk in the context of use of LABAs. In the SMART trial patients were randomized to receive salmeterol or placebo in addition to routine asthma therapy. The relative risk (RR) for those randomized to LABA vs. those randomized to placebo for the primary endpoint of the study (respiratory-related deaths and life-threatening experiences) was 4.1 in Blacks (95% CI 1.5-10.9) vs. 1.0 in Caucasians (CI 0.6-1.8). Similar differences in the pre-specified secondary endpoint (asthma-related deaths or life-threatening experiences) were noted (RR 4.9 vs. 1.1 respectively). The RR for these endpoints persisted even when the results were stratified by reported ICS use at the start of the study (RR=3.0, CI 0.8-11.1).

Due to some concerns about the research design and implementation of the SMART study, the US Food & Drug Administration convened an advisory committee, to examine potential adverse effects of LABAs in asthma. The meta-analysis by the FDA of trials utilizing LABAs once again suggested that Blacks may be at disproportionate risk for serious asthma deteriorations when they use LABAs (FDA 2008). In this analysis, high-risk events (asthma-related death, asthma-related intubation, and asthma-related hospitalizations) occurred in Blacks at an excess rate of 8.13 per 1000 when they used LABA as compared with placebo. A sensitivity analysis showed that this risk was not substantially altered even when the SMART data were excluded from this analysis. Thus, for reasons that are unclear, although LABAs may provide symptom control and even decrease exacerbations, they appear to be associated with an increased risk of severe deteriorations in asthma control that disproportionately affects Blacks. In an editorial in the New
England Journal of Medicine (NEJM) after the FDA hearings, Martinez called for an “urgent need to clear the air” (Martinez 2005).

A recent meta-analysis of 60,000 patients enrolled in trials using formoterol (Sears 2009), found that there was still a numerically increased risk for asthma mortality (2.32 [95% CI 0.30 -105]) when formoterol was used with an ICS. Editorialists reviewing this study were alarmed by this rate ratio and opined that an “urgent need to clear the air remains (Beasely 2009).” Their analysis also revealed that the rate ratio for mortality with LABA/ICS may have been underestimated since when LABA/ICS mortality was compared to non-LABA/ICS (as opposed to placebo ICS) the rate ratio for mortality was 3.67 (95% CI 0.41-174) (Beasely 2009).

I.B.4. The Knowledge Gap: When should LABAs be used? How effective are LABAs in Blacks?

Given the possible increased risk for mortality with LABAs, even when used with ICS, regulators, guideline committees, and practitioners are faced with the conundrum of making decisions about treatment. As pointed out by Kramer in a recent NEJM perspective article, the issue is one of “balancing benefits and risks” (Kramer 2009). In this case the NIH Asthma Guideline Committee (NAEPP 2007) (of which Dr. Yawn was a member, and for which Drs. Israel and Fuhlbrigge were reviewers) was faced with apparent unpredictable, rare, serious side effects on the one hand and data suggesting symptomatic and exacerbation benefits from adding a LABA to an ICS in the general population. The Committee decided to recommend delaying introduction of an ICS/LABA unless patients were symptomatic on ICS. In children, where there was not adequate data regarding benefit of ICS/LABA, the Committee did not recommend LABA/ICS unless patients failed moderate doses of ICS. In adults, where there was more data on LABA/ICS benefits in the general population, the Committee proposed LABA/ICS as one of the alternatives for patients on low dose ICS who were still symptomatic.

Other than the children/adult dichotomy, these recommendations were not individualized. However, concern about possible disproportionate risk of LABA/ICS in Blacks has led for calls to better determine the benefits and risks. In this regard, GlaxoSmithKline, the manufacturer of salmeterol, sponsored a study of salmeterol/ICS vs. ICS alone in 475 Blacks (Bailey 2008). In this study, patients on 100 ug fluticasone bid or equivalent, who still had a >12% improvement in FEV1 post-albuterol were randomized to fluticasone (100ug bid)/placebo (not another controller) or fluticasone/LABA (100ug fluticasone/50ug LABA bid) for one year. While this study was not powered to detect the serious loss of asthma control seen in the SMART study referred to above, or reported in the FDA analysis, it was intended to demonstrate that exacerbations were decreased and asthma control was improved by the addition of salmeterol. While there was a trend toward improvement in these indices, none of them reached statistical significance (except night-time awakenings) despite the fact that multiple studies of similar and smaller size, in predominantly

| Effect of LABA Added on to ICS (Blacks vs. Mixed Populations) |
|-----------------|-----------------|-----------------|-----------------|
|                 | Blacks Bailey 08 | Mixed Shapiro 09 | Mixed Ind 2003  |
| N               | 239             | 84              | 160            |
| Duration 12 mo  |                 | 3 mo            | 6 mo           |
| ICS dose (mcg/ day) | 100             | 250            | 250            |
| Δ FEV1 L (Δ%)    | 0.11 (3%)       | 0.23 (10%)      | -              |
| Δ AM PEF L/min   | 16              | 38             | 25             |
| Δ Rescue puffs/d | 0.2 (ns)        | 1.4            | -              |
| Δ% Sx free days  | 1.9 (ns)        | 18.4           | 21             |

Fig I.B-1. Comparison of study with Blacks alone (Blacks) vs. studies with a minority of Blacks (Mixed). Blacks had markedly reduced responses despite similar entry criteria even though they were treated with lower doses of ICS c/w 2 of 3 comparison studies.
Caucasian populations had demonstrated superiority in exacerbations, symptom control and medication use (Ind 2003; Kavuru 2000; Shapiro 2000).

The failure to demonstrate a benefit in Blacks in the Bailey study raises significant concerns. Figure 1.B-1 compares this study in Blacks (Bailey) to three studies that had only a minority of Blacks. As can be seen, Blacks showed substantially less improvement than patients in the other studies. Their symptom free days did not improve and the numerical effect was substantially less than the studies which had a minority of Blacks (1.9% vs. 15-21% improvements). A similar pattern was seen in the change in the number of rescue puffs needed per day. While AM PEF improved significantly (16 L/min) it was still substantially less in Blacks. FEV1 improved only 3% vs. 10% despite the fact that all patients had to demonstrate a 12% or greater improvement in response to bronchodilator, which tends to identify a population of asthmatics disproportionately responsive to \( \beta \)-agonists. In fact, in the Bailey study, the only asthma symptom outcome that improved significantly with addition of LABAs in Blacks was nighttime awakenings (data not shown since it was not measured in the other studies).

It is also important to note that the Shapiro and Ind studies utilized a higher dose of baseline-inhaled corticosteroid. One might therefore have expected that in those studies adding a LABA would have produced less of an improvement since there might be less room for improvement in patients already using a higher dose of inhaled corticosteroid. However, despite the fact that the Bailey study used less baseline ICS than these studies, the Blacks showed less improvement with addition of a LABA than did the patients in the other studies. These data disturbingly suggest that Blacks may have a disproportionately reduced benefit from adding a LABA to an ICS as compared to Caucasians.

Such data have led Dr. Wechsler, of the Brigham and Women's group, to examine the response of Blacks to LABAs, in contrast to Caucasians, across the NIH Asthma Clinical Research Network (ACRN) studies. These randomized, double-blind placebo controlled studies provided medications to all participants and standardized interventions and follow-up. In this analysis, reviewed below in the Preliminary Studies section, he found that when all ACRN studies over the past 15 years were combined, Blacks randomized to a LABA (even in combination with an ICS) experienced greater rates of exacerbations than Caucasians. Of note, Blacks not randomized to a LABA did not have greater rates of exacerbations than Caucasians, further reinforcing the possibility that Blacks may be at risk from LABAs.

Thus, the data described above suggest that Blacks may benefit to a lesser degree than the general population when a LABA is added to an ICS. As outlined in the letter of support by Dr. William Busse, Chairperson of the NIH National Asthma Education Program 2007 Guideline Expert Review Panel, clinicians add LABA to ICS because they provide greater benefits than alternative therapies and these benefits are generally believed to outweigh the risks in the general population. However, as one considers potential deleterious effects of LABAs in Blacks, this risk-benefit ratio shifts dramatically if Blacks do not experience a substantial improvement in asthma control from the addition of a LABA. Thus, a major gap in our knowledge is whether the benefits of adding a LABA to ICS accrue in Blacks. Further, the gap widens, if one can demonstrate, as suggested by our data below, that a subgroup of Black asthmatics may be even less responsive to the addition of a LABA to ICS. This leads us to our second question:

Are there subgroups of Blacks who may be even less responsive to LABAs than the general Black population?
I.B.5. The 2nd Knowledge Gap: Does ADRB2 Arg16Arg Identify Blacks Who Are Even Less Responsive to LABA/ICS?

Homozygosity for the arginine polymorphism at the 16th amino-acid position (Arg16Arg) of the β-2-adrenergic receptor (ADRB2) has repeatedly been associated with altered responses to β-agonist therapy in asthmatics. We first reported, in a retrospective analysis, that, as compared to homozygosity for glycine at that position (Gly16Gly), Arg16Arg was associated with adverse pulmonary function outcomes when patients used short-acting β-agonists regularly (Israel 2000) (Figure I.B-2). Others subsequently reported increased exacerbations in Arg16Arg patients using regular β-agonists (Taylor 2000) and we confirmed these effects in a prospective study (Israel 2004).

I.B.6. Arg16Arg and LABAs.

To examine whether these polymorphisms affect responses to LABAs, we genotyped subjects who had participated in ACRN studies in which LABAs had been used. In the study in which LABAs were used alone, we showed that Arg/Arg subjects treated with LABA had a 51 L/min lower AM PEF than Gly/Gly subjects (P=0.005) and also had higher levels of exhaled nitric oxide (Wechsler 2006). Further, we found, that even when LABAs were used with ICS, Arg/Arg subjects had a 37 L/min lower AM PEF (P=0.048) and a 420 ml lower FEV1 (P=0.003) than Gly/Gly.

While our analysis suggested a B16 genotype-specific effect related to LABA/ICS, the results of other investigations had been mixed. A cross-sectional study of reported asthma exacerbations in a cohort of children and young adults confirmed our finding and found that in those patients taking the LABA salmeterol, with an ICS, Arg/Arg patients had a higher rate of exacerbations than Gly/Gly patients (odds ratio Arg/Arg vs. Gly/Gly=3.40 (p=0.022) (Palmer 2006). In contrast, genotypic analyses of several trials utilizing LABA/ICS have not detected such an effect (Bleecker 2006; Bleecker 2007). We therefore conducted a prospective-genotype stratified trial examining whether Arg/Arg patients respond differently from Gly/Gly when salmeterol is added to ICS (Wechsler, 2009). This study, published in November 2009 in the *Lancet*, did not find a
difference in its primary outcome, AM PEF between Arg/Arg and Gly/Gly patients with asthma. There was a genotype specific difference in methacholine responsiveness in response to treatment (a pre-specified secondary analysis). However, as can be seen in Fig I.B-2, when we restricted our analysis to Blacks, Arg/Arg Blacks did not have an improvement in AM or PM PEF when LABA was added to ICS. Gly/Gly Blacks did experience an improvement (similar to that of their Arg/Arg and Gly/Gly Caucasian counterparts). Their AM PEF increased 29 L/min (p=0.013) compared to when they were crossed over to ICS alone (Placebo/ICS). The difference across genotypes was significant at p = 0.0024 (n=8). However, Arg/Arg Blacks (n=9) had no such improvement. Their AM PEF decreased 12 L/min (p=0.57) when crossed over to add LABA to ICS. The p value across genotypes was 0.09. PM PEF followed the same pattern. PM PEF rose 45 L/min (p=0.0005) in Gly/Gly Blacks when LABA was added vs. a 2 L/min decline in Arg/Arg Blacks (p=0.92). The p value across genotypes was 0.07. Further, AM PEF determined in the clinic (as opposed to the average of several weeks of electronically recorded PEF reported above) revealed the same results. When LABA was added, Gly/Gly Blacks improved 39 L/min (p=0.02) and Arg/Arg Blacks declined 4.8 L/min (p=0.73) with a p value across genotypes of 0.02 (Data not shown in graph).

Thus, in a mixed population, polymorphisms at ADRB2 Arg16Gly did not affect AM PEF responses to regular LABA/ICS (the primary outcome of the study) but did affect the methacholine response. However, in the Blacks in the study, Arg16Arg subjects appeared to have minimal if any response to the addition of LABA to the ICS in contrast to their Black Gly16Gly counterparts.

The cause of this race-specific genotype-differentiated response is unclear. Do the unknown factors that result in increased asthma morbidity in Blacks amplify the Arg16Gly associated differential response to \( \beta \)-agonists? Arg16Gly polymorphisms are known to be associated with different haplotypic combinations of ADRB2 SNPs in Caucasians and Blacks (Burchard 2003). Do these differing SNP combinations result in alterations in receptor interactions, or more likely, are they associated with other variations in the genome that may influence these responses?

While the etiology of race-specific responses to LABA remains to be investigated, the fact remains that several studies have demonstrated that Blacks do not benefit to the same degree as Caucasians when treated with LABA, and may even experience serious adverse effects with LABA use. Furthermore, 20% of US Blacks with asthma are Arg16Arg, and this subpopulation failed to demonstrate a benefit in the study cited above. Thus, considering the apparent disproportionate risk of LABA use in Blacks, we suggest that it would be important to confirm whether the ~3/4 million Blacks with asthma who are Arg16Arg, do indeed have minimal improvement when LABA is added to ICS. If confirmed, treatment guidelines would be modified for those patients.

I.C. Summary

- Blacks are at particularly high risk for asthma morbidity and mortality
- LABAs are associated with increased risk of rare but serious morbidity and mortality particularly in Blacks
- LABAs, in combination with inhaled corticosteroids, have become the most common asthma controller medications prescribed in the United States.
• Current national consensus guidelines recommend the addition of LABAs to inhaled corticosteroids for control of asthma due to a general perception that their apparent benefits, based on studies in the general population, outweigh their risks in patients poorly controlled on inhaled corticosteroids alone.
• It is unclear whether Blacks benefit from the addition of a LABA to an inhaled corticosteroid to the same degree as non-Blacks.
• Recent studies suggest that a polymorphism in the β-adrenergic receptor may identify a substantial subgroup of Blacks (20% of US Blacks) who have particularly diminished improvement from the addition of a LABA to an inhaled corticosteroid.

Based on these data we are led to the following major gaps in our knowledge:
1. In Blacks, what are the benefits of adding a LABA to an ICS? How do those benefits compare with using an alternative non-LABA medication? Is the response to LABAs in Blacks reduced to the level that the benefit does not outweigh the risk of rare but serious adverse events?
2. Do genetic polymorphisms identify a subgroup of Blacks who experience even further reduced benefit from this combination?

We are therefore conducting this real world, practice-based study to examine whether LABA/ICS is truly superior to an alternative bronchodilator (the anticholinergic Tiotropium) plus ICS in Black patients with asthma who are receiving, or require, combination therapy.
II. Preliminary Studies, Qualifications, Recruitment and Stakeholder Input

II.A. Effects of LABAs on Blacks Across ACRN Trials

While socioeconomic factors, disparities in access to care, and quality of care between Blacks and Caucasians have been used to explain differences in asthma outcomes between these groups, we compared Blacks and Caucasians who participated in the NIH Asthma Clinical Research Network (ACRN) clinical trials and thus had equal access to both asthma caregivers and asthma medications. We reviewed baseline phenotypes and treatment failure rates (with the latter defined by use of systemic corticosteroids, hospitalizations, emergency department visits, prolonged decrease in peak expiratory flow, increase in albuterol use, or safety concerns) stratified by race in subjects participating in 10 ACRN trials in which adherence did not differ between groups. 795 Caucasians and 233 self-identified Blacks were compared.

While there were no differences in baseline lung function, asthma quality of life, bronchial hyperreactivity or exhaled nitric oxide levels at baseline, Blacks had fewer asthma symptoms ($p<0.001$) and less average daily rescue inhaler use ($p=0.007$) than Caucasians. However, of 147 treatment failures observed, a significantly higher proportion of Blacks (19.7%, n=46) experienced a treatment failure compared to Caucasians (12.7%, n=101) ($OR=1.7$, 95% CI=1.2-2.5, $p=0.007$).

When stratified by study-allocated treatment, there were no differences between races in subjects that did not receive LABAs (Fig II.A-1.A top curves). However, when treated with LABAs, Blacks were more than twice as likely to experience a treatment failure ($OR=2.1$, 95% CI=1.3-3.6, $p=0.004$) than Caucasians despite similar baseline lung function (Fig II.A-1.A lower lines).
A significant difference in treatment failures persisted even when LABAs were used concurrently with other asthma controller therapies, e.g. inhaled corticosteroids (p=0.047) (Fig II.A-1.B) or leukotriene receptor antagonists (LTRA) (p=0.0008) (data not shown). In subjects taking ICS or LTRA as monotherapy (no LABA) there was no significant difference in treatment failures between Caucasians and Blacks. These data further support observations that have suggested that Blacks may not achieve the same degree of protection from LABAs as other racial groups and emphasize the importance of conducting a trial such as the BELT trial that we propose to study the real world effects of LABA/ICS as compared to another ICS and non-LABA regimen.

II.B. Research Team
This study will be conducted by experienced clinical investigators with a history of designing and carrying out clinical trials, a track record of success, and a demonstrated history of successfully recruiting asthma patients in trials. Additionally, to achieve the goals of comparative effectiveness it requires a real-world structure and setting. Dr. Israel has assembled a team that possesses these qualities with expertise in: 1) Asthma clinical trial design and execution (Israel, Wechsler – Brigham and Women’s Hospital (BWH)); 2) Asthma clinical epidemiology and outcomes measurement (Fuhlbrigge - BWH); 3) Execution of practice based trials in asthma (Yawn – Olmsted Medical Center (OMC)); 4) PBRN organizational infrastructure and practice recruitment (Pace – American Academy of Family Physicians National Research Network (AAFP NRN)); and 5) A Data Coordinating Center (DCC) with experience in execution, data handling, and building an infrastructure for multi-site studies (Harvard Clinical Research Institute (HCRI)). In addition Dr. Israel has collaborated with each of the teams outside of BWH. He has conducted a study with Drs. Yawn and Pace (Yawn 2007) and is currently conducting a study enrolling 900 patients with asthma with HCRI serving as the DCC. Below, we briefly describe the strengths of the teams.

II. B.1. Clinical Coordinating Center at Brigham and Women’s Hospital
The BWH team is lead by Dr. Wechsler, with co-investigators Drs. Kazani, Fuhlbrigge, and Raby.
II.B.2. Practice Based Research Networks: Olmstead Medical Center and AAFP National Research Network

The site activities will be coordinated and managed by OMC and AAFP NRN staff, lead by Drs. Yawn (OMC) and Pace (AAFP NRN). Both groups have experience directing Practice-Based Research Networks (PBRNs) in real-world clinical trials like the BELT study. They have collaborated to select and coordinate these sites and will be responsible for all aspects of site management as well as for acting as the liaison between the sites and the CCC and DCC.

II.B.2.a. Site Recruitment, Selection, and Initiation

For the BELT study, 15 practices will be enlisted and 5-10 additional sites will be identified should enrollment lag at any of the practices. These practices will be selected by OMC and AAFP and approved by the PI. All practices accepting the invitation to participate will be trained on the study protocol, procedures, and data collection at the study Investigators’ Meeting. Ongoing training will be provided by the OMC and AAFP with input from the DCC on the EDC system, the BWH on any clinical questions. All study regulatory documentation and necessary training certification will be collected by OMC and AAFP and stored in the Trial File. A percentage of these documents will be reviewed by the DCC as a quality control measure. Additional sites will be added as needed, with initiation and training being provided on-site by staff from OMC and AAFP.

II.B.2.b. Site Management and Monitoring

All site management will be coordinated by OMC and AAFP, with their activities overseen by the PI and his staff. OMC and AAFP will work closely with the sites and provide information, reports, and updates to the PI and the co-Investigators on a regular basis. Practices will each be assigned a liaison from OMC or the AAFP NRN who will work with the local study coordinator to create a recruitment plan, address any questions either directly, or by directing the coordinator to the appropriate study team member, ensure regulatory compliance, and to maintain ongoing training.

Throughout the study, some of the data in the EDC system will be monitored against site source documentation in order to verify the accuracy of all study data. Sites will be required to keep this documentation on site and make it available to study monitors as requested. At study start-up, coordinators will be provided with worksheets for source documentation and trained on this process. This will be done on a site-specific schedule using a Site Monitoring Plan established at study start-up. If issues are found during monitoring, they will be reported to the PI and DCC promptly so an appropriate action plan can be put in place to ensure data quality.

II.B.3. Data Coordinating Center and Statistical Analysis at Harvard Clinical Research Institute

HCRI will serve as the DCC for the BELT study under Dr. Israel's supervision and will carry out the statistical analysis of the study under the direction of Michael Pencina, PhD. HCRI has significant experience designing and building data capture systems, processing and cleaning data, and preparing study data for analysis. Dr. Pencina and the staff statisticians at HCRI will work closely with all study investigators to design the analysis plan, prepare DSMB reports, prepare the study dataset for analysis, and provide data for abstracts, presentations, and publications.
II.B.3.a. **Data Coordinating Center**

The data for the BELT study will be captured in an EDC system built and maintained by the DCC. Study data, including baseline information, study visit assessments, monthly patient questionnaires, adverse events, and medication usage will be captured on all randomized subjects. Additional data may be captured on paper screening logs on subjects that are screened but do not qualify so that the PI and investigative team can determine barriers to enrollment. Only trained study personnel will have access to the database. The data will be cleaned using the electronic query system built into the EDC database. DCC Data Managers will have the ability to issue queries as needed. All queries need to be addressed by site personnel before they can be resolved and a reason for any data changes must be provided. Throughout the study, reports on data submission and quality will be provided by the DCC to the PI and Co-Investigators in order to review and address any issues.

II.B.3.b. **Statistical Analysis**

All statistical analysis for the study will be conducted by the DCC. Tables will be generated on an ongoing basis for review by the DSMB and any required regulatory reports. At the conclusion of the study, the database will be closed and locked following DCC SOPs. The data will be exported in SAS and tables, listings, and figures will be generated following the analysis plan established in the study Statistical Analysis Plan, to be completed prior to the completion of study enrollment. Additional tables will be generated on an ad-hoc basis, with the approval of Dr. Pencina and the study PI for abstracts, presentations, or papers.

II.C. **Recruitment of Patients for the BELT Study**

While the OMC/AAFP NRN PBRN has been extremely productive, the study investigators recognize that recruiting patients from minority groups may represent a special challenge. In preparation for this project, usual practice recruitment methods and contact with regional PBRN networks such as the Moorehouse PBRN and the Central New York PBRN were used to identify practices. The latter PBRN networks report large practices with primarily Black patients. Conservatively, the rates of LABA/ICS use have been estimated as 70% with an estimated recruitment rate of only 30% (less than the 50% plus rate of recruitment that usually occurs for eligible subjects in these practices) and assumed an eligibility rate of 50%. Based on these assumptions, the study will recruit 15 practices with 5 to 10 additional practices identified as a backup in order to assure subject recruitment.

II.D. **Stakeholder Input**

As outlined in **Section I**, the increased morbidity experienced by Blacks with asthma is of considerable concern. The data questioning the possible reduced efficacy of LABAs in Blacks in the setting of possible increased risk is of concern both to practitioners, patients, and policy makers. The BELT investigators have reached out to patient groups, to associations of Black physicians, and to writers of National Guidelines. All stakeholders agreed that the issue of how to treat Blacks who are still symptomatic is one of great concern. This study will have a determinative effect. Perhaps most importantly, as evidenced by the rapid degree of interest expressed by practices that treat a high proportion of Blacks, there is great interest in the expected results of the BELT study. This interest, and the broad participation of such practices, combined with the AAFP resources, will also be key to the dissemination of these findings as indicated in **Section V** regarding Impact of anticipated findings.

In summary, our work and the work of others, suggests that LABAs when added to ICS in Blacks may not provide the benefits seen in the general population. Further, this lack of benefit
may be most pronounced in a genetically specific subgroup of Black patients. Considering the risk that LABAs may disproportionately pose to Blacks, it is critical to define the benefits, or lack thereof, of LABA therapy as compared to other alternatives. We believe that the **BELT** Study, described in the next section will allow us to do this.
III. Study Design, Treatments, and Procedures

III.A. Introduction

As outlined previously, LABAs, when used to treat asthma, appear to be associated with a risk of rare, but serious untoward events, particularly in Blacks. The primary rationale for LABA use in asthma is that the benefits outweigh the risks. However, as outlined both in sections I and II, there is an evidence gap. It is not clear that adding LABAs to ICS in Blacks provides significant benefits beyond other therapeutic alternatives. We therefore will conduct this real world, practice-based, prospective, randomized, parallel group trial in Blacks in which we compare the effectiveness of LABA/ICS to a regimen that does not contain a LABA.

The research question we pose is the following:

1. In Blacks with asthma, is a regimen containing LABA in addition to ICS, superior to a regimen using the anticholinergic tiotropium in addition to ICS?

Additionally, since as outlined in section I.B.6, it appears that Blacks who carry the Arg16Arg version of the β-2-adrenergic receptor may be a group that is particularly unresponsive to the effects of a LABA added to ICS, we also pose a second research question:

2. In Blacks with asthma who harbor Arg16Arg of ADRB2, is a regimen containing LABA in addition to ICS superior to a regimen using the anticholinergic tiotropium in addition to ICS?

We therefore propose the following Specific Aims:

- To determine, in a practice-based, real-world, randomized, prospective, parallel group, longitudinal comparative effectiveness trial with clinically important outcomes, whether in self-identified Black patients with asthma, treatment with LABA/ICS is superior to use of a non-β-adrenergic bronchodilator (tiotropium) combined with ICS (Tio/ICS).

- To determine, in the context of this trial, whether in the 20% of self-identified Black patients with asthma bearing Arg16Arg of ADRB2, treatment with LABA/ICS is superior to use of a non-β-adrenergic bronchodilator combined with ICS (Tio/ICS).

To accomplish these aims, in this study Blacks with asthma will be randomized in the physician’s office to receive open-label LABA/ICS or Tio/ICS. The study is designed to use real-world outcomes that are important to the patient and health care system (exacerbations) as well as to assess the impact of the interventions on important patient-reported outcomes, including health related quality of life and asthma control. The study is also designed to minimize the impact on the participating practices by allowing immediate randomization at the recruitment visit (if so desired by the patient) and by monitoring most outcomes via patient-completed questionnaires. The failure to demonstrate that LABA/ICS is superior to Tio/ICS in Blacks would alter treatment recommendations for this minority population which bears a disproportionate burden of asthma morbidity and may be at increased risk for untoward outcomes with current treatment recommendations.
III.B. Study Overview and Organization

The BELT study (Blacks & Exacerbations on LABA vs. Tiotropium) is a prospective, randomized, parallel group, open-label trial comparing the effectiveness of LABA/ICS vs. tiotropium/ICS in delaying the time to exacerbation in Black patients with asthma. A study schema is depicted in Figure III.B-1.

The study includes four to five visits over a six month to eighteen month time span depending upon when a subject is enrolled and evaluation of monthly questionnaires that are completed by the patients. The outcome variables are listed in Table III.B-1. The study will be performed in conjunction with the PBRN, a consortium of primary care sites that have performed clinical trials in asthma in the past. This network has thousands of Black asthmatic patients within its practices who meet entry criteria and would allow us to recruit up to 1500 Black asthmatics >18 years old to demonstrate that LABA/ICS is superior to Tio/ICS with respect to asthma exacerbations.

All study team members, co-investigators and study activity will be the ultimate responsibility of the study PI. Figure III.B-2 illustrates the study governance plan, with most entities reporting directly to Dr. Israel, who will provide reports to the funding agency. The study will be
 overseen by independent IRBs and a DSMB, who will review appropriate data as needed and provide approvals and recommendations for the study. The study sites will be managed by the OMC and AAFP, under the direction of Co-Investigators Drs. Yawn and Pace, respectively. The

**Fig. III.B-2 Study Governance**

DCC will also have responsibility for site conduct and data integrity with the support of the ARC PM, as represented by the dashed line on the diagram with the OMC acting as their primary contact. Dr. Kazani will be interfacing with the sites to over read the PFT and oversee overall study quality assurance.

This study has an aggressive time-line for recruitment, training and execution. It will require effort by the study team to assure constant and updated communication, early and increased auditing to identify and correct problems, and vigilant quality control. As a result there will be: biweekly co-investigator calls; biweekly calls with the site MDs attended by co-investigators, central staff, practice MD, and practice personnel; and biweekly operational calls with central study staff and site staff.

**III.B.1. Inclusion/Exclusion Criteria**

The inclusion and exclusion criteria for the BELT study are outlined below. To be enrolled subjects must meet all inclusion criteria and none of the exclusion criteria. Waivers will be provided for specific borderline eligibility cases upon review and approval by one or more of the study Principal Investigators. Waiver forms will be stored in the electronic trial files maintained at the DCC.
III.B.1.a.  Inclusion Criteria
1. Black (self-identified, with at least one biological parent identified as Black)
2. Subjects ages 18-75
3. Ability to provide informed consent
4. Clinical history consistent with asthma for > 1 year.
5. Ability to perform pulmonary function tests
6. FEV₁ ≥ 40% of predicted
7. Receiving ICS/LABA combination therapy, or moderate to high dose ICS monotherapy and baseline ACQ >1.25
8. Non-smoker for past year (total lifetime smoking history < 10 pack-years)

III.B.1.b.  Exclusion Criteria
1. Use of greater than the equivalent of 1000 mcg inhaled fluticasone daily
2. Chronic use of oral corticosteroids or Anti IgE for asthma
3. Lung disease other than asthma or diagnosis of vocal cord dysfunction.
4. Significant medical illness (other than asthma) that is not stable.
5. Pregnancy or lactation or an unwillingness to maintain effective birth control.
6. History of a significant exacerbation of asthma or respiratory tract infection in the prior 4 weeks
7. History of life-threatening asthma requiring treatment with intubation and mechanical ventilation within 5 years.
8. Hypo sensitization therapy other than an established maintenance regimen.
9. Use of inhaled anticholinergic therapy (ipratropium, tiotropium) in prior month
10. Known contraindication to inhaled tiotropium e.g. narrow angle glaucoma, history of bladder neck obstruction or significant symptoms related to prostatic hypertrophy.
11. Inability to speak and read English.

III.B.2. Subject Screening, Enrollment, and Follow-up

III.B.2.a.  Screening
Potential subjects will be recruited, consented, and screened for potential randomization at the first study visit. Utilizing study coordinators hired by each practice, the charts of patients scheduled for visits will be reviewed following procedures outlined in the study Manual of Operations and approved by their Institutional Review Boards (IRB)/Ethics Boards to identify patients who may qualify for the study. Patients interested in further information will be given the opportunity to meet with the study coordinator at the site who will explain the study. A web-based video describing the study will also be available for use. De-identified data will be captured on subjects who are screened but deemed ineligible or who decline to participate and this data may be reviewed by study investigators and the DSMB as needed.

III.B.2.b.  Enrollment and Follow-up
Subjects who are eligible to participate and provide informed consent will be randomized to treatment and enrolled in the study. They will undergo study procedures at the Baseline/Randomization visit, including a medical history and concomitant medication assessment, spirometry measures, study questionnaire completion, and saliva collection. The assigned medication will be prescribed and subjects will be provided education regarding filling the prescription and taking the medication, as well as information on completing monthly questionnaires and the next follow-up office visit. Medication adherence will be monitored through monthly nurse calls for possible exacerbations and from dispensing information from the site pharmacies (see section III.C.6.c. for further details).
Follow-up duration will vary from 6 months to 18 months (see Table IV B-2 below), depending upon when a subject was enrolled. Following the initial study visit, some subjects will have three subsequent office visits at the study site over the course of the study at 1, 6, and 12 months from randomization. For those subjects being followed for longer than 12 months, an additional close-out follow-up visit will occur at 14, 16, or 18 months. For those subjects enrolled from July of 2012 through October of 2012, the fourth study visit will occur at 8 or 10 months, and for subjects enrolled in November or December of 2012, the third study visit at 6 months will be the last study visit. Study procedures will be repeated at each follow-up visit (as outlined below in Table III B-3), subject safety will be assessed, medication adherence will be reviewed, and the assigned medication will be prescribed again as needed.

Between these visits, the subjects will complete monthly questionnaires. Certain questions on these questionnaires will be monitored by the DCC for safety signals and, if needed, the OMC and sites will be prompted to contact subjects to assess safety.

Specific details of each visit are outlined below in section III.C.

Table III. B-2. Follow-up Duration

<table>
<thead>
<tr>
<th>Enrollment Month(s)</th>
<th>Visit One Randomization</th>
<th>Visit Two (1 mo ± 10 d)</th>
<th>Visit Three (6 mo ± 10 d)</th>
<th>Visit Four (8-12 mo ± 10 d)</th>
<th>Visit Five Final Close-Out Visit at 14, 16, or 18 mo ± 10 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/2011 – 10/2011</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>12 months</td>
<td>18 months</td>
</tr>
<tr>
<td>11/2011 – 12/2011</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>12 months</td>
<td>16 months</td>
</tr>
<tr>
<td>01/2012 – 02/2012</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>12 months</td>
<td>14 months</td>
</tr>
<tr>
<td>03/2012 – 06/2012</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>12 months</td>
<td>NA</td>
</tr>
<tr>
<td>07/2012 – 08/2012</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>10 months</td>
<td>NA</td>
</tr>
<tr>
<td>09/2012 – 10/2010</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>8 months</td>
<td>NA</td>
</tr>
<tr>
<td>11/2012 – 12/2012</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

III.B.3. Rationale

Description and rationale of key study features are below.

III.B.3.a. Rationale for Study Design
The study is designed to be as close to real-world interventions as possible and to allow measures that could be undertaken in primary care practices. Thus, the patients can be enrolled and randomized at the screening visit. Screening criteria and qualifications have been kept to a minimum. Instead of a blood draw, patients need only provide a saliva sample for genetics. Only the 1-month visit will be outside of normal care as visits at 6 months, 12 months and the additional visits through 18 months would not be unusual for patients with asthma of this
severity. The PFT assessments have been successfully implemented in primary care practices by Drs. Yawn and Israel in a prior collaboration (Yawn 2007) and are described in Section III.C.5. The monthly patient surveys will be handled by the OMC/AAFP NRN and HCRI so as to minimize impact on the practices. Patient management decisions will be real world in that other than the randomization, all treatment decisions remain in the hands of the primary care practices. We believe that this real-world practice-based design will allow for improved translation of the study findings and allow more rapid uptake in clinical practice.

III.B.3.b. Enrollment and Restriction of Subjects

Eligibility for the BELT study is restricted to Black adults between 18 and 75 years old. The restriction to Blacks is due to the indication that LABA may not be very effective in this population. The evidence for this has been reviewed in previous protocol sections. The restriction to adults 75 or under is due to the fact that often these subjects do not truly have asthma or have other underlying conditions that affect their asthma diagnosis and thus make them inappropriate for this study.

III.B.3.b.ii. Inclusion of Children

The study is restricted to adults since there is currently an ongoing question about the efficacy of LABAs in children. This concern caused the National Asthma Education Prevention Program (NAEPP) to make a distinction between adults and children as to when LABAs should be introduced (NAEPP 2007). Thus, an inability to demonstrate that LABA/ICS is superior to Tio/ICS in a study that included children would not answer the question as to whether LABAs fail to add sufficient benefit in Blacks. Our plan is to examine this question first in adults, and based on the results of BELT, consider a study in children.

Additionally, tiotropium is currently approved for the COPD indication, which is a disease not seen in children; as such the treatment would require exemption from the FDA for administration to children.

Children ages 18 to 21 are considered adults for the purpose of this study and as such, will be included. No special procedures are in place for this group as they are able to provide their own informed consent. However, for subjects in this age group who are still dependents, study site personnel will be instructed to include the parents in the informed consent process and address any questions or issues they may raise. Documentation of parental involvement in the informed consent process should be maintained with documentation of the overall process.
III.B.3.b.i. **Inclusion of Women and Minorities**

Only Blacks will be enrolled in this study as the proposed research question addresses the treatment of asthma specifically in this population. Based on past research the researchers feel that this population has a significantly higher risk from this disease and that further study in this specific population is needed. As such no other races will be enrolled.

Women and members of both ethnic groups will be enrolled. Gender statistics available from the PBRN practices indicate that the percentage of women within the population to be enrolled will be approximately 70%. No specific statistics were available from these practices regarding ethnicity; however, census data leads us to expect that 4% of subjects will be Hispanic. The expected enrollment is detailed in Table III.B-3. While women and Hispanics will be enrolled, the study design does not allow for any clinically important differences to be detected or analyzed, as such differences are not expected.

### Table III.B-3: Targeted/Planned Enrollment

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>42</td>
<td>18</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>1008</td>
<td>432</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnic Category: Total of All Subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1050</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Categories</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian/Alaska Native</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>0</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1050</td>
</tr>
<tr>
<td>White</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Categories: Total of All Subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1050</td>
</tr>
</tbody>
</table>

### Table III.B-4: Current Guidelines, Estimated Comparative Daily Dosages for ICS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose</th>
<th>Medium Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone HFA 40 or 80 mcg/puff</td>
<td>80–240 mcg</td>
<td>&gt;240–480 mcg</td>
<td>&gt;480 mcg</td>
</tr>
<tr>
<td>Budesonide DPI 90, 180, or 200 mcg/inhalation</td>
<td>180–600 mcg</td>
<td>&gt;600–1,200 mcg</td>
<td>&gt;1,200 mcg</td>
</tr>
<tr>
<td>Flunisolide 250 mcg/puff</td>
<td>500–1,000 mcg</td>
<td>&gt;1,000–2,000 mcg</td>
<td>&gt;2,000 mcg</td>
</tr>
<tr>
<td>Flunisolide HFA 80 mcg/puff</td>
<td>320 mcg</td>
<td>&gt;320–640 mcg</td>
<td>&gt;640 mcg</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI: 44, 110, or 220 mcg/puff</td>
<td>88–264 mcg</td>
<td>&gt;264–440 mcg</td>
<td>&gt;440 mcg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 mcg/inhalation</td>
<td>100–300 mcg</td>
<td>&gt;300–500 mcg</td>
<td>&gt;500 mcg</td>
</tr>
<tr>
<td>Mometasone DPI 200 mcg/inhalation</td>
<td>200 mcg</td>
<td>400 mcg</td>
<td>&gt;400 mcg</td>
</tr>
<tr>
<td>Triamcinolone acetonide 75 mcg/puff</td>
<td>300–750 mcg</td>
<td>&gt;750–1,500 mcg</td>
<td>&gt;1,500 mcg</td>
</tr>
</tbody>
</table>

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler

III.B.3.c. **Patients with Asthma to be Included**

Consistent with the goals of a comparative effectiveness, real-world study, we are including Blacks on LABA/ICS, or those, who by current guidelines, would qualify for LABA/ICS (on moderate dose ICS (see Table III.B-4) but still symptomatic as indicated by an Asthma Control Questionnaire score \( \geq 1.25 \)).
While guidelines offer the addition of a LABA in patients on low dose ICS who are still symptomatic as an alternative to increasing ICS in adults (not in children as noted above), considering the concerns we raise about LABAs in Blacks, we do not advocate this approach.

### III.B.3.d. Use of Tiotropium

Guidelines call for the use of LABAs in asthma when low-moderate doses of ICS fail to control symptoms. While one might wish to compare LABA/ICS to Placebo/ICS in Blacks, we consider it unethical to fail to provide therapy for these patients who continue to remain symptomatic. Further, such a study design would not be consistent with comparative effectiveness goals. Anticholinergics result in bronchodilation and thus offer a reasonable substitute for β-agonists. While anticholinergics do not have a primary indication in asthma, they are often clinically used in this manner and both long- and short-acting anticholinergics have been studied in patients with asthma (Iwamoto 2008; Kapoor 2009; Wechsler 2009; Israel 2004).

### III.B.3.e. Blinding and Medications

Consistent with the goal of conducting a real-world clinical effectiveness study, this is not a blinded study. Several aspects were considered in this regard. First, training and study description videos are designed to present the two options with equipoise. Second, tiotropium is a once a day medication and ICS and LABA must be administered twice a day. This means that those on LABA/ICS will be taking two inhalers twice a day, and those on Tio/ICS will be taking two in the morning and one at night. This may be confusing to patients. We will prepare a video to instruct patients in this regard. While differential compliance is possible, in our experience with blinded studies, we find that if patients miss a time point, they miss all medications at that time point. Admittedly, if they are on Tio/ICS and miss their AM dose, they will miss that day’s tiotropium, but this is what would happen in a real world application. Further, we will be assessing medication adherence which should allow us to detect any such issues (see III.C.6 Adherence Measurement).

Third, we will be administering LABA/ICS as separate inhalers as opposed to the available combination device. Randomized studies have not been able to show a difference in outcomes between combination therapy and administration through separate devices. A meta-analysis of four different studies, sponsored by GSK, the maker of combination salmeterol/fluticasone, found a 5.4 L/min (p=0.006) difference in AM peak flow in favor of the combination product (Nelson 2003). While the difference may have been statistically significant, its clinical significance is felt to be minimal.

### III.B.3.f. Outcomes

Exacerbations represent real world outcomes important to the patient, practitioner, and the payor. The rationale of the choice of outcomes and their definition is reviewed in Section IV.

### III.B.3.g. Genetics

We will assess whether outcomes of pharmacogenetic testing can be used to guide treatment recommendations with a goal of individualizing and personalizing pharmacotherapy. To minimize the burden to subjects and therefore enhance recruitment, we are collecting genetic samples from saliva.
III.C. **Study Procedures**

III.C.1. **Informed Consent**

A copy of each site's informed consent template must be approved by staff at the OMC/AAFP NRN and appropriate IRB/Ethics Boards. These approvals must be obtained prior to enrolling any subjects into the study.

All subjects will be approached to obtain written informed consent prior to undergoing any study procedures. The consent process involves an explanation of the purpose of the research study, the expected duration of the subject's participation and a description of the procedures to be followed throughout the study. Because the duration of the study is extending for approximately half of the study subjects, an amendment to the existing consent form has been created which explains the additional follow-up visit. Subjects consented under the original protocol will be re-consented with this Informed Consent Form amendment. Subjects newly enrolled under this protocol amendment will be consented with a new Informed Consent Form that explains the current duration of the study. The subject should be provided a sufficient opportunity to review the consent form and ask questions. The subject must sign and date the consent form prior to performance of any study related procedures. Inability to provide informed consent renders the patient ineligible for the study (see inclusion criteria # 3, outlined in section III.B.1.a.). The informed consent process should be documented and the signed document retained at the study site for the full duration of the study.

Following screening, randomized subjects undergo visits according to the follow-up visit schedule outlined in Table III B-2. Details of all visits are below.

III.C.2. **Randomization**

III.C.2.a. **Randomization Scheme**

Randomization will be stratified in blocks of four within each stratum based on patient age (<40, ≥40), baseline LABA use (yes/no), FEV1 (<60%, 60-79% or ≥ 80% predicted), and smoking environment (yes/no).

With each new subject randomization, the specific sites will log onto a central study specific website and will receive automated randomization assignment. Once developed, the randomization scheme will be uploaded into a pre-programmed panel in the Inform EDC database. The first eCRF for all subjects will be a screening form where informed consent date will be confirmed, eligibility will be verified, and the data needed for matching will be entered. As subjects are screened, site personnel will enter the data into the form and indicate that the subject meets criteria and should be randomized. The system will check against the data entered and to access the randomization scheme. The system will then provide the subject number and treatment assignment (either LABA/ICS or Tio/ICS) for that subject. This data will be stored in the system along with all other subject data and will be exported as part of the final study database.

III.C.2.b. **Randomization Visit (Visit 1)**

Once the patient meets initial entry and exclusion criteria, he/she will be offered an opportunity to review the study consent and enroll in the study at that time. If he/she does not have adequate time or wishes to take the consent home for further review, he/she will be invited to
return within the next few weeks to complete the study enrollment activities with the study coordinator.

Once consent is obtained, the Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), and Asthma Symptom Utility Index (ASUI) -- all validated instruments described in Section IV.C. Outcome Measures -- will be administered. In addition, the Asthma Symptom-Free Day Questionnaire will be administered. A medical history will be obtained and concomitant medications will be assessed and recorded. Baseline spirometry will be performed. Saliva for genetics will be obtained. (See section III.C.5 for further detail on study procedures). If the subject is female, a pregnancy test will be done and the subject will be instructed on acceptable birth control procedures that must be maintained throughout the study. The subject will be educated on completing the monthly study questionnaires by the study coordinator.

As outlined in section III.C.2.a, once a subject has signed the Informed Consent Form and is deemed eligible for participation in the study, the site will enter the screening and randomization data and the system will generate a subject ID and randomization assignment.

Subjects will be given two prescriptions once randomized. The first will be for ICS monotherapy – it is recommended that the prescription be for the dose equivalent of the corticosteroid they had been previously prescribed (either as part of a combination product based on Table III.C-1 or as ICS monotherapy). The second prescription will be either a prescription for tiotropium one puff once a day or LABA, one puff twice a day. The recommended LABA for subjects currently on a LABA and for those currently only on ICS, is salmeterol (Serevent® Diskus® 50 mcg). When possible, subjects should be prescribed the medications as recommended by the protocol, however, the Investigators should take into account the subjects' health needs and insurance situation and are free to prescribe another approved ICS or LABA as needed. Subjects will be instructed about the use of each inhaler and each subject will watch a web-based video support tool demonstrating how to properly use each inhaler. A web-based video particular to the treatment arm assignment will also be available.

De-identified data should be recorded at this point using the InForm Electronic Data Capture (EDC) system. The subject's specimen will be de-identified and sent to the Partners and Harvard Center for Pharmacogenetic Medicine (PHCPGM) following pre-specified instructions that will be provided to the sites in the Manual of Operations. The coordinator will also fill out a web-based form for the preferred contact for the patient for follow-up by OMC/AAFP NRN coordinators in the case that the patient records an exacerbation (see Section IV.C Outcome Measures). Data needed to deliver monthly questionnaires will also be specified. This patient contact information will be delivered via secure web communication to OMC/AAFP NRN. The DCC will not receive this or any other de-identified information.
III.C.3. Follow-up Visits

III.C.3.a.  Visit 2 (1 Month, +/- 10 days)
After 1 month, each subject will be scheduled to return to the office for a safety review, to assess medication use and to answer questions regarding potential adverse events or asthma exacerbations. A pregnancy test will be performed. The asthma questionnaires (ACQ, symptom free day, as well as the asthma exacerbation/medication review questionnaires (Section IV.B.1) will be reviewed by the coordinator at each practice site to ensure that they were well understood and completed correctly. The AQLQ and ASUI questionnaires will be completed at this visit. Having been previously instructed to withhold bronchodilators the day of the visit (as long as no asthma symptoms preclude this), subjects will perform spirometry both pre and post four puffs of albuterol to characterize their bronchodilator responsiveness. Subjects will be encouraged to adhere to the medication regimen but since this is a real world study, adherence will not be enforced. Subjects will be re-educated on the survey component of the study and on medication use, and scheduled for the 6-month visit, Visit 3.

III.C.3.b.  Visit 3 (6 Months, +/- 10 days)
Each subject will be scheduled to return to the office at approximately 6 months to complete asthma questionnaires (AQLQ, ASUI), review medication use, answer questions regarding adverse events, asthma exacerbations, and to perform spirometry , and whether this has changed since the first visit. A pregnancy test will be performed. The questionnaires (ACQ, symptom free day, as well as the asthma exacerbation/medication review questionnaires (Section IV.B.1) will again be reviewed by the coordinator at each practice site to ensure that they were well understood and completed correctly. Changes in corticosteroid dose will be captured and prescriptions will be provided as per treatment assignment. Subjects will be re-educated on the survey component of the study, will be re-instructed on use of the inhaler, and scheduled for the 12-month visit, Visit 4.

For subjects enrolled in November and December of 2012, this 6-month visit will be their final study close-out visit. The final asthma questionnaires (ACQ, Symptom Free Day) as well as the asthma exacerbation/medication review questionnaires will be reviewed by the coordinator at each practice site to ensure that they were well understood and completed correctly. The AQLQ and ASUI questionnaires will be completed at this visit. A final pregnancy test will be performed. Medication and rescue inhaler usage will be reviewed, and subjects will be asked if they prefer to maintain their current medication or return to their original treatment. Data on this preference will be captured as part of the study exit. At this visit there will be a discussion between the patient and their physician to determine the medications to be continued at the end of the study. At this visit, spirometry will again be performed.

<table>
<thead>
<tr>
<th>Table III.C-2 Schedule of Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
</tr>
<tr>
<td>Informed Consent</td>
</tr>
<tr>
<td>I/E Criteria Assessment</td>
</tr>
<tr>
<td>Study Questionnaires (ACQ, AQLQ, ASUI, ASFDQ)</td>
</tr>
<tr>
<td>Saliva Collection</td>
</tr>
<tr>
<td>Medical History</td>
</tr>
<tr>
<td>Concomitant Medications</td>
</tr>
<tr>
<td>Spirometry</td>
</tr>
<tr>
<td>Med Prescribed/Pt Education</td>
</tr>
<tr>
<td>Pregnancy Test (Female Subjects)</td>
</tr>
<tr>
<td>Safety Assessment</td>
</tr>
<tr>
<td>Med Adherence Assessment</td>
</tr>
</tbody>
</table>

† Bronchodilators should be withheld if not precluded by asthma symptoms
III.C.3.c. Visit 4 (8 Months, 10 Months or 12 Months, +/- 10 days)
For subjects enrolled from March 2012 through October of 2012, this visit will be their final study closeout visit (Visit 4) at either 8 months, 10 months or 12 months as outlined in Table III B-2. The final asthma questionnaires (ACQ, symptom free day, as well as the asthma exacerbation/medication review questionnaires will be reviewed by the coordinator at each practice site to ensure that they were well understood and completed correctly. The AQLQ and ASUI questionnaires will be completed at this visit. A final pregnancy test will be performed. Medication and rescue inhaler usage will be reviewed, and subjects will be asked if they prefer to maintain their current medication or return to their original treatment. Data on this preference will be captured as part of the study exit. At this visit there will be a discussion between the patient and their physician to determine the medications to be continued at the end of the study. At this visit, spirometry will again be performed.

III.C.3.d. Visit 5 (14, 16, or 18 Months, +/- 10 days)
For subjects enrolled from April 2011 through February 2012, an additional visit will be scheduled at either 14, 16, or 18 months of follow-up +/- 10 days. This will be the final study closeout visit for these subjects. The final asthma questionnaires (ACQ, symptom free day, as well as the asthma exacerbation/medication review questionnaires will be reviewed by the coordinator at each practice site to ensure that they were well understood and completed correctly. The AQLQ and ASUI questionnaires will be completed at this visit. A final pregnancy test will be performed. Medication and rescue inhaler usage will be reviewed, and subjects will be asked if they prefer to maintain their current medication or return to their original treatment. Data on this preference will be captured as part of the study exit. At this visit there will be a discussion between the patient and their physician to determine the medications to be continued at the end of the study. At this visit, spirometry will again be performed.

All study visits are outlined in table III.C-2.

III.C.4. Study Questionnaires
As mentioned above, the trial is designed to mimic "real world" conditions to a significant extent and to minimize the burden on the patients. For this reason, we are not having patients fill out daily diaries. Instead, on a monthly basis, subjects will fill out several questionnaires detailing “patient-reported outcomes,” including the ACQ, the Asthma Symptom Free Day Questionnaire, and a study-specific asthma exacerbation/medication questionnaire (Table III.C-3). At the study office visits, subjects will also fill out the Asthma Quality of Life Questionnaire and the Asthma Symptom Utility Index (see below and Table III.C-3). Study investigators have experience using these questionnaires in several studies, including yearlong studies co-led by Dr. Israel (Boushey, 2005, Wechsler 2009).

III.C.4.a. Monitoring of Questionnaire Data
Beginning in the second month of the study, reminders via phone and/or email will be sent to subjects as needed to remind subjects to complete the monthly asthma surveys. If data entered on these surveys suggest that the subject has experienced an adverse event or asthma exacerbation, the OMC/AAFP NRN team will be notified by the DCC. OMC/AAFP NRN will be given the subject’s ID number and specific information on the exacerbation that was reported by the subject. The OMC/AAFP NRN study coordinator or research assistant will link the Subject study ID to the informed consent which provides the preferred subject contact information. This form also gives permission for the study team to follow up personally for additional data collection or clarification. During the call, the OMC/AAFP NRN staff (a nurse) will clarify the
nature of the exacerbation, the visit location of the exacerbation (e.g. hospital or doctor office), and the approximate date. Additional data on medication use and adverse effects will be collected. The OMC/AAFP NRN study coordinators will be responsible for entering these data into the EDC database.

While subjects will always be encouraged to be adherent to medications at study visits, the monthly surveys/interviews will ask patients about their adherence for the prior week. We are aware that limitations of this mechanism for monitoring adherence are accuracy of the subjects’ recall and honesty, because the timing and confirmation of dosing cannot be verified directly. To attempt to address this issue, we have implemented an adherence assessment plan described in section III.C.6.

III.C.4.b. Asthma Control Questionnaire & Asthma Quality of Life Questionnaire
We will use the Asthma Control Questionnaire (ACQ) (Juniper 1994; Juniper 1999) and Asthma Quality of Life Questionnaire (AQLQ) (Juniper 1992; Juniper 1993) both of which have strong measurement properties and have been fully validated for use in both clinical practice and trials in adults (Juniper 1996; Juniper 1997). The ACQ has six questions regarding symptoms, rescue short-acting β-agonist use and one about FEV1 % predicted. We will use a version of the ACQ that has been validated for patient computer-based entry (http://www.qoltech.co.uk/Interactive_versions.html). The AQLQ has 32 questions in four domains (symptoms, activity limitation, emotional function, and environmental stimuli) and measures the functional problems that are troublesome to individuals with asthma.

III.C.4.c. Asthma Symptom Free Day Questionnaire
We will use the Asthma Symptom-Free Day Questionnaire (Appendix XI.D), an instrument that we have successfully used in the past (Boushey 2005). The asthma symptom free day questionnaire quantifies the number of days with neither daytime nor nighttime asthma symptoms, nor awakenings due to asthma symptoms (Sullivan 2001).

III.C.4.d. Asthma Symptom Utility Index
We will also employ the Asthma Symptom Utility Index (ASUI), an 11-item preference-based outcome measure used in clinical trials and cost-effectiveness studies for asthma (Revicki 1998). It is designed to assess the frequency and severity of cough, wheeze, dyspnea, nighttime awakenings, and side effects, weighted according to patient preferences.

III.C.4.e. Asthma Exacerbation/Medication Review Questionnaires
The monthly questionnaires will contain questions regarding the criteria for exacerbations and questions regarding medication use. As mentioned, all possible exacerbations will be followed-up by OMC/AAFP NRN personnel to verify accuracy. In addition, we will test questions for interpretability and validity with this population before implementation.
III.C.5. **Study Procedures**

### III.C.5.a. Spirometry testing

All spirometry testing will be done using standard techniques to meet American Thoracic Society criteria for accuracy and validity (ATS 1995). All testing will be completed in the sitting position using a nose clip for each patient (clips are provided to the practices). Subjects will be encouraged to come in for their visits at the same time of day in order to decrease diurnal variation and effects related to timing of medications. At each of the follow-up visits, spirometry will be performed, with spirometry at Visit 2 being performed both before and following inhalation of four puffs of albuterol with at least 30 seconds between puffs. The post bronchodilator testing will begin no sooner than 15 minutes after inhalation of the albuterol. For the bronchodilator reversibility testing at Visit 2, controller medications will be withheld the morning of the visit according to standardized protocols. For the other visits, medications will not be withheld (Wechsler 2009).

#### III.C.5.a.i. Equipment and Training

All practices will receive an EasyOne spirometer system marketed by NDD (Andover, MA). This handheld spirometer is the only one currently available that has a built-in modem that allows the spirometry results to be sent directly to another site. In this case, data will be transmitted to the study physician who will be doing the over-reading of all spirometry testing. In addition, the EasyOne has been shown to be a very stable system that does not require daily calibration in most practices, and with which we have direct experience (Yawn, 2007). We will recommend weekly calibration.

All practices will participate in the spirometry training session and updates presented at the central training meeting will be presented in web-based seminars. All spirometry testing will be completed by the person trained to complete this testing during the central study training sessions. Interpretation will be completed by the local site’s lead study physician with over-reading and feedback as outlined below.

#### III.C.5.a.ii. Over-reading and Feedback

All spirometry will be reviewed and interpreted by the physician at the study site. The spirometry test results will be entered into the Inform database by the site and also sent via a secure website “Box.net” to Dr. Shamsah Kazani, pulmonologist at Brigham and Women’s Hospital, who is over-reading study spirometry results. This is done by the site simply placing the EasyOne equipment in the “cradle” that comes with the device and then pushing “send” which sends the data file to a shared folder on the Box.net website. Dr. Kazani will then enter the results of her over-reads into the Inform database. The spirometry interpretation used for the study will be that of the study physician Dr. Kazani and not the local primary care physician if the two interpretations disagree.

Dr. Kazani will serve as the central study physician who will review all spirometries and give feedback to OMC, the DCC and the individual study sites in cases of poor performance. She will arrange for retraining for sites with < 80% passing grade on their spirometries. Weekly and monthly reports of PFT acceptability will be compiled by the DCC. Additionally, the central study physician may choose to call the practice at any time for further support or education. The practice will be able to contact a central study physician if an immediate consultation about interpretation is required.
III.C.5.b Genotyping

III.C.5.b.i. Saliva Collection for Genotyping
Genomic DNA will be collected at the first study visit utilizing the Oragene Saliva DNA self collection kit (DNA Genotek, Inc, Ottawa Canada). This an all-in-one system for the collection, preservation, transportation, storage and purification of DNA from saliva provides an easy way to collect large amounts of DNA from donors, with minimal cost and complexity. The subject simply delivers saliva into the collection container. Capping the container releases DNA-preserving fluid which then mixes with saliva and stabilizes the DNA for long-term storage. The sample will then be transferred to the genotyping facility for further DNA analysis (see below). This system offers major benefits over blood collection due to higher donor compliance with painless self-collection; lower collection costs with no phlebotomy required; safer handling, eliminating infectious risk; and relative ease of DNA purification. Compared to mouthwash or buccal swabs, this system provides higher DNA yield and quality. Furthermore, this system eliminates costs of refrigeration and storage by preserving the DNA for long-term storage at room temperature without degradation. Lastly, the Oragene kit includes a DNA Purification Kit that uses a simple protocol to extract high molecular weight DNA from the saliva sample.

III.C.5.b.ii Genotyping Process
Samples will be genotyped quarterly using Taqman assay, as previously described (Wechsler 2009). Genotyping and analysis will be performed with the collaboration of Vance Morgan, PhD, Michael Murray, M.D., and Birgit Funke, PhD in consultation with David Kwiatkowski and Scott Weiss, MD, MPH, all members of the PHCPGM. It will be run through the Laboratory of Molecular Medicine (LMM), a CLIA-certified clinical diagnostic laboratory operating within the Harvard Medical School. The LMM provides genetic and genomic testing for patients around the world. It is also a leader in the development of new approaches to genetic testing and its integration into health care.

At PHCPGM, the specimens will be batched; DNA will be extracted and genotyped at the Arg16Gly locus, and stored for future ADBR2 sequencing and haplotype analysis. Prior to study start-up, the PHCPGM and the DCC will work to establish a data transfer protocol by which the screening genotype data will be uploaded into the study database. At pre-determined, regular intervals, the PHCPGM will transfer this data. Clinical sites will not be informed of the subjects’ genotypes.

At the end of the project, we will perform a focused rare variant genetic association study of the participants enrolled in BELT. This will represent the largest study of the genetics of the ADRB2 locus in non-whites. We will perform targeted resequencing of the ADRB2 locus. Sequencing will follow standard NIH resequencing guidelines, targeting all exons, conserved-intronic sequences, and 2kb flanking upstream and downstream genomic sequence (6kb total). Sequencing reactions are performed by standard Sanger protocol (Carlson, 2004) modified for dye-terminator dideoxy sequencing chemistry (BigDye Terminator v3.1, ABI) using 20 ng DNA. Reaction primers are designed with Primer 3.0 (de Bakker 2005; Pritchard 2001; Kruglyak 1999) using sequence data from the NCBI database. Sequence readout is performed using the 3730XL Sequence Detector (ABI). Chromatograms are analyzed with Phred/Phrap/Consed (Loots 2004; Loots 2002). Variant identification is automated with PolyPhred (Matys 2003, 2006) and verified manually. An informatics pipeline at Brigham & Women’s Channing Laboratory facilitates the efficient analysis of sequence data. This pipeline produces a series of reports and graphical displays, including tables of SNP allele frequency, plots of pair-wise LD, and imputed
haplotypes. Haplotype imputation will be performed using PHASE (Stephens 2001ab). Two sets of analyses will be performed, including haplotype-specific association testing to assess for pharmacogenetic effects of common haplotypes, using linear regression models as implemented in the haplo.stats R package, to estimate haplotype frequency and incorporates the phase uncertainty into the association test models. Second, we will perform a rare-variant analysis to identify low frequency variants with strong genetic effects that would not be identifiable from haplotype-based analysis.

Lastly, to correct for racial admixture we will also do additional genetic testing of ancestry informative markers to better depict subject ethnicity and ancestry (see Section IV.C.5.b. Racial Admixture)

III.C.6 Medications and reimbursement

III.C.6.a. Medications
In order to qualify for the study, patients will either be on ICS/LABA prescribed by their MD for at least one month, or on at least moderate dose ICS (as per NAEPP definitions in NAEPP 2007). In the latter case, the patient must have an ACQ ≥1.25 to qualify for addition of a LABA to their ICS. All enrolled patients on combination (LABA/ICS) therapy will be prescribed ICS (at dose equivalent to baseline ICS dose) and asked to stop their combination regimen. Patients on ICS monotherapy will be continued on the baseline ICS medication. For patients randomized to receive LABA, they will be asked to stop their current LABA/ICS combination medication, and to start an equivalent of the LABA component of their medication. For those subjects randomized to receive tiotropium, prescriptions will be given for tiotropium (18 mcg/puff), one puff QD. The dose equivalencies of ICS and LABA are outlined above in Table III.C-2.

III.C.6.b. Reimbursement
Subjects will be reimbursed to cover the cost of medication copayment and to enhance subject retention and study participation. Specific details of subject reimbursement will be worked out with each center.

III.C.6.c. Adherence Measurement
We will use two methods to monitor medication adherence. Medication adherence will be monitored through monthly questionnaires and using dispensing information from the pharmacy.

1) At all monthly surveys/interviews patients will be asked about their adherence for the prior week. We are aware that limitations of this mechanism for monitoring adherence are accuracy of the subjects’ recall and honesty, because the timing and confirmation of dosing cannot be verified directly. To attempt to address this issue, we have implemented a second adherence assessment plan utilizing dispensing information from the pharmacy.

2) Medication purchases made by the study subjects using their study-issued debit cards (Clinocard) will be monitored. The information obtained for each Clinocard charge includes names and doses of medications dispensed, date dispensed, and cost to the study. In addition, some of the pharmacies call to report refills even when no charges are made to the Clinocard. One of the OMC staff is appointed as research drug coordinator and has oversight for all medications for all randomized patients. For any patient in any month in which no or incomplete information is provided (e.g. only one medication noted), the research drug coordinator will call the site coordinator to assess whether any medication samples were dispensed and the dose of these samples. If no data is available from the Clinocard system or from the site coordinator, either the site coordinator or the research
drug coordinator will call the patient directly to verify medication purchases using their Clincard or insurance co-pays (some patients choose to pay small co-pays rather than use the Clincard system). These methods allow information on dispensing for close to 100% of patients for each month in the study. We understand that dispensing does not equate with actual doses taken, however, as above, we will collect information on the monthly questionnaires and during study visits and follow-up phone calls on the type and doses of medications taken during specified time intervals. Medication data is entered on the Concomitant Medication eCRF and is part of the study dataset that will be included in the final analysis.

III.D. Practice and Patient Recruitment and Retention

III.D.1. Practice Recruitment

Practice identification and recruitment are described in Preliminary Data Section III.C. For the BELT study, 15 practices will be enlisted and 5-10 additional sites will be identified should enrollment lag at any of the practices.

III.D.2. Subject and practice retention

The study personnel will maintain close contact with enrolled patients through the monthly study questionnaires, calls to schedule the follow-up office based interactions, and the office based interactions for patients who return all materials without any reminders. We have found that the regular contact and developing a relationship with the practices and the central study team is instrumental in retaining the practices. Practices are sent acknowledgements of their work and thank you notes from the study team on a regular basis. OMC and the AAFP NRN have been able to retain up to 30 practices for three years of active participation in studies in these PBRNs. The PI and DCC will monitor study enrollment and subject retention, as well as data submission and quality metrics and follow-up with OMC/AAFP NRN to address any issues. In addition, the PI will hold regular calls with the site PIs in order to maintain contact with them and address issues proactively.

III.E. Data Collection and Quality

III.E.1. Database Design and Administration

For the BELT study, the DCC will coordinate all data necessary for study analysis and safety monitoring. This data will be captured in the study electronic Case Report Form (eCRF).

Following HCRI SOPs, the eCRF specifications will be programmed to build the EDC database. This database will undergo full User Acceptance Testing (UAT) and Quality Assurance (QA) validation before being made available to sites for data entry. Throughout the study, the system will be monitored for issues by the DCC, with quality issues being logged and action plans developed as needed following HCRI's processes and procedures.

Access to the EDC database is strictly controlled, with all users requiring appropriate documentation and training. All access to the system is documented as part of the study master file. DCC personnel are not provided with rights to delete or change data – only the site and central site users will have this ability. Any data cleaning required will be done by automatic or manually created queries to the site users who will need to confirm or change data in response. As sites enter data into the database and the data management or monitoring staffs issue queries, any changes are tracked by the system and stored in a database audit trail which can
be accessed as needed. All these security measures ensure that only authorized personnel can enter study data into the system.

Core lab and study questionnaire data will be transferred into the study database using protocols determined with the core lab and third party vendor, respectively. The panels to hold the data will be built and tested following the same processes as the study database and test transfers will take place prior to any actual data being transferred. This data will not be cleaned by DCC staff, but record-count verification will be performed following each transfer.

III.E.2 Data Monitoring and Site Auditing

The DCC, PBRN central sites, and ARC staff will work together to ensure that the data entered by the sites and central site staff are source-document verified and monitored. At study start-up, all site coordinators and staff who will be entering data will undergo an online training on the EDC system. They will also be trained by the central site staff on the study-specific eCRFs and study procedures. The DCC will provide all sites with appropriate source documents which they can use during the study to supplement the documentation that is part of the subject's medical record. Sites will be required to keep all study documentation for subjects including visit notes, lab results, and information on adverse events.

On a regular basis, central site staff will visit the sites in order to monitor and verify the data entered into the study database. The percentage and type of data to be verified will be determined at study start-up and documented in a study Monitoring Plan. Documentation that the appropriate data has been source-data verified will be part of the study database and must be completed before the eCRFs can be locked and transferred for data analysis. Any issues identified in the monitoring process will be communicated to the DCC and study PI and an appropriate action plan will be developed to address these issues. In addition to regular monitoring, the DCC data management and project management staff will generate and review site compliance and performance reports with the PBRN central site staff and ARC Project Manager to identify site issues and implement plans to address such issues as they arise.

Prior to study closeout, the OMC’s trained site management PBRN study coordinator will visit each site for a final study audit which will ensure that all regulatory documentation and source data is in place at the site and central sites. These site audits will be documented following HCRI SOPs in a Site Visit Report and provided to the study PI for review. Any issues identified will be discussed and addressed immediately with documentation of any action taken.

III.E.3 Methodology for Collecting Questionnaire Data

During the Investigators Meeting held during study start-up and during new site training sessions, OMC and AAFP staff as well as site coordinators were provided training regarding the proper administration of study questionnaires to subjects. During the study enrollment and follow-up periods, sites will batch ship completed clinic visit questionnaires to the DCC on a monthly basis. OMC staff will send questionnaire packets to all subjects on a monthly basis and subjects will be instructed to return completed questionnaire packets to OMC. These completed questionnaire packets will subsequently be batch shipped to the DCC for data entry on a monthly basis.

On a pre-determined schedule, the DCC will use this data for reporting, monitoring, and analysis. For monitoring purposes, the DCC will work with the study investigators to identify key questions and answers that will indicate a subject may have experienced a potential asthma exacerbation or may be having study drug compliance issues. These reports will be aggregated for overall study safety monitoring by the investigators and appropriate data and safety monitoring committee members. Individual reports will be created and sent to the central PBRN...
sites for follow-up to confirm exacerbations. In a follow-up call, the OMC staff (a nurse) will ask additional questions to confirm missed school or work days and attempt to clarify the injection medications to distinguish between IV antibiotics given in the hospital and IM injections of long acting steroids that might be given in the office, the ED, or the hospital. The central site staff will then be able to enter any relevant information into the study InForm database. They will also be able to follow-up on any issues subjects may be having with their study drug and report back to the DCC or study investigators if any action is needed to address such issues.

At the conclusion of the study, all questionnaire data will be exported as SAS datasets along with all other study data and will be provided to the statistical group for table generation and analysis. These tables will be available to study investigators and committee members for use in publications or other analyses.

III.E.4. Database Lock and Data Analysis

The study database, including all monitored site data, safety data, transferred genotype and questionnaire data, will be closed, and locked following DCC SOPs to ensure that the datasets provided for analysis are complete and accurate. The final dataset will be exported into SAS and provided to study biostatisticians as password-protected files. All analysis tables distributed to study investigators will be double-programmed and reviewed and will also be password-protected. No data will be changed or modified after database lock without appropriate authorization from the study PI and documentation of all changes. Any such changes will require the database to be re-closed and locked prior to analysis.
IV. Study Outcomes and Statistical Analysis

In assessing the effectiveness of an intervention, the use of multiple measures is important; different measures assess different manifestations of disease and may not correlate with one another. Factor analyses utilizing, outcomes commonly included in clinical trials, has demonstrated several independent factors are important in the assessment of asthma. These are listed below as our study outcomes. (Holt 2008, Juniper 2004). We have chosen clinically important and patient based outcomes and will also assess relevant physiological outcomes. Below we outline the importance and validity of the chosen outcomes to the patients, practitioners, and the health care system. The proposed analysis plan will look at these primary and secondary outcomes as well as investigate several exploratory analyses.

IV.A. Primary Outcome

**Time to asthma exacerbation, defined as an event of worsening asthma requiring oral or parenteral corticosteroids, such as an unscheduled physician visit, ER visit, hospitalization, or physician judgment of clinical asthma status over the follow-up duration of the study.**

The primary study outcome is time to asthma exacerbation, defined as an event of worsening asthma requiring oral or parenteral corticosteroids, such as an unscheduled physician visit, ER visit, hospitalization, or physician judgment of clinical asthma status over the one year after randomization. These will be captured by subject self report directly to the study staff or via monthly questionnaires. While a limitation of this definition is that it requires the subjective assessment by the patient and/or physician, the ATS/ERS Statement on Asthma Control and Asthma Exacerbations recommends this definition of severe exacerbation for use in clinical trials because these criteria are “clinically relevant and intuitively valid”, and “such a change in asthma status is severe enough to warrant… intervention” (Reddel 2009).

We have selected this outcome because prevention of asthma exacerbations has been identified in all asthma treatment guidelines (NAEPP 2007) as an important component of establishing ideal asthma control. It has been argued that exacerbations are the most important outcome, because they constitute the greatest risk to patients, are a cause of anxiety to patients and their families, result in the greatest stress on health care providers, and generate the greatest cost to the health care system (Reddel, 2009). Indeed, over the past 10 years, exacerbations have been increasingly used as a primary outcome variable in research into the efficacy of drug treatment in asthma (Pauwels 1997; O’Byrne 2001) and have been shown to be responsive to intervention (O’Byrne 2005). Exacerbations are recognized as a common clinical manifestation in patients with severe asthma, and are known to increase the risk of asthma mortality (Jorgensen 2003). However, even in patients thought to have mild asthma, the rates of severe asthma exacerbations have been much higher than expected (O’Byrne, 2001). In clinical practice, exacerbations are recognized as episodes that are troublesome to patients, and that prompt a need for a change in treatment. This is what will be captured in this study. Characterization of what constituted each exacerbation will also be reported. As outlined in **Section IV.E Methodology for Collecting Outcomes**, for this critical primary outcome, we will call patients to confirm and validate these events.
IV.B. Secondary Outcomes

Patient-reported outcomes (Asthma Quality of Life, Asthma Control, Asthma symptom Utility index, Symptom Free Days)
Spirometry (FEV1)
Rescue Medication Use
Moderate Asthma Deterioration

IV.B.1 Patient Reported Outcomes
IV.B.1.a. Relevance of Patient Reported Outcome Measures
As mentioned in the [Study procedures section] we will use the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ), both of which have strong measurement properties and have been fully validated for use in both clinical practice and trials in adults (Juniper 1996; Juniper 1997).

IV.B.1.b. Health Related Quality of Life (HRQOL): AQLQ
Quality of Life is an important measure for use in evaluation of clinical effectiveness, as it assesses the functional problems that are troublesome to individuals with asthma. The AQLQ has been fully validated, with excellent test-retest reliability, cross-sectional validity, and longitudinal validity. In addition, the minimal important difference has been evaluated and found to be 0.5. (Juniper 1994) Prior evaluations have demonstrated that the correlation between HRQOL as assessed by the AQLQ and other measures of asthma such as FEV1 and day and nighttime symptoms are low suggesting that the AQLQ identifies unique attributes not fully explained by these other variables. The AQLQ is extensively used in clinical trials of asthma interventions including studies demonstrating the benefits of long acting beta agonists to ICS (Juniper 2002).

IV.B.1.c. Asthma Control: ACQ
In addition to HRQOL, the assessment of asthma control is a key outcome in the assessment and management of asthma interventions. The most recent guidelines highlight asthma control as the central concept for the monitoring and adjustment of therapy (NAEPP 2007). Asthma control is an important outcome to include in a comparative effectiveness trial, as it has been used in clinical practice as well as clinical trials. The ACQ has strong discriminative and evaluative properties; it can detect small differences between patients with different levels of asthma control and it is very sensitive to within-patient change in asthma control over time. The minimal important difference has been defined for the ACQ: a change or difference in score of 0.5 is the smallest that can be considered clinically important. The ACQ is able to identify the adequacy of asthma control in individual patients; for well-controlled asthma, the optimal cut-point is 0.75 (NPV 0.85) and inadequately controlled asthma, the optimal cut-point is 1.25 (PPV 0.88). (Juniper 2006). Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale (0=no impairment, 6= maximum impairment). The questions are equally weighted and the ACQ score is the mean of the seven questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

IV.B.1.d. Preference Based Quality of Life: Asthma Symptom Utility Index
The ideal outcome measure for any comparative effectiveness analysis captures the risks and benefits for each of the interventions. While other outcomes independently capture some of the important aspects of asthma, they do not capture adverse events and other health changes that may occur due to treatment. Therefore the use of a preference based HRQOL instrument, the Asthma Symptom Utility Index (ASUI), will be a valuable addition to the study. The important
difference in a preference based instrument, compared with a health status measure, is that it includes an assessment of the preference of individuals for alternative health states or outcomes, and reflects the tradeoff or net effect of the positive and negative aspects of the health state from the respondent’s point of view. In addition, preference based measures provide a common unit of analysis and thereby allow the outcomes of different types of programs to be compared on the same scale. The instrument contains 11-items designed to assess the frequency and severity of four asthma symptoms (cough, wheeze, dyspnea, and awaken at night) and side effects, weighted according to patient preferences. (Revicki 1998) The ASUI has been previously studied in large multicenter clinical trials (Boushey 2005). In a study evaluating the ability to predict episodes of poor control in patients with asthma, symptom questionnaires, including the ASUI, were the best predictors of episodes of poor asthma control in persons older than 10 years of age (McCoy 2006).

IV.B.1.e. Symptom Free Day

The symptom-free days, the count of symptom free days in the past two weeks, has been successfully employed in large clinical trials (Evans 1999, Lozano 2004, Guilbert 2006). In addition, the SFD has been recommended as the optimal outcome for CEA by the National Asthma Education and Prevention Task force on cost-effectiveness of asthma care and is included in the recommended outcome by the Health Resources and Services administration (HRSA) sponsored asthma collaborative. HRSA provides tools and proven strategies to change the way asthma care is delivered. One limitation of the SFD is that the instrument weights each of the symptoms evenly; a patient who has an exacerbation is counted equally to a patient who has shortness of breath and this is why assessment using a preference based HRQOL instrument, the ASUI, will be included in the evaluation of subjects.

IV.B.2. FEV1

Part of the justification for using LABA/ICS despite the possible increased risk of rare serious asthma outcomes relates to their benefit with regard to improved airway caliber and resultant decrease in symptoms that these drugs provide. Our sub-analysis of the LARGE trial suggests that Arg16Arg Blacks with asthma have little if any improvement in airway caliber when treated with LABA/ICS. Thus, one of the critical reasons to use these medications would be eliminated. While LABA use is associated with decreased rates of exacerbation, this is usually in the context of associated improvements in airway caliber, even in the context of ICS use (e.g. Pauwels 1997; Bleecker 2007). When decreased levels of improvement of airway caliber occur, decreased improvements in exacerbations appear to follow (Bailey 2008). This relationship is in contradistinction to other asthma medications that have little effect on airway caliber, yet decrease exacerbations and/or symptoms (Israel 2002; Milgrom 1999). Thus, we seek to assess whether Blacks in general, or Arg16Arg Blacks in specific, will have diminished improvement in airway function when LABA is added to ICS compared with tiotropium. Since many patients enrolled will already have been on LABA/ICS, we will assess the FEV1 at the end of the trial in the two treatment arms to assess whether LABA/ICS is superior to TIO/ICS. We will compare the pre-bronchodilator FEV1 at the end of the study. We will also examine the “maximal achievable FEV1”at the end of the study and the change (if any) in this value over the course of the study. On visit two we will assess bronchodilator response after a withhold to obtain additional characterization information. This change in FEV1 has been shown to predict responsiveness to therapy and correlates well with asthma severity (Szefler 2003, Boushey 2005).

IV.B.3. Rescue Medication Use

Use of rescue medication in patients with asthma is considered to be a sign of poor asthma control that would warrant consideration of a change in therapy and is associated with asthma
exacerbations (NAEPP 2007). We will keep track of rescue medication use as a sign of asthma control by evaluating the number of puffs per day of albuterol as reported in the prior week on the monthly questionnaires.

**IV.B.4. Moderate Asthma Deterioration**

The primary outcome for this study will be asthma exacerbations as defined above. As a secondary outcome, the investigators will analyze the exacerbations or asthma deteriorations that are not severe enough to meet the above criteria but that otherwise would meet criteria as a moderate exacerbation as defined per current consensus guidelines. A moderate asthma deterioration is an event that, when recognized, should result in a temporary change in treatment (e.g., ICS, LTRA), in an effort to prevent the deterioration from becoming severe. The definition of a moderate asthma deterioration should include one or more of the following: deterioration in symptoms, deterioration in lung function, or increased rescue bronchodilator use. These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalization. ER visits for asthma (e.g., for routine sick care), not requiring systemic corticosteroids, may be classified as a moderate asthma deterioration.

**IV.C. Statistics and Analysis: Biostatistical Analysis, Statistical Design, and Sample Size**

All longitudinal data analyses will be performed using SAS. A Statistical Analysis Plan will be developed prior to the completion of study enrollment outlining these planned analyses in further detail.

**IV.C.1. Primary Analyses: Specific Aim 1**

The study is designed as a prospective, randomized, open-label trial comparing the effectiveness of LABA/ICS vs. Tio/ICS in delaying the time to exacerbation in Black patients with asthma. In particular, we hypothesize that the time to exacerbation during the course of the study (ranging from 6 to 18 months) will be significantly delayed in the LABA/ICS group as compared to the Tio/ICS group. The two-sided log-rank test will be conducted at the 0.05 level of significance. Patients discontinuing the study without the event of interest will be censored at the time of their discontinuation. Sensitivity analysis will be conducted in which censored individuals are considered as treatment failures (events) at the time of discontinuation.

**IV.C.1.a. Sample Size**

The sample size for this study was determined assuming constant hazards corresponding to annual event rates of 0.15 in the LABA/ICS arm and 0.21 in the Tio/ICS arm. To attain 80% power with the two-sided log-rank test conducted at the 0.05 level, we need an evaluable sample of 575 patients per arm, or 1150 total. If 1500 subjects are enrolled (1274 evaluable, 637 per arm), after accounting for 15% loss to follow-up, the power of the study would be 85%.

**IV.C.1.b. Justification of Assumptions in Sample Size Calculation**

The event rate of 0.15 was calculated from Bailey’s reported annual rate of 0.20 exacerbations in Blacks on LABA/ICS (Bailey 2008), decreased by 25%, since Bailey had included changes in PEF as part of the definition of exacerbations. The assumption that 75% of the exacerbations reported by Bailey would meet our definition was based on the proportion of different types of
exacerbations reported by Pauwels (Pauwels 1998). The corresponding annual rate in the Tio/ICS arm was set after consulting experts in asthma and asthma guidelines, and the assumptions made by the NIH Asthma Clinical Research Network in its Salmeterol or Corticosteroids Study (Lazarus 2001). In that study, the sample size was set to have 80% power, at a p<0.05, to detect a 20% or greater treatment failure rate in the LABA arm vs. a 5% rate in the ICS arm. Considering the fact that our failure rate over the year is likely to be 15% detecting a difference between Tio/ICS and LABA/ICS if Tio/ICS reaches 21% appears appropriate. Clinically, we would not consider LABA/ICS superior to Tio/ICS if the Tio/ICS exacerbation rate were less than 21%, especially in the context of the potential risks of LABA/ICS in this population.

IV.C.2. Primary Analyses: Specific Aim 2
We hypothesize that in the LABA/ICS arm, time-to-exacerbations and exacerbation rates will differ according to the presence of the arginine polymorphism, with highest rates in the Arg/Arg group and lowest rates in the Gly/Gly group. At the same time, there will be no such differences in the Tio/ICS arm. We will test this interaction of treatment arm with presence of the arginine polymorphism using Cox proportional hazards regression model treating the Arg/Arg, Arg/Gly and Gly/Gly groups as ordinal exposure. Furthermore, we will conduct separate analyses within the two treatment arms. Additional analyses will compare LABA/ICS to Tio/ICS within each of the three genotypic groups.

IV.C.3. Power
Assuming variability around the estimated hazard ratios similar to what was observed in the Palmer study [Palmer 2006], and evaluable sample size of 637 subjects per arm, we will have 80% power to detect an increase of hazard of approximately 1.45 per each copy of the Arg polymorphism. Furthermore, the evaluable sample size of 637 per arm, will give us 80% power to detect a 1.65 increase in the group specific ordinal hazard in the LABA/ICS arm as compared to the Tio/ICS arm using a two-sided test at the 0.05 level.

IV.C.4. Secondary Analyses
Secondary outcomes will be analyzed using standard statistical methods. Continuous outcomes will be compared using two independent samples t-test or Wilcoxon rank-sum test if the assumption normality is violated. Binary outcomes will be analyzed using the chi-square test of Fisher’s exact test if the number of events is below 10. Time-to-event outcomes will be compared using the log-rank test. As part of an “intent-to-treat” analysis, all available data on randomized patients will be included in the statistical analysis, regardless of whether a patient had missed visits or censored data. Missing data will be handled using multiple imputation techniques for continuous and binary outcomes and/or completers analysis. For time-to-event outcomes, subjects with missing data will be censored at the time of discontinuation. We will also compare these results to a last observation carried forward method as part of an intent-to-treat analysis (Lazarus 2001).

IV.C.5. Exploratory Analyses
IV.C.5.a. ADRB2 Rare-Variant Genetic Association Study
We will perform a focused rare variant genetic association study of the participants in BELT. We will perform targeted resequencing of the ADRB2 locus, targeting all exons, conserved-intronic sequences, and 2kb flanking upstream and downstream genomic sequence (6kb total). Two sets of analyses will be performed. First we will perform haplotype-specific association testing to assess for pharmacogenetic effects of common haplotypes using linear regression models to estimate haplotype frequency. Tests will be declared significant only if both a global test and a haplotype-specific test are associated at p<0.05. Second, we will perform a rare-variant analysis
to identify low frequency variants with strong genetic effects that would not be identifiable from haplotype-based analysis.

In this analysis, we will first enumerate all rare variants that map to coding and highly conserved non-coding sequence and then assess whether subjects with such variants have differential therapeutic response compared to subject who do not. Comparisons of the genetic associations between treatment arms, including use of formal interaction terms in linear modeling, will enable differentiation of true pharmacogenetic effects from non-treatment related (i.e. severity) effects.

IV.C.5.b. Racial Admixture
We will correct for racial admixture by genetic testing of ancestry informative markers. Individual admixture estimates will be determined using the program STRUCTURE as previously performed for other asthma studies (Tsai 2005). Potential confounders that will be considered include but will not be limited to age, sex, race/ethnicity, BMI, asthma duration, medication use, and recruitment site. Height and height-squared will be covariates in the longitudinal model to account for age related changes in height in the adolescents.

V. Protection From Risk, Adverse Events, Asthma Exacerbations, and Safety Monitoring
Risks and benefits of participation in this trial are reviewed below, along with the details of the protections planned. Additional risks to patients in this trial are minimal as patients with this level of asthma are, or should be receiving, the levels of therapy that we are comparing. Adverse events and asthma exacerbations will be closely monitored throughout the study and there will be regular safety monitoring by study sites, study investigators, and an independent Data and Safety Monitoring Board (DSMB). Processes for ensuring adequate monitoring are outlined below.

V.A. Human Subjects Involvement and Characteristics.
V.A.1. Human Subject Enrollment
Human subjects will be involved in the proposed study. Subjects will undergo all study tests and procedures and be randomized to one of two approved treatment options. Up to 1500 Blacks ≥ age 18 will be enrolled in this study. All subjects will have a clinical history consistent with asthma and a prescription for a LABA, or will be on moderate doses or higher of ICS and have asthma symptoms consistent with an ACQ>1.25 (indicating a lack of control). Other than asthma, the subjects are expected to be in stable health. As this study is examining the effects of the proposed treatments in Black asthmatics, subjects of other races will not be enrolled. However, Black subjects of either gender will be enrolled and subjects can be either Hispanic or non-Hispanic. No special classes of vulnerable populations will be involved in the proposed study. Detailed Inclusion and Exclusion criteria are listed in section III.

The data collected from the subjects in this study will be de-identified and entered into a database maintained by Harvard Clinical Research Institute (HCRI) in Boston, Massachusetts. HCRI will serve as the Data Coordinating Center (DCC) for this study and will review, and clean all study data in preparation for analysis. The saliva specimens from the subjects will be processed for genotyping at the Partners HealthCare Center for Personalized Genetic Medicine (PHCPGM) in Boston, Massachusetts. Study sites from the American Academy of Family Physicians National Research Network (AAFP NRN) will be engaged to recruit, screen, and enroll study subjects. These sites will be responsible for performing study tests, collecting all required data, and entering it into the study database, and complying with study regulatory and
monitoring requirements, including the timely reporting of all adverse events, as described in the sections below.

V.A.2. Sources of Materials
Data on all subjects will be collected and entered in a de-identified fashion into the study database. Each subject will be assigned study screening and randomization numbers. Only these numbers will be used by the DCC to match subject data. The DCC will not receive any data that contains subject identifiers and no one at the DCC will have access to such information at the sites. Study coordinators, in the course of their treatment of the subjects, will have access to their subjects’ medical records and will be responsible for de-identifying any source documentation required for monitoring or study data collection purposes. The EDC database will not contain any identifying subject data.

The data captured in the study database on all subjects will include information on ethnicity and gender, relevant medical history and birth control methods (if applicable), asthma medication usage, results of study-specific testing, asthma-related quality of life, certain concomitant medications, and adverse events and asthma exacerbations. eCRFs will be designed at study start-up based on existing study CRFs for similar studies. These eCRFs will be designed by the DCC and reviewed with the study PI and leadership before being approved and released to the sites for data entry. In addition, the subjects will enter their own information directly into an online survey utility. This utility will be provided by a vendor to the study and will contain appropriate privacy and security methods including passwords and secure URLs. These data will then be transferred into the study database. The data to be collected and the manner of de-identification will be discussed with the subject as part of the informed consent process.

At different subject visits, saliva samples will be collected and sent to the PHCPGM lab in Boston for genotyping. These samples will be identified using the study-assigned screening numbers – no identifying information will be sent to the lab and thus the lab does not have the ability to identify the subjects using these specimens. Genotypes will be matched with the subjects using the study assigned numbers and will be used to provide the subject randomization assignment and analysis only. The collection of specimen for analysis will be discussed with the subject as part of the informed consent process.

V.A.3. Change in Medications
At baseline, patients will either be on ICS/LABA combination, or on at least moderate dose ICS monotherapy (as per NAEPP definitions) (NAEPP 2007) and baseline ACQ >1.25. All enrolled patients will be prescribed ICS (recommended to be at dose equivalent to baseline ICS dose) and asked to stop their combination regimen. For patients randomized to receive LABA plus an ICS, they will be asked to stop their current LABA/ICS combination medication, and to start a LABA component (recommended to be salmeterol as outlined in section III.C.2.b). For those subjects randomized to receive tiotropium, prescriptions will be given for tiotropium (18 mcg/puff), one puff QD. For patients not on LABA at baseline who are randomized to the LABA arm, patients will be prescribed a LABA (preferably salmeterol per section III.C.2.b). The dose equivalencies of ICS recommended in this study are outlined in table III.C-1.

V.B. Risks to Human Subjects
V.B.1. LABA Risks
The proposed study is a comparison of the effect of a long-acting beta-agonist compared to an inhaled anti-cholinergic in patients with asthma, receiving inhaled corticosteroids in addition to long-acting β-agonists or who are uncontrolled on moderate dose ICS (as evidenced by an ACQ >1.25). There is some controversy surrounding the use of LABA in the treatment of asthma. A recent study known as SMART suggested that there may be a risk of life threatening events in
patients treated with salmeterol, particularly in Blacks (Nelson, 2006). Nonetheless, treatment with a LABA and an inhaled corticosteroid continues to be an accepted part of treatment for asthma of moderate severity. Newly revised national asthma treatment guidelines continue to approve and advocate for this treatment in patients not well controlled on single agent therapy (NAEPP, 2007). For the majority of patients, the decision to use a LABA for treatment will have already been made by the treating physician and thus participation will not result in patient exposure to a LABA for the sake of the study. In addition, the SMART study suggested that the risk of LABA treatment might be diminished by the concomitant use of inhaled corticosteroids. All patients in this study will be receiving concomitant inhaled corticosteroids and we will reinforce the importance of the use of both agents.

The SMART study (Nelson 2006) further suggested that using the LABA, salmeterol, was associated with a small increase in the risk of fatal and severe life-threatening asthma attacks (1 in 10,000). Although the SMART study did not find a statistically significant increase in the risk of these severe attacks when salmeterol and inhaled corticosteroids were used together, the study results could not exclude the possibility that an increase in severe attacks may occur even when salmeterol is used with an inhaled corticosteroid. No LABA will ever be taken alone in this study; it will be taken with an inhaled corticosteroid. Furthermore, in the SMART study, the patients did not do any home monitoring and did not have any return visits to the clinic. In this study, asthma symptoms will be monitored by monthly questionnaires and by visits and phone calls with the clinic. Medications and instructions will be given by the patient’s primary care physicians in case of asthma worsening, so that any attack may be treated promptly.

In both the BAGS (Drazen 1996) and BARGE (Israel 2004) studies, we found that in one subgroup defined by the B16-Arg/Arg genotype, the use of albuterol on a regularly scheduled basis resulted in a significant drop in AM PEF. Similarly, in the SOCS and SLIC studies (Lazarus 2001, Lemanske 2001), we found that the use of the long-acting beta-agonist salmeterol was associated with a detrimental effect on airway function in subjects with the B16-Arg/Arg genotype. Increased exacerbations were noted in Arg/Arg patients using a short-acting β-agonist (Taylor, 2000) and recently it was suggested that increased exacerbations occur in patients possessing the arginine allele using LABA/ICS (Palmer, 2008). Nonetheless, there have been other studies, including the LARGE trial (Wechsler 2009), that suggest that such risk may be minimal. One of the aims of the proposed research is to define whether such risks do in fact exist in a specific racial and/or genetic group. Since most patients will already have been placed on LABA/ICS or Tio/ICS by their physician, this study should not result in significant number of additional patients receiving such treatment. Further, since we are monitoring patients for exacerbations we may decrease such risk. Other side effects of long-acting beta agonists (LABA) include tremors, nervousness, rapid heart rate, headaches, dizziness, lightheadedness, sweating, nausea, and less frequently, insomnia, chest pain, and irregular heart beat. This study hopes to find out if taking this class of medication makes some people’s asthma worse because of race or because of one’s genetic makeup. In this study, the LABA is used in combination with an inhaled corticosteroid, a controller medication. LABA’s have also been used alone to treat asthma. Studies that we have performed, as well as those performed by others, suggest that LABA’s should not be used without a controller medication, because, when used alone, it does not protect well against asthma attacks.

V.B.2. **Tiotropium Risks**

Tiotropium is a long acting inhaled anti-cholinergic medication. It has been used extensively in COPD and has been associated with dry mouth, cough, nervousness, nausea, dizziness, and headache. There are limited studies in asthma alone (Iwamoto, 2008; Kapoor, 2009). However,
these studies do suggest that there is efficacy in asthma, although somewhat less than in COPD. Of note, ipratropium bromide, a short-acting anti-cholinergic, has been used in a number of asthma clinical trials as the primary rescue therapy (GlaxoSmithKline, 2004; Israel 2004; Polosa 1991) without any difficulties. In addition, Arg/Arg patients that were simultaneously taken off beta-agonists and placed on ipratropium had a preferential improvement in their lung function (Park 2009). However, it is possible that the asthmatic patients may experience increased exacerbations when switched from LABA/ICS to Tio/ICS. Alternatively, it is possible that some patients, the Arg/Arg patients in particular, may actually do better. This study is designed to monitor these outcomes and patients will be withdrawn if they experience repeated exacerbations. Subjects who experience more than two protocol defined asthma exacerbations within any 6-month period or more than three asthma exacerbations during the 12-month treatment period will be withdrawn from the study.

We have extensive experience in performing studies of such a nature, including studies where patients on inhaled corticosteroids have their inhaled corticosteroids withdrawn (Deykin 200x, Lazarus 2001, Lemanske 2001). All patients will be given the safety instructions that we have successfully used in our previous studies, including how to recognize worsening of asthma control. In addition, a 24-hour emergency clinician/practice contact number will be given.

Two recent publications, a combined analysis of 17 trials and a study of Veterans Administration databases, have suggested that treatment of COPD patients with anti-cholinergic drugs (e.g.: tiotropium bromide) is associated with increased cardiovascular events (heart attack, stroke) and/or death. These increased risks were not observed in individuals treated with tiotropium bromide for less than 6 months, or in patients treated with the short-acting anti-cholinergic drug, ipratropium, when it was combined with an inhaled corticosteroid (ICS).

Boehringer-Ingelheim is the company that makes and sells tiotropium bromide. Boehringer-Ingelheim has reported no increase in either cardiovascular events or deaths in patients treated with tiotropium bromide in their integrated tiotropium bromide database of 10,846 patients who were treated with this drug. This includes a recently published 4 year trial, UPLIFT, where 2987 patients received treatment with tiotropium bromide for four years (Tashkin 2008).

V.B.3. Inhaled Corticosteroids Risks
All subjects will have been on inhaled corticosteroids prior to enrollment in the study. Corticosteroid dosing will not be changed for this study. Nonetheless, subjects will be informed that when taken at high doses for extended periods, inhaled corticosteroids can produce hoarseness, sore throat, and thrush, as well as cause adrenal gland suppression, weight gain, bruising of the skin, and diabetes. These side effects are not anticipated in our studies because of the doses we propose using and the duration of the study. Inhaled corticosteroids have also been associated with reduced growth velocity in children, but subjects in our study will all be age 18 and over.

V.B.4. Risk of Severe Asthma Exacerbation
The risk of increased severe asthma exacerbations will be protected against by close monitoring of the subjects’ data to discover potential severe exacerbations and the outlining of a clear rescue algorithm for any such exacerbations. All study site investigators and personnel will be trained on these potential severe exacerbations and the required rescue procedures. Subjects who experience more than two protocol defined severe asthma exacerbations within any 6-month period, more than three severe asthma exacerbations during the 12-month treatment period or more than four severe asthma exacerbations during the 18-month treatment period will be withdrawn from the study. All subjects will be given the appropriate safety instructions.
regarding the use of study medications. In addition, subjects will be shown a video demonstrating inhaler technique and reviewing the study.

V.B.5. Genetics/Genotyping Risks
A major component of the proposed study is the assessment of the genetic basis for the observed variance in treatment responses in patients with asthma. At present, the clinical significance of the genetic component of variance in the treatment response is unknown. Thus, there are no clear recommendations for genetic counseling for patients who have been genotyped (Kimay-Asadi, 1997; Ober, 1998). Questions also exist about the potential harm to patients in the form of psychosocial consequences from classification with a genotype associated with adverse outcomes. Two areas warrant careful consideration: (a) the psychological stress on the patient and his or her family that comes from knowledge that one is a carrier of a genetic predisposition to an adverse outcome; and (b) the potential for genetic discrimination by employers and insurance companies who may cancel coverage by considering genetic test results proof of preexisting conditions (Kimay-Asadi 1997).

Information about participation in a genetic study may influence insurance and/or employers regarding health status. To help prevent disclosure, information about participation and the result of the research will not be placed in medical records.

V.B.6. Asthma Questionnaires Risks
There are no risks associated with questionnaires.

V.B.7. Procedural Risks

V.B.7.a. Spirometry
Occasionally, individuals may develop a slight dizzy feeling and/or temporary cough and/or chest discomfort when performing breathing tests. These tests are used in hundreds of laboratories throughout the world on a daily basis without harmful effects.

V.B.7.b. Bronchodilator Reversibility Testing
Taking the four puffs of albuterol that are required for this test can make the heart race or make one feel jittery. Less often it can increase blood pressure, or cause nausea or headache. These feelings are temporary and have not been associated with significant adverse effects in clinical practice.

V.C. Adequacy of Protection Against Risks
V.C.1. Recruitment and Informed Consent
For this protocol amendment, the DCC Site Management group will work with the PI and study team to draft an Informed Consent Amendment template for re-consenting those subjects currently in the study that will explain the increase in study duration and assessments. For subjects enrolled under this amended protocol, a new Informed Consent Form template will be provided that reflects the current parameters. These templates will be approved by site IRBs along with the amended study protocol. Once approved, the templates will be provided to all participating sites to be tailored to their site-specific needs. All site informed consent forms for the proposed studies will need to be approved by the DCC and by the site’s IRB. All subjects will be provided with the applicable informed consent form when the study site investigators have determined they may be an acceptable candidate for randomization. The Informed Consent form, the aims of the study, the tests and procedures, data collection, follow-up requirements, and all potential risks and benefits of the study will be discussed with the subject
by qualified study site personnel. Informed consent will be obtained before any study data is captured and before specimens are collected. Documentation of this process will be required. Subjects enrolled under the original protocol must sign the Informed Consent Amendment form, subjects enrolled under this protocol amendment must sign the new Informed Consent Form and these documents must be maintained at the site as part of the subject’s records (which will be separate from their medical records). No subjects will be enrolled without documentation of informed consent and no waivers of this process will be sought or granted.

V.C.2. Adverse Event Monitoring
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 will be monitored throughout the study and reported to a DSMB and will be managed according to processes described below.

V.C.2.a. Asthma-Related Adverse Events
Asthma exacerbations are defined using current consensus guidelines. All asthma exacerbations will be closely monitored as outlined above in section V.B.4. A dedicated eCRF will be designed to capture data on any reported asthma exacerbations. The subjects’ monthly questionnaire responses will be monitored for potential asthma exacerbations as outlined and subjects will be contacted to ensure that adequate information has been provided on each event and appropriate actions have been taken by the study sites regarding the exacerbation. Any subject who experiences more than two protocol defined severe asthma exacerbations within any 6-month period, more than three asthma exacerbations during the 12-month treatment period or more than four severe asthma exacerbations during the 18-month treatment period will be withdrawn from the study.

V.C.2.b. Non-Asthma Adverse Events
Adverse events (AEs) due to concurrent illnesses other than asthma may be grounds for termination from the trial if the illness is considered significant by the investigator or if the subject is no longer able to participate effectively 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.

All subjects will be trained to recognize adverse events associated with their asthma control. They will receive written instructions on the use of medications and asthma monitoring devices. If a subject experiences an adverse event, the subject will contact his local physician. The local physician will evaluate the subject, either on the phone and/or in-person if needed, and determine the nature and severity of the event, and whether or not it is related to the study procedures or medications. The investigator will ensure appropriate site documentation, subject management, and follow up to resolution.

Documentation of an AE unrelated to asthma and any relevant treatment will be recorded by the site in the EDC database on appropriate forms that will capture a description of the illness, dates of illness, treatment of illness (if medications doses and dates will be recorded), whether hospitalization or emergency treatment was required, and the outcome.
V.C.2.c. **Serious Adverse Events**

Serious Adverse Events (SAEs) will be defined following ICH Guidelines as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, in-patient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse study medication experience when, based upon appropriate medical judgment, they jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Site personnel will be instructed to report any AEs meeting these criteria within 24 hours of their knowledge of the event so study investigators can determine if any expedited reporting or source documentation review is necessary. All SAEs will be monitored by the DSMB.

IV.C.3. **Management of Asthma Exacerbations**

Following randomization, asthma management, including management of all asthma exacerbations, will continue under the direction of the patient’s primary care or specialist physician. Patients will be asked to continue their assigned tiotropium or salmeterol medication while still participating in the study regardless of changes in their inhaled corticosteroid or systemic corticosteroid dose unless the treating physician considers such therapy to be contraindicated. Patients will be asked to keep a record of all medications and dosages during exacerbations.

V.C.4. **Data and Safety Monitoring Plan**

A Data Safety Monitoring Board (DSMB) or appropriate equivalent as deemed necessary by the funding organization will be established. The DSMB members will be chosen following appropriate guidelines and will be managed by the CCC at Brigham and Women's Hospital ARC. Pseudo-unblinded statistical tables will be prepared for the board by the DCC. The DSMB will have access to this subject data on a pre-determined regular basis in the form of reports to the Board. The group will have authority to end the trial preemptively if mandated by pre-specified stopping rules determined at the start of the study. Any adverse events will be reported in the study database and documented in appropriate progress reports. Annual reports will also be prepared by the CCC for annual IRB approvals as needed.

All study data will be monitored and source-verified by the PBRN central site staff with additional auditing and oversight by the DCC. The percentage and type of data to be monitored, the frequency of monitoring and specific monitoring procedures will be outlined in a Monitoring Plan created at the start of the study.

The involved sites will be instructed to report all adverse events on the study case report forms in a timely fashion to the DCC and to their IRB per IRB guidelines. Furthermore, sites will be trained that any events meeting serious criteria (Serious Adverse Events (SAEs)) should be reported to the DCC and their site IRB within 24 hours of their knowledge of the event. The DCC will ensure that the study PI is notified of reported SAEs immediately, following Standard Operating Procedures and using a fully validated system.

V.C.5. **Data Confidentiality**

Potential risks to data confidentiality will be mitigated by requirements for the de-identification of all study data and by security protocols for all data capture systems. All users of the EDC system will be tracked and provided access in a secure fashion following established DCC Standard Operating Procedures (SOPs) for this process. Specifically regarding the genotyping
data, to provide the best protection to research participants, subjects will be assured of complete confidentiality of the test results. As with all research data, information gathered by the study will be used only for aggregate analysis; it will not be released with any information that identifies research participants. Information about genotypes, in particular, will be coded and unlinked to individual respondent identifiers. The genotyping facility will not have access to patient-identifying information. The code to link respondents and their genotype will be securely stored and accessible only to the database programmer at the DCC. The DCC does not have access to the identities of patients. That information is retained at the clinical centers. Respondents will be informed that genotyping at loci related to asthma is valuable for research purposes, and in aggregate form only.

V.D. Potential Benefits and Importance of the Knowledge to be Gained

V.D.1. Benefits to Human Subjects and Others

While there is a small potential benefit to those individual subjects (particularly the Arg/Arg subjects) randomized to the Tio/ICS treatment arm, overall, there are no expected direct benefits to the majority of individual subjects; however, there is a potential benefit to patients with asthma in general as the possibility of a more rational basis for therapy is devised. As outlined above, there is a large evidence gap in the treatment of asthma with LABA’s in this population and there is certainly a great deal of risk of mortality and exacerbation in the population. Any chance to determine a method to close this gap and learn how better to treat these subjects in clinical practice, presents a clear benefit to Black asthmatics as a whole.

The risks associated with the treatments in this study are identifiable and are not significantly worse than those associated with treatments of asthma outside the study. The proposed study has considered the potential risks and identified procedures and methods to protect subjects against these risks. As such, the risks to study participants seem reasonable in relation to the large potential benefit to patients.

V.D.2. Knowledge to be Gained

Based on the published literature examining Blacks and the data presented in our Preliminary Data, we expect that we will not be able to demonstrate that LABA/ICS combination therapy is superior to Tio/ICS as judged by time to exacerbation. We further expect that based on the data published, that LABA/ICS will not be superior to Tio/ICS in many of the secondary outcomes related to asthma control, quality of life, and symptom free days. However, in the context of the potential risk to Blacks from regimens containing LABA, we anticipate that these results will weigh heavily on reconsideration of the national treatment recommendations for Blacks. As indicated in a letter from Dr. William Busse, Chair of the National Asthma Education Program 2007 Guidelines Committee, this study would cause the Committee to strongly consider revising its guideline recommendations. To the extent that a component of the current excess mortality and/or serious morbidity from asthma in Blacks may be contributed to by the effect of LABAs, such a change would serve to narrow some of the disparity between Blacks and Caucasians related to asthma.

If we do find that LABA/ICS is superior to Tio/ICS, we will have provided important comparative effectiveness data to fill the knowledge gap. Specific data in Blacks provided by this study in regard to the effects of LABA/ICS vs. an alternative will fill the current knowledge gap regarding the effects of these drugs in Blacks. Thus, the information from this study will allow us to use make evidence-based decisions which balance the benefits and risks for LABAs, as advocated in by leading authorities (Kramer 2009).
The work of our second aim will provide further insurance that this comparative effectiveness study has significance. If LABA/ICS is found to be superior to Tio/ICS, it is likely that our pharmacogenetic aim will identify a group of Blacks that more strongly contribute to the lack of response and in whom the risk-benefit analysis would therefore be altered. Further, while we were unclear whether support for the cost of a genome-wide association study was in the purview of this grant, we plan to collect samples to be able to conduct such a study in the future. Thus, this study would further the ability to personalize therapy for this severely impacted population. If we confirm our findings at the Arg16Gly locus of ADRB2, we will have identified an important marker that identifies a subpopulation that may not benefit from LABA/ICS and that shifts the risk/benefit ratio for the use of this product. Lastly, while we believe it unlikely, it is possible that LABA/ICS might be found to be superior to Tio/ICS. That may be reassuring to those Blacks who require add-on therapy for treatment of moderate to severe asthma.

In summary, it is clear than an urgent need to “clear the air” remains in regards to LABA treatment for asthma (Martinez 2005, Beasley 2009). While this study will not clear the air for the entire population, it will allow us to address the risk-benefit for the Black population, and individualize therapy for a population that bears a disproportionate share of the asthma burden.
VI. Anticipated Results and Impact Assessment

Based on the published literature in Blacks and data presented in our Preliminary Data, we expect that we will not be able to demonstrate that LABA/ICS is superior to Tio/ICS as judged by time to exacerbation. We further expect that, based on the data published, LABA/ICS will not be superior to Tio/ICS in many of the secondary outcomes related to asthma control, quality of life, and symptom free days.

VI.A. Impact of Anticipated Results

In the context of the potential risk to Blacks from regimens containing LABA, we anticipate that these results will weigh heavily on reconsideration of the national treatment recommendations for Blacks. As indicated by the letter from Dr. William Busse, Chair of the National Asthma Education Program 2007 Guidelines Committee, this study would cause the Committee to strongly consider revising its guideline recommendations. National asthma-related policy for quality assessment, pay for performance, insurer reimbursement decisions, and care recommendations are based on these NHLBI/National Asthma Education Prevention Program’s asthma guidelines. Thus, such a change would have large repercussions on the national level.

Further, to the extent that a component of the current excess mortality and/or serious morbidity from asthma in Blacks may be contributed to by the effect of LABAs, such a change would serve to narrow some of the disparity between Blacks and Caucasians related to asthma.

If we do find that LABA/ICS is superior to Tio/ICS, we will have provided important comparative effectiveness data to fill the knowledge gap regarding the effects of LABA/ICS vs. an alternative in Blacks. Thus, the information from this study will allow us to make evidence-based decisions which balance the benefits and risks for LABAs, as advocated by leading authorities (Kramer 2009).

The work of our second aim will provide further insurance that this comparative effectiveness study has significance. In the unlikely event that LABA/ICS is superior to Tio/ICS, it is likely that our pharmacogenetic aim (if we confirm our findings at the Arg16Gly locus of ADRB2) will identify a group of Blacks that more strongly contribute to the lack of response and in whom the risk-benefit analysis would therefore be altered. Further, while a genome-wide association study is not the main purpose of the BELT study, we plan to collect samples to be able to conduct such a study in the future. Thus, this study would further the ability to personalize therapy for this severely impacted population.

Additionally, this study would be one of the first practical examples of personalized medicine using data and processes derived from primary care practices (as opposed to efficacy trials based in academic centers). The results (whether they indicate that all Blacks should be using alternative therapies or just those that are Arg/Arg) could be operationalized directly in daily primary care practice by altering treatment regimens for Black patients with asthma. Since the study, including genetic testing will be completed in PBRN practices, the results are more likely to be accepted and more rapidly integrated into daily primary care practice. This would enhance the AHRQ, NIH, and DHHS goals of providing treatment based on the latest advances and tailored to the personal characteristics of individual patients (http://health.nih.gov/topic/PersonalizedMedicine).

All practices participating in this study will also benefit from training in spirometry testing and interpretation of results. Some of the practices have used spirometry testing for several years and others are new to this testing. Each practice will participate in both didactic education and regular audit and feedback on actual patient’s spirometry testing results and interpretation. This
should also facilitate increased use of spirometry in primary care practice. Drs. Yawn, Pace and Israel previously completed an NHLBI study that demonstrated the positive impact of increasing use of spirometry in primary care practices. (Yawn, 2007) We expect similar impact in this study.

In summary, it is clear than an “urgent need to clear the air” remains in regards to LABA treatment for asthma (Martinez 2005, Beasley 2009). While this study will not clear the air for the entire population, it will allow us to address the risk-benefit for Blacks and individualize therapy for a population that bears a disproportionate share of the asthma burden.

VI.B. Data Sharing and Trial Information

VI.B.1. ClinicalTrials.gov
This trial will be registered on clinicaltrials.gov prior to study start-up and updated on an annual basis or as the protocol changes.

VI.B.2. Data Sharing Plan
The Investigators are committed to ensuring that study results are disseminated to stakeholders and clinicians in order to allow the study results to be translated into practice. The plan for this dissemination and translation is outlined in section IV.L. In addition, the PI and Co-investigators recognize the importance of data sharing to optimizing the value of supporting this trial, and also the obligation to allow access to data in this proposed study funded by tax dollars. The study investigators is committed to allowing access to data scrubbed of any patient identifying information, including names, initials, dates of birth, or medical record numbers. The study PI and Co-Investigators will review applications for ancillary studies and distributing study data to qualified parties. After the study is completed and its results thoroughly disseminated, the data sets will be placed in public archives scrubbed of identifying information as described in NIH notice NOT-OD-02-035.
### VII. List of Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AAFP NRN</td>
<td>American Academy of Family Physicians National Research Network</td>
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<td>ACRN</td>
<td>Asthma Clinical Research Network</td>
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<td>ACQ</td>
<td>Asthma Control Questionnaire</td>
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<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>AHRQ</td>
<td>Agency for Health Research and Quality</td>
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<tr>
<td>AQLQ</td>
<td>Asthma Quality of Life Questionnaire</td>
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<td>ASFDQ</td>
<td>Asthma Symptom-Free Day Questionnaire</td>
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<tr>
<td>ASUI</td>
<td>Asthma Symptom Utility Index</td>
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<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>BWH</td>
<td>Brigham and Women's Hospital</td>
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<tr>
<td>CCC</td>
<td>Clinical Coordinating Center</td>
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<tr>
<td>DCC</td>
<td>Data Coordinating Center</td>
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<td>DSBM</td>
<td>data and safety monitoring board</td>
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<tr>
<td>eCRF</td>
<td>electronic case report form</td>
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<td>EDC</td>
<td>electronic data capture</td>
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<td>GWAS</td>
<td>genome wide association study</td>
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<tr>
<td>HCRI</td>
<td>Harvard Clinical Research Institute</td>
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<tr>
<td>HRQOL</td>
<td>health-related quality of life</td>
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<td>ICS</td>
<td>inhaled corticosteroid</td>
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<tr>
<td>IRB</td>
<td>institutional review board</td>
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<td>LABA</td>
<td>long-acting beta agonists</td>
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<tr>
<td>LTRA</td>
<td>leukotriene receptor agonists</td>
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<tr>
<td>MOP</td>
<td>manual of operations</td>
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<tr>
<td>NEJM</td>
<td><em>New England Journal of Medicine</em></td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>OMC</td>
<td>Olmsted Medical Center</td>
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<tr>
<td>PBRN</td>
<td>practice-based research network</td>
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<tr>
<td>PEF</td>
<td>pulmonary function test</td>
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<tr>
<td>PFT</td>
<td>pulmonary function test</td>
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<tr>
<td>PHCPGM</td>
<td>Partners and Harvard Center for Pharmacogenetic Medicine</td>
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<tr>
<td>SAE</td>
<td>serious adverse event</td>
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<tr>
<td>Tio.</td>
<td>tiotropium</td>
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</table>
VIII. References


(Isreal 1993). Israel, E., A. Fischer, M. Rosenberg, C. Lilly, J. Cohn, P. Rubin and J. Drazen. Inhibition of the physiological response and mast cell activation


