Asthma Clinical Research Network

Measuring Inhaled Corticosteroid Efficacy (MICE)

Study Protocol

A study to evaluate parameters of efficacy for beclomethasone dipropionate and fluticasone propionate administered at doses of increasing biosystemic effect in patients with persistent asthma.

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Measuring Inhaled Corticosteroid Efficacy (MICE)

I.   Purpose: To Obtain Measures of Efficacy

Purpose: To obtain estimates of the degree of variability for various efficacy parameters in relation to systemic effect for two inhaled corticosteroids, specifically beclomethasone dipropionate and fluticasone propionate.

To develop a model to proceed to study the efficacy/systemic effect relationship of selected inhaled corticosteroids.

The overall goal is to develop methodology to define a therapeutic index for the efficacy-systemic effect for inhaled corticosteroids.

II.   Background and Rationale

A.   Introduction

Inhaled corticosteroids are being recommended for use in asthma treatment both more frequently and at higher doses than before (1,2). Since corticosteroids have multiple and potential adverse systemic effects (1,2), it is essential to be able to compare the different inhaled corticosteroids and delivery systems available with respect to both beneficial and systemic effects. While several inhaled corticosteroids (with differing *in vitro* potencies and pharmacokinetic characteristics) and inhaled delivery systems are presently available, and others are expected to be introduced in coming years, *in vivo* beneficial and systemic effects data comparing these inhaled corticosteroids and delivery systems are lacking. Early beneficial effects are apparent in measurements of pulmonary function, specifically FEV_1, FEV_1/FVC, PEFR and PEFR variability, while effects on methacholine and exercise induced bronchospasm are recognized over several weeks. However, the time course of effect on altering measures of airway inflammation, such as induced sputum cytology, is not known. In this MICE study we propose an experimental paradigm in which inhaled corticosteroids and delivery systems are characterized in terms of efficacy and systemic effect parameters so that doses which produce "equi-systemic" effects can be compared in relation to selected efficacy parameters.

As a network, we acknowledge that growth in children and connective tissue parameters are important indicators of systemic absorption; but due to the slow rate of change in these outcome measures, they do not lend themselves to rapid evaluation. We, therefore, propose to use plasma cortisol profiles (determined over time) which are a sensitive and reproducible indicator of basal adrenal function (3,4) as our index of systemic steroid effect. Urine cortisol excretion will be a secondary measure of adrenal suppression.

There have been few comparisons of the efficacy of inhaled corticosteroids one to another. Available data consist of: 1) head-to-head studies of beclomethasone dipropionate (BDP) and budesonide (BUD) or fluticasone propionate (FP) and 2) comparison of the ability of BDP, triamcinolone acetonide (TAA), and flunisolide (FLU) to inhibit antigen-induced bronchoconstriction (5).

Based on the minimal available data the revised Expert Panel Report 2, National Asthma Education and Prevention Program Guidelines for the Diagnosis and Management of Asthma (2) provided dosing guidelines that reflect an equivalency ranking with an approximate ratio 2:1:0.5 based on microgram equivalents:

TAA = FLU > BDP = BUD (Metered dose inhaler) > BUD (Turbuhaler) = FP

These ratios are based largely on corticosteroid receptor binding properties and rank order in the vasoconstrictor assay for the various corticosteroids. Unfortunately, there is very limited information to substantiate these comparative ratios based on clinical parameters, specifically measures of beneficial effect and adverse systemic effects.

The British Thoracic Society asthma treatment guidelines are somewhat similar (6). It is important to note that the data supporting these rankings and ratios are limited and are not derived from a single comparative study, but rather from multiple studies, not all of which examined efficacy in the treatment of persistent asthma (7). Because of the importance of this question to the practitioner treating subjects with asthma, a clinical study is needed on which to base dose comparisons.

We propose upon completion of this study to compare the efficacy in chronic asthma treatment of three different doses of selected inhaled corticosteroids (and their respective delivery systems) in a full protocol entitled "Measuring Inhaled Corticosteroid Efficacy (MICE)." We plan to use doses which have been demonstrated to have comparable systemic effects (suppression of cortisol) in the preceding ACRN trial entitled "Dose of Inhaled Corticosteroids with Equisystemic Effects" (DICE). We propose to use doses of inhaled corticosteroid for the full MICE protocol as derived from DICE which induce minimal (highest deliverable dose that caused less than 5% cortisol suppression) cortisol suppression, 20-30% cortisol suppression, and 40-60% cortisol suppression. The intent is to determine if different inhaled corticosteroids which have equisystemic effects have differential salutary therapeutic effects in chronic asthma or if therapeutic efficacy parallels systemic effects.

The design of this study originally intended to use FEV_1 as the primary efficacy variable and to evaluate data on the following secondary efficacy variables: post-bronchodilator maximum FEV_1, bronchial responsiveness to methacholine, exercise-induced bronchospasm, peak expiratory flow, variability in peak expiratory flow, FEV_1/FVC ratio. In addition, for research purposes, exhaled nitric oxide, and inflammatory airway infiltration as measured in induced sputum will be evaluated. Unfortunately, there is no study that matches the proposed study design and it is therefore not feasible to utilize previous studies to determine sample size. For

example, based on a careful review of the literature, specifically data available on the FEV_1 response to inhaled corticosteroids, it was determined that it would be necessary to randomize 116 subjects to each of the inhaled corticosteroid treatment arms. This study would be cost prohibitive. There is a single study on exercise challenge (8) that did show a dose response relationship with budesonide and this may be a promising method to define a dose response relationship. However, skepticism has been raised regarding the reproducibility of these data, thus necessitating validation of the procedure. To date, there have been no studies that have examined the efficacy/systemic effect of any inhaled corticosteroid on methacholine bronchial challenge, exhaled nitric oxide, or airway inflammation as measured in induced sputum. The latter are promising methods to evaluate clinically meaningful measures of inhaled corticosteroid efficacy.

Before the full MICE protocol can begin, it is important to conduct a smaller study to explore, utilizing two prototypical drugs, whether any of the proposed efficacy/systemic effect relationships suggest that: 1) The variability of the efficacy/systemic relationship is small enough that the main MICE study would be practical, and 2) There might be a difference in therapeutic index between drugs. This study will also incidentally provide insight into the time and dose response effect on selected indicators of clinical response. To date, this has not been defined despite the recommendation to use incremental doses based on level of severity and for extended periods of time. This study alone could produce enough preliminary data to provide insight into the proper use of inhaled corticosteroids in managing moderate to severe asthma safely and effectively.

B. Specific Aims

The specific aims of this study are:

1. to measure the variability of the efficacy/systemic relationship of two inhaled corticosteroids (ICS) for different outcome measures of efficacy using beclomethasone dipropionate (BDP) and fluticasone propionate (FP) both with the Opti-Chamber spacer device. The ICS will be administered in doses of increasing systemic effect to examine the corresponding effects on pulmonary function, bronchial hyperresponsiveness, asthma control, and resolution of airways inflammation in subjects with persistent asthma.
2. to confirm the estimates of systemic effect for BDP and FP, derived from the DICE pilot trial, where it was administered in one week intervals to that which occurs when BDP and FP doses are administered over three - six week intervals with incremental increases in dose.
3. to explore which efficacy/systemic relationships, if any, suggest that there may be a difference between the two prototype inhaled corticosteroids, BDP and FP.

C. Research Questions

Despite the variety of inhaled corticosteroids which can be used for asthma therapy, there remains confusion and continued controversy as to the relative efficacy and risk for systemic effects from these agents. Because of this, the choice of inhaled corticosteroid is often made based on convenience (number of micrograms per actuation, taste, or subject preference) or cost. The confusion surrounding the choice of an inhaled corticosteroid will be further confounded by the anticipated introduction of newer and potentially more potent inhaled corticosteroids and novel inhaled drug delivery systems. The goal of this trial is to determine the feasibility of identifying an efficacy/systemic relationship for changes in pulmonary function and markers of inflammation following incremental increases in systemic effect of the doses of BDP and FP. The doses of BDP and FP are selected based on the results of a pilot study that measured cortisol suppression following increased doses of these two inhaled corticosteroids with each steroid dose administered over a one week interval.

Ultimately, we would like to determine whether any of the available inhaled corticosteroids, when administered by their respective delivery systems at doses with comparable systemic effects, possess superior efficacy.

In this study, we will evaluate post-pubertal adolescents and adults up to 55 years of age with persistent asthma (FEV$_1$ 55-85% of predicted), a bronchodilator response ($\geq$12% and >200 ml improvement of FEV$_1$ after treatment with albuterol metered dose inhaler), and a PC20 to methacholine $\leq$8 mg/ml to answer the following questions:

1. What is the degree of variability in the efficacy/systemic effect relationships for the various measures of efficacy (pulmonary function, bronchial hyperresponsiveness and asthma control), using inhaled corticosteroids BDP (Vanceril Double Strength, 84 mcg per inhalation) and FP (Flovent-44, 44 mcg per inhalation), when they are administered with the Opti-Chamber spacer in doses resulting in minimal cortisol suppression (<5%), 20-30% cortisol suppression and 40-60% cortisol suppression?

2. Are the equisystemic doses based on short term administration (one week) in the DICE pilot trial for beclomethasone dipropionate similar to that obtained with long term administration (six weeks)?

3. What is the time-response relationship of the various markers of efficacy for an inhaled corticosteroid, such as BDP and FP, when they are administered over a treatment period of 18 weeks consisting of an integrated increase in dose over three treatment periods?

4. Are there apparent differences in the efficacy/systemic relationships between BDP and FP? Can we derive a useful model to evaluate efficacy/systemic effect relationships of inhaled corticosteroids?

In the full MICE study, we intend to study the same type of subject population as the MICE study and compare six different inhaled corticosteroids to answer the following questions:

1. Do the equisystemic doses of steroid-inhaler combinations as determined from the DICE trial provide equivalent therapeutic efficacy in the treatment of chronic persistent asthma?
2. Does any steroid-inhaler combination possess a superior risk:benefit ratio, defined by the efficacy/systemic effect relationship, in the treatment of subjects with persistent asthma?

D.   Rationale for Choosing These Questions

It is clear from previous work that while inhaled corticosteroids remain potent and important anti-inflammatory agents in the arsenal of medications used to treat asthma, our understanding of these drugs as they relate to one another is extremely limited. Whether dose-response relationships exist and whether a plateau of beneficial effects occur are also not known. It is generally recognized that there is some risk for systemic adverse effects from inhaled corticosteroids, however, considerable controversy persists over the magnitude of such risks. The relative potencies of different inhaled corticosteroid preparations and the impact of new delivery systems on the risks for adverse effects are unclear, and the available data provide little information regarding the optimal dose or steroid of choice, if any exists, among the presently available agents (7). As inhaled corticosteroid therapy is now recommended earlier in the course of treatment of asthma (1,2), it is important to further our understanding of these medications so they can be optimally used. This is especially important with new and potentially more potent inhaled corticosteroids, as well as the different inhalation delivery systems on the horizon. Further understanding of the differences between the available inhaled corticosteroids, if any, will allow for more rational selection and prescribing.

Eventual comparison of the newer agents, budesonide and fluticasone propionate, in the full MICE protocol will help determine whether their purported advantages and those determined from drug pharmacokinetic studies, *in vitro* assays, and animal models, translate to clinically significant improvements in their efficacy and safety profiles. The impact of the new dry powder delivery devices on efficacy and risk for adverse effects can also be evaluated using this model.

Further, this study will allow us to choose the most appropriate outcome variables to answer these questions and help us to determine the necessary sample size.

E.   Rationale for Choosing these Outcome Indicators

In assessing potency relationships of the available inhaled corticosteroids, most studies have relied on peak flow measurements and FEV_1. While these pulmonary

function measures can be correlated to improvements in clinical outcome, their sensitivity in defining an efficacy/systemic relationship for a specific inhaled corticosteroid is limited (7,8). Nevertheless, we will use this base of literature to designate FEV_1 as our primary efficacy measure. It is also recognized that near maximal improvements in FEV_1 and peak flow occur within a few weeks of treatment, but significant improvements in other outcome measures are slower in onset. Specifically, measures of airway sensitivity to methacholine and exercise, take longer but could be more sensitive measures of an efficacy/systemic effect relationship. These measures are thought to be indicators of resolving inflammation. Some of the more direct measures of airway inflammation, such as cytology from induced sputum and exhaled nitric oxide, have not been examined for their time of onset and their ability to reflect efficacy/systemic effects. The combination of these parameters in the MICE study will define the time of onset of effect and sensitivity to systemic effects of different doses for each of these important measures of effect. Once a clear efficacy/systemic effect is determined for a specific measure, then the number of efficacy measures applied in further studies can be limited. This will have a significant effect on the resources needed and the number of procedures performed per subject to conduct an adequate study of comparative effects of the various inhaled corticosteroids. This will reduce the cost, inconvenience and risk of performing studies to define the efficacy/systemic effect relationship of inhaled corticosteroids.

Therefore, in evaluating the results of this study, measures of pulmonary function (peak flow, spirometry), airway hyperresponsiveness (exercise and methacholine challenge), medication use, and asthma control will be of clinical interest. In addition, measures of induced sputum cytology and exhaled nitric oxide will be of research interest only with limited clinical application at this time.

F.   Limitations on Interpretation

1.   The age band will be post-pubertal to 55 years. Thus, the results cannot be directly applied to older or younger age groups.
2.   The short duration of this study will not provide information on effects of chronic inhaled corticosteroid use; e.g. maximal effect on pulmonary function and airways responsiveness to exercise and methacholine, and resolution of inflammation. There will also be no assessment of the potential risk of clinically significant adverse effects such as glaucoma, cataracts and osteoporosis.
3.   The results will not necessarily be predictable of efficacy/systemic effect of other inhaled corticosteroids and delivery devices.

III.   Protocol Overview (See Figure 1, page 8)

This will be a 24-week, randomized, open-label, prospective multicenter trial examining the effect of inhaled BDP and FP administered via Opti-Chamber on different outcomes in subjects with persistent asthma. A total of 30 subjects will be enrolled with 15 subjects randomized to each of the two inhaled corticosteroids. The
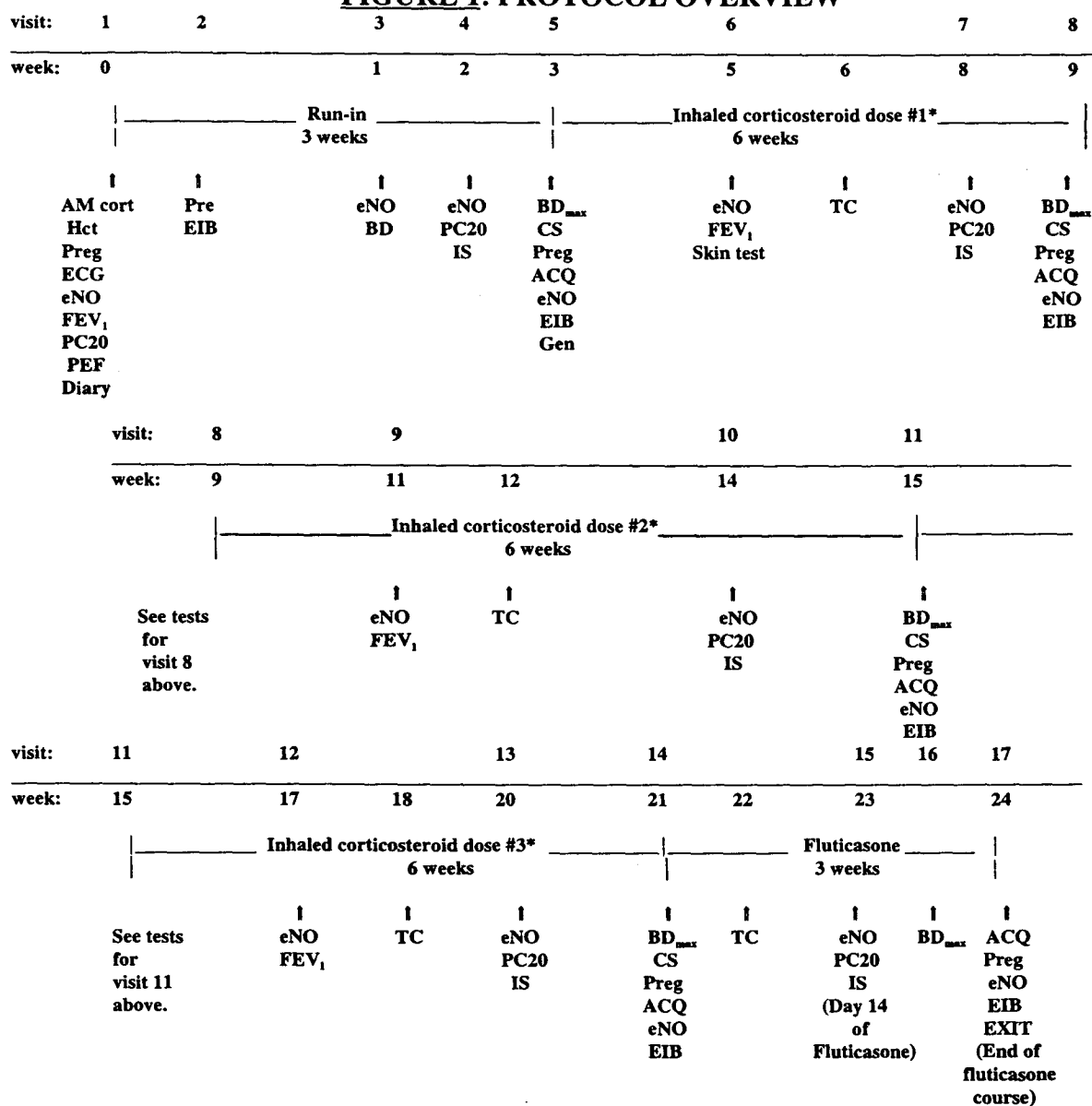
doses selected for BDP and FP are based on doses that result in minimal (< 5%), 20-30%, and 40-60% cortisol suppression as derived from data in the DICE pilot protocol. After a three week run-in period, during which the subjects will receive placebo inhaler and as needed albuterol, to reinforce training and compliance, subjects will receive either BDP or FP with Opti-Chamber at a dose that results in an anticipated minimal cortisol suppression. For BDP, subjects will receive Dose #1, one inhalation twice daily (168 mcg per day) for the next 6 weeks. After 6 weeks, the subjects will then increase their dose to Dose #2, 4 inhalations twice daily of BDP (672 mcg per day), a dose anticipated to result in 20-30% cortisol suppression for an additional 6 weeks. After 6 weeks, the subjects will then increase their dose to Dose #3, 8 inhalations twice daily of BDP (1344 mcg per day), a dose anticipated to result in 40-60% cortisol suppression for an additional 6 weeks. The corresponding doses of FP will be: Dose #1, 1 inhalation twice daily (88 mcg per day); Dose #2, 4 inhalations twice daily (352 mcg per day); and, Dose #3, 8 inhalations twice daily (704 mcg per day).

Following the 18 weeks of inhaled corticosteroid administration, the subjects will discontinue the study dose of inhaled BDP or FP with Opti-Chamber and administer fluticasone propionate, Flovent Diskhaler 250, 4 inhalations twice daily (2000 mcg per day), inhaled for 21 days to achieve maximal possible steroid effect in order to determine if a plateau was reached with the previous course of inhaled corticosteroid. This dose of inhaled fluticasone propionate has been demonstrated to provide a comparable effect to a starting dose of 40 mg per day of oral prednisolone followed by a 5 mg per day titration schedule in the treatment of a severe asthma exacerbation (9).

Beginning with the screening period, the subjects will record in a daily diary their daytime and nighttime symptoms (dyspnea, wheeze, cough, each scored 0 - 3), AM and PM PEF, β-agonist use, and intercurrent illnesses and hospitalizations. They will visit the clinical center every 2-3 weeks for an interval history and physical examination, diary review and spirometry. Cortisol suppression and exercise challenge will be performed upon entry into the study (week 3) and at the end of each inhaled corticosteroid dose (weeks 9, 15 and 21). Exercise challenge will also be performed at the end of the inhaled fluticasone propionate treatment arm (week 24). Bronchial challenge with methacholine and sputum induction for analysis of markers of inflammation will be conducted prior to randomization (week 2), within one week prior to ending each inhaled corticosteroid dose (weeks 8, 14 and 20), and two weeks after starting inhaled fluticasone propionate (week 23).

The efficacy parameters that will be evaluated in the study include FEV_1, post-bronchodilator maximum FEV_1, change in PC_{20} based on methacholine-induced bronchospasm and inhibition of exercise-induced bronchospasm. Additional outcomes will include, resolution of inflammation based on changes in sputum cytology, rate of improvement in FEV_1 over time, changes in exhaled nitric oxide, symptom free days, and changes in asthma control as assessed by the asthma control questionnaire (10).

FIGURE 1: PROTOCOL OVERVIEW

visit:	1	2		3	4	5	6		7	8
week:	0			1	2	3	5	6	8	9

|—————————— Run-in ——————————|——————————Inhaled corticosteroid dose #1*——————————|
       3 weeks   6 weeks

AM cort	Pre		eNO	eNO	BD_max	eNO	TC	eNO	BD_max
Hct	EIB		BD	PC20	CS	FEV₁		PC20	CS
Preg				IS	Preg	Skin test		IS	Preg
ECG					ACQ				ACQ
eNO					eNO				eNO
FEV₁					EIB				EIB
PC20					Gen				
PEF									
Diary									

visit:	8	9		10	11
week:	9	11	12	14	15

|——————————Inhaled corticosteroid dose #2*——————————|——————|
                     6 weeks

See tests	eNO	TC	eNO	BD_max
for	FEV₁		PC20	CS
visit 8			IS	Preg
above.				ACQ
				eNO
				EIB

visit:	11	12		13	14		15	16	17
week:	15	17	18	20	21	22	23		24

|—————————— Inhaled corticosteroid dose #3* —————————|——————— Fluticasone ———————|
                6 weeks   3 weeks

See tests	eNO	TC	eNO	BD_max	TC	eNO	BD_max	ACQ
for	FEV₁		PC20	CS		PC20		Preg
visit 11			IS	Preg		IS		eNO
above.				ACQ		(Day 14		EIB
				eNO		of		EXIT
				EIB		Fluticasone)		(End of
								fluticasone
								course)

*Beclomethasone dipropionate (84 mcg per inhalation of Vanceril Double Strength with OptiChamber) doses are based on results from the DICE pilot study: dose #1 = 1 inhalation twice daily (168 mcg per day), dose #2 = 4 inhalations twice daily (672 mcg per day), and dose #3 = 8 inhalations twice daily (1344 mcg per day). Inhaled fluticasone propionate (Flovent Diskhaler 250), four inhalations twice daily.

*Fluticasone propionate (44 mcg per inhalation of Flovent-44 with OptiChamber) doses are based on results from the DICE pilot study: dose #1 = 1 inhalation twice daily (88 mcg per day), dose #2 = 4 inhalations twice daily (352 mcg per day), and dose #3 = 8 inhalations twice daily (704 mcg per day). Inhaled fluticasone propionate (Flovent Diskhaler 250), four inhalations twice daily.

key: AM cort = morning plasma cortisol concentration; Hct = hematocrit; Preg = pregnancy test; ECG = electrocardiogram; eNO = exhaled nitric oxide measured before spirometry; FEV₁ = spirometry; PC₂₀ = methacholine challenge; PEF = peak flow (daily throughout the study); diary = symptom diary (daily throughout the study); Pre EIB = Pre-exercise challenge; BD = spirometry before and with reversibility after bronchodilator treatment; BD _max_ = spirometry before and with maximum reversibility with bronchodilator; IS = induced sputum; CS = cortisol suppression measured by 24-hour urinary cortisol (7 am - 7 am) and 12-hour, hourly plasma cortisol concentrations (7 pm - 7 am) beginning 24 hours before pulmonary function testing; gen = genetics analysis; EIB = exercise challenge; ACQ = Asthma Control Questionnaire; skin tests = allergen skin tests; TC = telephone call; EXIT = completion and discharge from study.

A. Screen

1. Subject meets inclusion criteria (see Section IV, A).
2. No exclusion criteria present (see Section IV, B).

B. Subjects

This study will require a total of 30 post-pubertal adolescents and adults with asthma. Since this is a small study population we will waive the usual requirement of distribution by gender (50% female) and by ethnicity (33% ethnic minority). The rapidity of recruitment is greatly facilitated by the involvement of several geographically dispersed study sites in a multicenter collaboration. Subjects will be recruited from the "standing" populations of the participating centers, by advertisement, and by referral from participating physicians. The ACRN Data Coordinating Center (DCC) will distribute monthly accrual reports for each clinical center, listing the number of subjects entered. This routine monitoring will allow early identification and resolution of potential problems in recruitment.

C. Treatment

This is a two treatment, parallel study incorporating two inhaled corticosteroids, BDP and FP, in increasing doses. The treatment arms design will start with placebo, then one inhalation, four inhalations, and eight inhalations twice daily of Vanceril Double Strength (84 mcg per inhalation), and one inhalation, four inhalations, and eight inhalations twice daily of Flovent-44, each administered with an Opti-Chamber.

In addition to randomized treatment with escalating doses of the two inhaled corticosteroids, BDP or FP, all subjects will receive a three week course of inhaled fluticasone propionate (Flovent Diskhaler 250, four inhalations twice daily) to determine whether a maximal or plateau effect on the various asthma control parameters has been achieved.

D. Inhaled Corticosteroid Administration

BDP or FP will be administered twice daily at 5-10 AM and 8 PM -12 AM, with specific μg doses determined from the DICE pilot trial. The doses selected have been shown to cause, <5%, 20-30% and 40-60% cortisol suppression (overnight plasma cortisol determination) in the DICE pilot study.

The same inhaled corticosteroid, propellant, and delivery device will be used throughout the study for each subject in order to minimize variability attributed to medication. The Opti-Chamber spacer device will be incorporated. A mouth rinsing technique will be applied following each medication administration to minimize oral absorption.

E. Rationale for Increasing Doses Without a Washout Period

The study proposed will utilize a classic dose-response design in which the dose of the inhaled corticosteroid is progressively increased. While we could have proposed a design in which the doses are administered randomly with washout periods, we feel there are scientific and practical drawbacks to such a design. A random design would be subject to the significant possibility of carryover effects when a larger dose of an inhaled corticosteroid preceded a smaller dose of an inhaled corticosteroid. In order to try to eliminate such carryover effects, we would have to introduce a washout period long enough to assure that prior effects of the larger dose had waned and that the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis had recovered. The appropriate length of such a washout period has not been experimentally established, and would likely need to be relatively long, especially with high doses of an inhaled corticosteroid. Utilizing the classic escalating dose-response design minimizes these uncertainties. Furthermore, we considered that even in the very unlikely case that a carryover effect did exist from prior use of a lower dose of an inhaled corticosteroid, it would be no greater than any effect that would occur when these medications are used as currently prescribed, specifically for long term, extended use. We therefore saw no advantage to introducing a washout period since it would appear to merely extend the length of this study.

F. Study Visits

1. Visit 1 (Begin run-in)
   a. informed consent (if not already obtained)
   b. plasma cortisol concentration (prior to 9:30 AM) and hematocrit; pregnancy test for female subjects
   c. long physical exam
   d. electrocardiogram
   e. low dose ACTH test, if needed
   f. exhaled nitric oxide followed by spirometry
   g. methacholine challenge (if needed to meet eligibility requirements)
   h. inhaler technique reviewed and rescue medication (albuterol) dispensed (refills dispensed as needed throughout remainder of trial)
   i. placebo (identical to Vanceril Double Strength) inhaler (administered as 2 inhalations twice daily) dispensed
   j. AirWatch™ dispensed and appropriate technique assured
   k. diary cards explained and dispensed

2. Visit 2 (Continue run-in)
   a. subject returns 1-4 days after Visit 1
   b. qualifying exercise challenge performed

3. Visit 3 (Continue run-in)
   a. subject returns one week after Visit 1 (screening visit)
   b. exhaled nitric oxide followed by spirometry with reversibility (before and after treatment with bronchodilator, 2 inhalations albuterol MDI)
   c. AirWatch™ and OptiChamber technique reviewed and adherence to protocol assessed; placebo inhaler (administered as 2 inhalations twice daily) continued
   d. symptom diary reviewed and dispensed
   e. AirWatch™ continued

4. Visit 4 (Continue run-in)
   a. subject returns one week after Visit 3
   b. exhaled nitric oxide followed by spirometry
   c. methacholine challenge
   d. induced sputum
   e. symptom diary, and OptiChamber and AirWatch™ techniques reviewed
   f. dispense urine collection materials and provide instructions on collection procedures

5. Visit 5 (Randomization, begin inhaled corticosteroid dose #1 in am)
   a. subject returns one week after Visit 4
   b. beginning 12 hours before scheduled visit start 24 hour urine collection (7 am - 7 pm, 7 pm - 7 am) for measurement of cortisol suppression
   c. administer Asthma Control Questionnaire
   d. placebo inhalers returned, compliance reviewed
   e. obtain spirometry before and after increasing doses of bronchodilator for maximum reversibility
   f. pregnancy test for female subjects
   g. randomize to treatment arm if eligibility criteria are met
   h. collect blood for genetics analysis
   i. admit for twelve hour overnight plasma cortisol (7 pm - 7 am)
   j. exhaled nitric oxide followed by spirometry after collection of last plasma cortisol sample
   k. exercise challenge following completion of exhaled nitric oxide test.
   l. symptom diary, and OptiChamber and AirWatch™ techniques reviewed
   m. study medication (dose #1 = inhaled BDP or FP - to be taken as one inhalation twice daily) dispensed and taken as next dose that day following completion of testing.

6. Visit 6 (Week two of inhaled corticosteroid dose #1)
   a. subject returns two weeks after Visit 5
   b. exhaled nitric oxide followed by spirometry

      c.   symptom diary, and OptiChamber and AirWatch™ techniques reviewed

      d.   allergen skin tests following AirWatch™ Quality Control

      e.   study medication (inhaled corticosteroid dose #1) returned, compliance reviewed

      f.   study medication (inhaled corticosteroid dose #1) dispensed

7.   Telephone call between weeks 6 and 7 to assess adherence to study protocol

8.   Visit 7 (Week five of inhaled corticosteroid dose #1)

      a.   subject returns three weeks after Visit 6

      b.   exhaled nitric oxide followed by spirometry

      c.   methacholine challenge

      d.   induced sputum

      e.   symptom diary, and OptiChamber and AirWatch™ techniques reviewed

      f.   study medication (inhaled corticosteroid dose #1) returned, compliance reviewed

      g.   study medication (inhaled corticosteroid dose #1) dispensed

9.   Visit 8 (Week six of inhaled corticosteroid dose #1, begin inhaled corticosteroid dose #2 after visit)

      a.   subject returns one week after Visit 7

      b.   beginning 12 hours before scheduled visit start 24 hour urine collection (7 am - 7 pm, 7 pm - 7 am) for measurement of cortisol suppression

      c.   administer Asthma Control Questionnaire

      d.   obtain spirometry before and after bronchodilator for maximum reversibility

      e.   pregnancy test for female subjects

      f.   admit for twelve hour overnight plasma cortisol (7 pm - 7 am)

      g.   exhaled nitric oxide followed by spirometry after collection of last plasma cortisol sample

      h.   exercise challenge following completion of exhaled nitric oxide test.

      i.   symptom diary, and OptiChamber and AirWatch™ techniques reviewed

      j.   study medication (inhaled corticosteroid dose #1) returned, compliance reviewed

      k.   new study medication (dose #2 = inhaled BDP or FP-to be taken as four inhalations twice daily) dispensed and first dose to be taken after completion of testing.

10.   Visit 9 (Week two of inhaled corticosteroid dose #2)

      a.   subject returns two weeks after Visit 8

      b.   exhaled nitric oxide followed by spirometry

      c.   symptom diary, and OptiChamber and AirWatch™ techniques reviewed

      d.   study medication (inhaled corticosteroid dose #2) returned, compliance reviewed

      e.   study medication (inhaled corticosteroid dose #2) dispensed

11.   Telephone call between weeks 12 and 13 to assess adherence to study protocol

12.   Visit 10   (Week five of inhaled corticosteroid dose #2)
      a.   subject returns three weeks after Visit 9
      b.   exhaled nitric oxide followed by spirometry
      c.   methacholine challenge
      d.   induced sputum
      e.   symptom diary, and OptiChamber and AirWatch™ techniques reviewed
      f.   study medication (inhaled corticosteroid dose #2) returned, compliance reviewed
      g.   study medication (inhaled corticosteroid dose #2) dispensed

13.   Visit 11 (Week six of inhaled corticosteroid dose #2, begin inhaled corticosteroid dose #3 after visit)
      a.   subject returns one week after Visit 10
      b.   beginning 12 hours before scheduled visit start 24 hour urine collection (7 am - 7 pm, 7 pm - 7 am) for measurement of cortisol suppression
      c.   administer Asthma Control Questionnaire
      d.   obtain spirometry before and after brochodilator for maximum reversibility.
      e.   pregnancy test for female subjects
      f.   admit for twelve hour overnight plasma cortisol (7 pm - 7 am)
      g.   exhaled nitric oxide followed by spirometry after collection of last plasma cortisol sample
      h.   exercise challenge following completion of exhaled nitric oxide test.
      i.   symptom diary, and OptiChamber and AirWatch™ techniques reviewed
      j.   study medication (inhaled corticosteroid dose #2) returned, compliance reviewed
      k.   new study medication (dose #3 = inhaled BDP or FP - to be taken as eight inhalations twice daily) dispensed and first dose to be taken after completion of the testing.

14.   Visit 12 (week two of inhaled corticosteroid #3)
      a.   subject returns two weeks after Visit 11
      b.   exhaled nitric oxide followed by spirometry

      c.   symptom diary, and OptiChamber and AirWatch^{TM} techniques reviewed

      d.   study medication (inhaled corticosteroid dose #3) returned, compliance reviewed

      e.   study medication (inhaled corticosteroid dose #3) dispensed

15.   Telephone call between weeks 18 and 19 to assess adherence to study protocol

16.   Visit 13 (week five of inhaled corticosteroid dose #3)
      a.   subject returns three weeks after Visit 12
      b.   exhaled nitric oxide followed by spirometry
      c.   methacholine challenge
      d.   induced sputum
      e.   symptom diary, and OptiChamber and AirWatch^{TM} techniques reviewed
      f.   study medication (inhaled corticosteroid dose #3) returned, compliance reviewed
      g.   study medication (inhaled corticosteroid dose #3) dispensed

17.   Visit 14 (week six of inhaled corticosteroid dose #3, begin high dose inhaled fluticasone propionate treatment after visit)
      a.   subject returns one week after Visit 13
      b.   beginning 12 hours before scheduled visit start 24 hour collection (7 am - 7 pm, 7 pm - 7 am) for measurement of cortisol suppression
      c.   administer Asthma Control Questionnaire
      d.   obtain spirometry before and after bronchodilator for maximum reversibility.
      e.   pregnancy test for female subjects
      f.   admit for twelve hour overnight plasma cortisol (7 pm - 7 am)
      g.   exhaled nitric oxide followed by spirometry after collection of last plasma cortisol sample
      h.   exercise challenge following completion of exhaled nitric oxide test.
      i.   symptom diary, and AirWatch^{TM} techniques reviewed
      j.   study medication (inhaled corticosteroid dose #3) returned, compliance reviewed
      k.   inhaled fluticasone propionate (Flovent Diskhaler 250) dispensed; administered as 2000 mcg daily - four inhalations twice daily to be taken after completion of testing.

18.   Telephone call one week after visit 14 to assess adherence to study protocol

19.	Visit 15 (week two of fluticasone propionate treatment)
    a.	subject returns fourteen days after Visit 14 (on day 14 of fluticasone course)
    b.	exhaled nitric oxide followed by spirometry
    c.	methacholine challenge
    d.	induced sputum
    e.	symptom diary and AirWatch™ techniques reviewed
    f.	fluticasone propionate returned, compliance reviewed
    g.	fluticasone propionate continued

20.	Visit 16 (late afternoon or evening prior to final visit)
    a.	Obtain spirometry before and after bronchodilator for maximum reversibility.

21.	Visit 17	(End of fluticasone treatment, study conclusion)
    a.	subject returns (at conclusion of three week fluticasone proprionate course)
    b.	administer Asthma Control Questionnaire
    c.	obtain pregnancy test in female subjects
    d.	perform long physical exam
    e.	exhaled nitric oxide
    f.	exercise challenge following completion of exhaled nitric oxide test
    g.	symptom diary and AirWatch™ reviewed
    h.	participation concludes and recommendations given for further care

22.	Telephone call one week after Visit 17 to assess the status of the subject's asthma and to confirm that his/her asthma is under adequate control.

## IV.	Inclusion and Exclusion Criteria

## A.	Inclusion Criteria

1.	Male and female subjects post pubertal to 55 years of age.
2.	History of asthma with baseline FEV_1 55-85% of predicted.
3.	The subjects also need to have a history of reversible airflow obstruction ($\geq$12% and >200 ml improvement in FEV_1 following 2 - 4 inhalations of albuterol MDI and a PC20 to methacholine $\leq$ 8 mg/ml.)
4.	Exercise-induced bronchospasm, as defined as a fall of FEV_1 of $\geq$12% following exercise challenge in the absence of bronchodilator pretreatment.
5.	Baseline (pre-study) morning plasma cortisol concentration ($\geq$5 µg/dL)
6.	Nonsmoker (less than 10 pack-years and no smoking within the previous year)

7.	Ability to provide informed consent, as evidenced by signing a copy of the consent form approved by the Institutional Review Board of the subject's respective study institution.

8.	Compliance during run-in period in regard to medication and protocol adherence.

## B.	Exclusion Criteria

1.	Steroid treatment for any condition within the defined intervals prior to enrollment (route)
	a.	Oral - None within one year prior to enrollment; maximum of two weeks of use between one and two years prior to enrollment. If subject used any oral steroids between one and two years prior to enrollment, eligibility must be proven through low dose ACTH Stimulation test (details follow).
	b.	Inhaled/Nasal - None within 6 months prior to enrollment; if subject used any inhaled/nasal steroids between 6 and 12 months prior to enrollment, eligibility must be proven through a low dose ACTH Stimulation test (details follow).
	c.	Topical (prescription) - Criterion for inhaled/nasal steroids in b. applies.
	d.	Topical (over-the-counter) - Criterion for inhaled/nasal steroids in b. applies.
	e.	Injectable - Criterion for oral steroids in a. applies.

	Low dose ACTH Stimulation test for eligibility:

	This test will use an injected dose of 1.0 mcg cortrosyn (ACTH), regardless of bodysize. Plasma cortisol concentrations will be measured pretest and at 20 and 30 minutes post-ACTH (11-13). Subjects must achieve a cortisol concentration >18 mcg/dl on at least one of the post-ACTH samples to be considered eligible for the MICE study.

2.	Current or prior use (within the previous 6 weeks of enrollment) of medications known to significantly interact with steroid disposition, including but not limited to carbamazepine, erythromycin or other macrolide antibiotic, phenobarbital, phenytoin, rifampin, ketoconazole or other systemic and oral antifungal drugs, and sibutramine (Meridia).

3.	Presence of lung disease other than asthma

4.	Significant medical illness other than asthma in particular, thyroid, diabetes mellitus, Cushing's, Addison's and hepatic disease or concurrent medical problems that could require oral prednisone during the study. In addition, a history of cataracts, glaucoma or other medical disorder associated with an adverse effect to corticosteroids. Also, the presence of or a history of any significant cardiovascular disease which would prevent subject participation in the exercise challenge procedure.

5.	History of respiratory tract infection within the 6 weeks prior to screening visit

6. History of significant exacerbation of asthma within the 6 weeks prior to screening visit
7. History of a life-threatening asthma exacerbation requiring intubation and mechanical ventilation - within 10 years
8. Receiving hyposensitization therapy other than an established maintenance (continuous for 3 months duration or longer) regimen
9. Inability, in the opinion of the Study Investigator, to coordinate use of a metered-dose or dry powder inhaler or comply with medication regimens, or inability to comply during the run-in period
10. Pregnancy or lactation
11. Use of oral contraceptives or other hormonal therapy such as Norplant, Depo-Provera, or estrogen replacement therapy (ERT). (Acceptable birth control methods include abstinence and double barrier methods.)
12. Altered day-night cycle
13. Body stature consistent with morbid obesity; i.e., BMI exceeding 35 kg/m^2. Exceptions will be allowed with Principal Investigator's approval.
14. Inability to perform required study procedures
15. HCT at enrollment less than the lower limit of acceptability as specified by the individual clinical center's Institutional Review Board. Samples may be drawn up to 1 week prior to Visit 1 for HCT determination.
16. Use of any drugs listed in Table 1 during the designated washout period prior to Visit 1 or intention to take the drug during the study.

Table 1. Drugs to be withheld throughout the study	Washout prior to Visit 1
Cromolyn/Nedocromil for asthma	≥6 weeks
Leukotriene modifiers (zileuton, zafirlukast, montelukast)	≥4 weeks
Oral beta-adrenergic agonists	≥1 week
Monoamine oxidase inhibitors	≥4 weeks
Tricyclic antidepressants	≥4 weeks
Beta-blockers	≥4 weeks
Inhaled beta-adrenergic agonists (intermediate-acting eg. albuterol, terbutaline, metaproterenol, pirbuterol)	≥6 hours
Salmeterol	≥48 hours
Anticholinergics	≥48 hours
Short-acting theophylline (eg, Slophyllin tablets)	≥12 hours
Long-acting theophylline (eg, Theo-Dur, Slo-bid)	≥24 hours
Ultra long-acting theophylline (eg, Theo-24, Uniphyl)	≥48 hours
Antihistamines (except Astemizole)	≥72 hours
Astemizole	≥80 days
Drugs withheld prior to pulmonary function and/or methacholine and exercise testing per MOP	Specified time period
fexofenadine*	≥48 hours
Methylxanthine-containing foods or beverages (e.g. coffee, tea)	≥8 hours
Alcohol-containing foods or beverages	≥8 hours
*fexofenadine may be used during the study for treatment of allergic rhinitis but should be withheld prior to pulmonary function and/or methacholine challenge testing per the MOP.	

C. Criteria for Assigning Drop-out Status During Treatment Period

1. Subject becomes pregnant.
2. Subject withdraws consent.

V. Outcome Variables

A. Asthma Efficacy

Several measures of asthma efficacy will be employed in this trial. Spirometry before and after bronchodilator including maximum reversibility will be obtained at screening, after the run-in, and periodically over each inhaled corticosteroid treatment period, and at the conclusion of each 6-week inhaled corticosteroid treatment periods and the 21 day inhaled fluticasone propionate treatment period. Exercise challenges will be performed during the run-in, after six weeks of each inhaled corticosteroid treatment, and after three weeks of inhaled fluticasone propionate treatment. Methacholine challenges and induced sputum for analysis of cytology and markers of inflammation will be obtained during the run-in, after five weeks of each treatment period, and after two weeks of treatment with high dose fluticasone propionate. Measurement of exhaled nitric oxide will be obtained prior to each measurement of spirometry including those that precede the beginning of bronchodilator or challenge procedures. Subjects will record daily symptoms and rescue inhaled bronchodilator (albuterol) requirements, and AirWatch^{TM} PEF and FEV$_1$ measures in a diary. Symptom free days will be incorporated as well as information on the need for rescue therapy. In addition, an Asthma Control Questionnaire will be administered and evaluated for change with increasing dose (10).

B. Cortisol Suppression

For comparison of cortisol suppression between different doses of individual corticosteroids and between steroid-inhaler combination, the measure of cortisol suppression is based on conclusions from the DICE pilot protocol and will include a 24 hour urine cortisol measurement (7 am - 7 pm, 7 pm - 7 am) and a twelve hour plasma cortisol collection (7 pm - 7 am) that will begin 12 hours before the scheduled visit for pulmonary function and challenge studies. This will commence at the time of the run-in and at the conclusion of each 6-week inhaled corticosteroid treatment period, but not after the high dose inhaled fluticasone propionate treatment period.

VI. Protocol

A. Recruitment

Each clinical center involved in the ACRN was chosen, in part, based on documentation for subject availability and, to date, there have been no problems in fulfilling the recruitment needs of prior ACRN studies. As this trial requires a relatively limited number of subjects as compared to other ACRN clinical trials, no difficulties in recruitment are anticipated.

As mentioned above, each clinical center involved in ACRN was chosen based on documentation, among other things. It is, however, worthy to note the specific plans of each center.

Harvard Clinical Center/Boston

1. Need

The Boston Center will access the population at Harvard Community Health Plan to achieve enrollment goals.

2. Potential Participants Stratified by Severity

To assess the number of potential participants, computerized pharmacy records of all individuals who had been Plan members for at least 3 months, who were between 12 and 65 years of age, who had pharmacy benefits and who had received prescriptions for asthma medications were selected.

3. Results

9,885 asthmatic individuals were identified of whom 7,588 (76.7%) met the definition of mild asthma, 1,883 (19.0%) met the criteria for moderate asthma and 414 (4.3%) met the criteria for severe asthma.

4. Recruitment Strategy

The Boston Center will contact a fraction of the individuals identified as having mild to moderate asthma by the pharmacy search by letter. In this solicitation, attention will be paid to postal zip code to achieve the needed minority subjects.

National Jewish Medical and Research Center/Denver

Research subject recruitment has been very successful for all types of asthma subjects at the National Jewish Medical and Research Center.

1. National Jewish Outsubject Clinic

The adult clinic saw 1,079 new asthmatic subjects over the last year with 503 being from the Denver metropolitan area. Another 335 from the Denver area were seen in follow-up. The severity of asthma varies among these subjects, but approximately 50% are in the mild to moderate category. National Jewish has changed markedly over the last decade. It has evolved from a primary inpatient facility with a small clinic to a very active outsubject service. Thus, the Denver Center has access to many more asthmatic subjects of all degrees of severity.

2. National Jewish Asthma Research Pool

There are over 400 asthma subjects (not followed in the National Jewish outsubject clinic) that have participated in research studies conducted at the Denver Center. Many of these subjects have been through various medication studies and bronchoscopies with lavage/biopsies. Their FEV_1s range from 30-110% of predicted.

a. Denver Health Medical Center -
Dr. James Fischer, Acting Head of Pulmonary Medicine, is supporting efforts of the Denver Center by helping to recruit from the asthmatic subject population at the Denver Health Medical Center. This is a large county hospital whose subject population comprises mainly Hispanic and African-American people.
b. Denver Veterans Administration Hospital - Dr. Carol Welsh, acting Pulmonary Director, will support this grant. The VA hospital has a large outsubject clinic of subjects with asthma, but not chronic obstructive pulmonary disease.
c. Denver Kaiser Permanente HMO - Dr. Timothy Collins is the Director of Pulmonary Medicine and Dr. William Marsh is the Director of Allergy at Kaiser. Drs. Collins and Marsh have been actively involved in supporting research at National Jewish in the past by referring subjects. Their groups will continue to play an active role in clinical research support.

University of Wisconsin/Madison

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

Harlem Prevention Center/New York

Central Harlem has a residentially stable population of approximately 115,000 of whom 98% are African American or Hispanic, and 53% are women. The prevalence of asthma in Central Harlem is 3-4 times that in the U.S. population. Harlem Hospital and its network of community-based clinics, together comprise the Northern Manhattan Network. Through the Network, the Harlem Asthma Research Center (HARC) has identified more than 2,000 asthmatic subjects who are in stable primary care relationships, and established collaborative arrangements with their primary care providers.

The Harlem Asthma Research Center will initially recruit participants in ACRN clinical trials through this network of collaborating providers. While the Center will specifically target people of color, it will never turn anyone away.

The investigators anticipate no difficulty in recruitment of women. Accrual of participants will be monitored for all protocols. If targeted approaches are needed, the HARC will consider strategies which have been used successfully to recruit and sustain

the participation of women in this community. These have included provision of transportation, meals, child care, home visits, utilizing peer educators, the formation of a woman's support group, culturally appropriate education efforts and linkages to support services.

Primary care physicians from the Northern Manhattan Network will approach their subjects about their willingness to participate in the clinical trials. If they are interested, the screening and all follow-up visits will take place at the Harlem ACRN Clinical Center. Because asthma clinical trials will require procedures that are not performed routinely in primary care offices, appropriate procedures will be followed so that subjects participate fully in ACRN protocols while staying in contact with their primary care providers as needed.

Thomas Jefferson Medical College/Philadelphia

All subjects with a diagnosis of asthma currently cared for in the outsubject offices of the Division of Pulmonary Medicine and General Internal Medicine and the Departments of Family Medicine and Pediatrics are listed in a computerized database. Approximately 85% of 2,600 asthmatics in this database have "mild to moderate" asthma. Terminals located at each clinic site are linked to the ACRN file server located in the study coordinator's office. Subjects fulfilling every criteria for a given study will be identified by the database, and personal contact will be made by the study coordinator for the purpose of explaining the study and enlisting their participation. If on initial contact, the subject agrees, they will return to the study center to verify entry qualifications and further discuss the study. Subjects are also recruited from the local community by radio and newspaper advertising.

University of California/San Francisco

The approach to recruiting subjects with asthma for research studies at the San Francisco Center relies heavily on community advertising. Advertisements are placed in editions of the San Francisco Chronicle and Examiner, in small neighborhood newspapers, and on bulletin boards on the UCSF campus, in community health centers, and at campuses of colleges and universities in the Bay Area. Advertisements are also placed on two popular radio stations (one "soft rock" station; one "soul" station). Finally, fliers are placed in the subject waiting areas of the Pulmonary Medicine and Allergy Clinics at the major teaching hospitals of UCSF (Moffitt-Long, San Francisco General Hospital, Ft. Miley V.A. Hospital, and Mt. Zion Hospital). Responses to these advertisements are made to a dedicated telephone number equipped with voice mail. A full-time recruiter was hired to respond to each inquiry and to obtain basic information about the subject's demographics and about the severity, duration, required treatment, and frequency of symptoms of asthma. To date, well over 500 subjects have been screened for the database. Of those screened at the Moffitt-Long site, less than 10% are members of ethnic minorities.

B.   Drug Supplies

Drug supplies for this study will consist of two steroid-inhaler combinations, BDP (Vanceril Double Strength, Schering) or FP (Flovent-44, Glaxo Wellcome) administered with the OptiChamber, Flovent Diskhaler 250 (Glaxo Wellcome) for the three week final phase, as well as albuterol MDIs and prednisone tablets. These will be purchased. Placebo for the run-in period will be arranged through Schering Pharmaceuticals and Glaxo Wellcome.

C.   Compliance and Monitoring

The following mechanisms will be employed to determine compliance and measure outcomes:

1.   Diary card: At each visit the symptom diary card will be reviewed with the subject. Limitations are accuracy of subject's recall and honesty in completing the diary.

2.   The AirWatch^{TM} flow meter with diary recording will be used to record peak expiratory flows (PEF) and FEV_1, and serve as a check of compliance in general as date and time are electronically recorded.

3.   Due to prior failure and poor reliability of the Chronolog device, it will not be used in this trial. The beclomethasone dipropionate and fluticasone propionate will be administered with the Opti-Chamber device. Clinic Coordinators will use diary data to aid in compliance assessments with subjects at each clinic visit. In addition, a dose counter (Doser) will be used for the MDI inhaled steroids to assess subject compliance.

4.   Watches with alarms will be set at the specific dosing times to remind subjects to use their inhaled corticosteroid medications.

D.   Inhalation Technique

Since the manner in which an inhaled corticosteroid will in part deliver more or less medication to the lungs is critical in reducing variability, the subject's medication technique will be reviewed at each visit. Thus, objective feed-back can be given to a subject to improve performance.

E.   Special Study Techniques

1.   Methacholine challenge - The methacholine challenge procedure will be identical to that applied for previous Asthma Clinical Research Network protocols and is detailed in the Manual of Operations.

2.   Exercise challenge - This procedure is newly applied to the Asthma Clinical Research Network. The exercise challenge will consist of running on a treadmill to determine the speed and incline of the treadmill that will allow the subject's heart rate to reach greater than or equal to 80% of maximum for height and age.

To control for the effect of temperature and humidity of the inspired air during exercise, the subject will inspire compressed air at a fixed flow

rate from a 170-liter balloon reservoir (Douglas bag) fitted with a face mask. The temperature of the room in which this testing is to be done will be maintained between 20 to 25 degrees Celsius.

The exercise challenge will be based on an initial trial where the subject runs on a treadmill to determine the speed, duration and treadmill incline that will allow the subject's heart rate to reach greater than or equal to 80% of maximum for the subject's heart rate for six minutes. Of the five subjects each center is to recruit, one will be allowed to have the duration of the exercise challenge procedure be less than 6 minutes (3-6 minutes), provided the subject's heart rate still reaches 80% of maximum. The same duration should be attempted for all future exercise challenges. The speed and grade required to reach each target heart rate will be recorded. This set of conditions will be used in all subsequent challenges. The treadmill incline will ordinarily be no greater than 15%. Heart rate will be measured by a cardiotachometer or other accurate device. The critical requirement for a valid exercise test is for the subject to maintain target heart rate for six minutes. Most subjects will achieve the target heart rate under these conditions. However, some subjects may need adjustment of duration or incline in order to achieve target heart rate. This will be detailed in the Manual of Operations. Appropriate safety measures will be incorporated, including the measurement of oxygen saturation, in the study procedures to identify and manage potential adverse effects.

FEV_1 will be measured prior to and 5, 10, 15, 30, 45, and 60 minutes after the exercise test or until a maximum fall of 50% from baseline in FEV_1 has occurred. The maximum postexercise absolute fall and percentage decrease in FEV_1 from baseline will be used as the primary endpoint for the analysis of the efficacy/systemic relationship with each inhaled ICS arm (8). Two other end-points will be analyzed: 1) area above the postexercise decrease (from preexercise baseline) in FEV_1 versus time curve through 60 minutes [AUC $_{(0-60)}$] and 2) the time required after maximal decrease for FEV_1 to return to within 10% of preexercise baseline (time to recovery) (14). Subjects will be monitored carefully during the exercise testing procedures and will be allowed to recover without pharmacologic intervention in most cases. However, for purposes of subject comfort and safety, albuterol MDI rescue will be implemented whenever warranted.

The trapezoidal method will be used to calculate the AUC $_{(0-60)}$. Only areas below the preexercise baseline will be included when in the computation of the AUC $_{(0-60)}$ to capture only the extent and duration of the bronchoconstriction below the preexercise baseline. The parameter provides a single number that integrates intensity and duration of bronchoconstriction.

If a subject requires albuterol MDI rescue for asthma symptom relief or low FEV_1 (or the FEV_1 value is not available), the last valid FEV_1 will be used for all subsequent time-points for analysis in that period. If the exercise-induced bronchoconstriction is completely blocked (maximal

decrease in $FEV_1 < 5\%$), the time to recovery will be assigned a value of 0 minutes.

Exercise challenge will be measured prior to ICS Dose #1, six weeks after starting each ICS dose, and three weeks after beginning high dose inhaled fluticasone propionate in the last phase of the study.

3. Maximum Reversibility - To determine the maximal improvement in FEV_1 after albuterol treatment, the standard procedure for spirometery will be followed. Following baseline spirometry, 4 puffs of albuterol will be administered. After waiting 15 minutes, 3 post bronchodilator spirometry maneuvers will be obtained and the best value selected. Two more puffs of albuterol will be administered. After waiting 15 minutes, 3 post brochodilator spirometry maneuvers will be obtained and the best value selected. The percent difference in FEV_1 between the FEV_1 measured after receiving 360 mcg (4 puffs) albuterol and the FEV_1 measured after receiving 540 mcg (6 puffs) albuterol will be calculated. The test is terminated if the FEV_1 percent difference is < 5.0% or if a total of 8 puffs albuterol (720 mcg) have been administered. If the FEV_1 percent difference is < 5.0%, the maximal improvement in FEV_1 following albuterol treatments is then identified.

4. Allergen skin tests - The allergen skin test procedure will be identical to that applied for previous Asthma Clinical Research Network protocols and is detailed in the Manual of Operations.

5. Genetics analysis - The genetics analysis procedure will be identical to that applied for previous Asthma Clinical Research Network protocols and is detailed in the Manual of Operations. This will be limited to genetics analysis related to allergy, asthma and inflammation.

F.   Risks/Benefits

This study compares the efficacy and systemic effects of various doses of inhaled BDP and FP administered with the Opti-Chamber device. While not a minor concern, the degree of systemic effects anticipated with the doses to be studied should not pose any greater risk as compared to conventional asthma treatment since the selected doses are in the range of prescribed doses and NAEPP guidelines. Since these subjects will be placed on inhaled BDP or FP therapy, we expect their asthma to gain better control. However, to ensure the safety of individuals whose asthma worsens during the study period, specific criteria from the ACRN's Beta-Agonist Trial (BAGS) and Colchicine in Moderate Asthma (CIMA) for assigning "treatment failure" status, and for initiating appropriate asthma therapy will be used (15,16). There is the possibility of systemic adverse effects from high dose inhaled fluticasone propionate, however the regimen will be similar to that used in the management of severe persistent asthma. Thus, while there may be some risk for systemic effects, asthma control will not be compromised. There will be no direct benefit to the subjects participating in this study. The results may be of potential benefit to the entire group of subjects with asthma as it may lead to a better definition of guidelines for asthma therapy.

G.   Anticipated Results

It is anticipated that, using the doses of inhaled BDP and FP administered with the Opti-Chamber derived from the DICE pilot trial, differences in asthma control will be observed. Efficacy/systemic relationships (efficacy and cortisol suppression) for inhaled BDP and FP with the Opti-Chamber are also anticipated. Risk:benefit ratios, defined by the efficacy/systemic relationship, for inhaled BDP and FP and the Opti-Chamber will be analyzed. Finally, the degree of cortisol suppression observed will be used for confirmation of data obtained from the DICE pilot trial.

The primary outcome measure for efficacy in the MICE protocol is FEV_1. Based on a review of the literature there is no study that is exactly like the study proposed here in relation to the initial FEV_1 of the study population, the strategy for selecting study doses, the combination of three inhaled corticosteroid doses, and the incorporation of an inhaled fluticasone propionate treatment arm to assess maximum response. Most studies of comparative efficacy have either used a study population with milder asthma or used a study population with persistent asthma who were already on inhaled corticosteroids and then transferred to the inhaled corticosteroid incorporated in the study. Also, most studies use a single inhaled corticosteroid dose and compare the results to a single dose of another inhaled corticosteroid. Therefore, in this study we will compare the effect of three doses of the same inhaled corticosteroid using two inhaled corticosteroids, BDP and FP, on suitable efficacy parameters to examine the efficacy/systemic effect relationship.

Two critical variables in assessing significant differences in response include the change in FEV_1 with the treatment and also the standard deviation of the efficacy measure, in this case FEV_1. Data was obtained from a comparative study of inhaled fluticasone propionate and inhaled triamcinolone acetonide from Glaxo Wellcome in a study population similar to that proposed for the MICE protocol (17). In this study subjects were maintained on 400 mcg of inhaled triamcinolone acetonide prior to randomization. They were then randomized to placebo, 500 mcg of fluticasone propionate or 800 mcg of triamcinolone acetonide per day. Several important observations were made in this study:

1. In the placebo treatment arm, there was a 55% drop-out rate by week 6. The remaining study population had a 0.24 L (0.06) mean (SE) increase in FEV_1; however, using end-point analysis, the overall change at the end of the 24 week study period was -0.18 (0.06). The end-point analysis uses the measured FEV_1 in a subject upon completion of the study or the last measurement prior to the time of drop-out.

2. In the fluticasone propionate treatment arm, 500 mcg per day, there was only a 12% drop-out rate at week 6. The remaining study population had a 0.32 L (0.04) increase in FEV_1. Using end-point analysis there was a 0.27 L (0.05) increase in FEV_1 at the end of the 24 week study period. Therefore, the difference in fluticasone propionate and placebo using end-point results was 0.45 liters or 450 ml. In evaluating the results of this study most of the efficacy for the FEV_1 parameter was obtained in the first six weeks and approximately half of the drop-outs occurred in the first six weeks.

3. In the triamcinolone acetonide treatment arm, 800 mcg per day or approximately twice the dose of the run-in period, there was a 23% drop-out rate by week 6. The remaining study population had a 0.15 L (0.05) increase in FEV_1. Using end-point analysis, there was a 0.07 L (0.05) increase in FEV_1 over baseline. The difference from placebo is therefore 0.25 L for the triamcinolone acetonide treatment arm. Once again, the maximum effect for the triamcinolone treatment arm occurred at approximately 6 weeks of treatment.

Based on these results as well as other available studies, we anticipate an increase in FEV_1 of at least 200 ml for the treatment arms with inhaled corticosteroids as compared to the baseline value. With the result of the above fluticasone propionate vs. triamcinolone acetonide study, we anticipate that there could also be a difference of 200 ml between two inhaled corticosteroid treatments. We will also anticipate a standard deviation of 0.40 L for FEV_1 based on a previous ACRN study where inhaled corticosteroids were withdrawn from a treatment arm (16). Available literature including the Glaxo Wellcome study suggests this is a reasonable assumption for this study population (18-22).

A secondary outcome variable is PC_{20} derived from methacholine challenge. To date, limited information is available regarding the effect of inhaled corticosteroids on methacholine PC_{20} in a comparable study population. Most studies detect at least a 0.6 doubling dose increase in PC_{20} to histamine (20, 22-26). We anticipate an improvement or increase of at least a 0.625 doubling dose for PC_{20} methacholine for our study population.

There is even less information regarding the effect of inhaled corticosteroids on changes in inhibition of fall in FEV_1 following an exercise challenge. The study by Pedersen and Hansen (8) prompted the inclusion of an exercise challenge in the MICE protocol since they were able to define a dose response relationship for budesonide that was more sensitive than FEV_1 in identifying differences in the three doses selected for their study in asthmatic children, specifically 100, 200 and 400 mcg per day budesonide via metered dose inhaler and large volume spacer. Despite the remarkable post-exercise decrease in FEV_1 seen in this study as compared to the ACRN investigators' clinical experience, this appears to be a worthwhile parameter to measure due to the observed relationship between dose and the attenuation of exercise-induced airway obstruction. The percent fall in FEV_1 following the run-in period was 55.4%. The percent fall in FEV_1 following 100, 200 and 400 mcg per day of treatment for 4 weeks each was 25.7, 20.1, and 9.97 respectively, all significantly different from each other and the run-in period.

There is no information on the efficacy/systemic relationship of inhaled corticosteroids on inflammatory cell changes measured from induced sputum samples. This should prove to be a very interesting facet to the MICE protocol. It could prove to be the differentiating parameter in assessing correlations among physiologic changes following inhaled corticosteroid therapy and their relation to a measurement of airway inflammation. In addition, although exhaled nitric oxide may be affected by steroid

administration, an efficacy/systemic effect relationship to inhaled corticosteroids has not been evaluated.

VII. Adverse Events

A. Definitions

An adverse event shall be defined as any detrimental change in the subject's condition, whether it is related to an exacerbation of asthma or to another unrelated illness. Adverse events related to asthma exacerbations will be assigned Treatment Failure status and managed according to rescue algorithms outlined in previous ACRN trials (15, Appendix A).

An adverse event is deemed serious if it suggests a significant hazard contraindication, side effect, or precaution. Serious adverse events include any experience that is fatal or life-threatening, is permanently disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly, cancer, or overdose. Serious adverse events must be reported to the DCC within 72 hours of notification. Once notified, the DCC will disseminate information about the event to the Data Safety and Monitoring board and to the Steering Committee.

B. Adverse Events Unrelated to Asthma

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

Documentation of an adverse event unrelated to asthma will be recorded on an Adverse Event Report Form and will include the following information:
- Description of the illness
- Dates of illness
- Treatment of illness and dates (medications, doses, and dose frequency)
- Whether emergency treatment or hospitalization was required
- Treatment outcome

C. Adverse Events Related to Asthma Exacerbations

Definition - for this protocol, an asthma exacerbation is defined as the development of an increase in symptoms of cough, chest tightness, and wheezing in association with one or more of the following:

- An increase in "as needed" or rescue albuterol use of ≥ 8 inhalations per 24 hours over baseline use (baseline defined as average daily use during the two weeks prior to randomization) for a period of 48 hours or ≥ 16 total inhalations per 24 hours for a period of 48 hours.

- A fall in PEFR to $\leq 65\%$ of baseline (baseline is defined as the average over two weeks prior to randomization) or FEV_1 $\leq 80\%$ of baseline (baseline is defined as FEV_1 at the randomization visit).

We do not anticipate many significant asthma exacerbations in this protocol since we are adding inhaled corticosteroids to the treatment regimen of subjects not currently receiving them. However if this does occur, then the rescue algorithm in Appendix A will be followed.

D.   Treatment Failure

If a subject receives systemic corticosteroids for an exacerbation (or any other corticosteroid other than the study drugs) the subject will be assigned Treatment Failure status. Subjects can also be assigned treatment failure status if the physician decides it is necessary for subject safety.

E.   Study Center Visits Following Treatment Failure

Criteria for assigning treatment failure status during the treatment period are described in Section VII.D. Subjects who are assigned treatment failure status will continue to participate in the data gathering aspects of the protocol until they complete the trial. All regularly scheduled procedures will be done provided it is safe for the subject to do so. However, methacholine challenge, induced sputum and exercise challenge will not be done for at least four weeks after a treatment failure. Trial medications will be continued during and after an exacerbation unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. Reinstitution of trial medications will occur when the exacerbation has resolved at the discretion of the investigator.

VIII.   Cost, Liability, and Payment

All tests will be performed without cost to the participating subjects. Since this is a trial comparing established asthma treatments, liability for subject care costs incurred by subjects during the course of the trial will in most cases be borne by the subject or their insurer. Details of the National Institutes of Health policies concerning this issue can be found in NIH Documents #5305 and 6352-2, Research Patient Care Costs Supported by NIH Sponsored Agreements, which are in the ACRN Manual of Operations. Each subject will be paid an amount determined by their local center for study reimbursement. For subjects who drop out, reimbursement will be pro-rated for the length of time they stayed in the study.

IX.   Data Recording

Recording of all data including informed consent, history, physical examination, results of pregnancy tests, adverse events, confirmation of medication dispensation, methacholine challenge testing, exercise challenge testing, and initial data entry will be done at each Clinical Center and forms will be forwarded to the DCC for confirmatory entry.   Results from pulmonary function tests and compliance will be transmitted electronically to the DCC where all data will be stored and analyzed.

X.   Statistical Design and Analysis

A.   Data Collection and Data Management

Each center will have a computer configuration that includes an X-terminal, a post-script printer, and a modem. This will give each center the capability of logging directly into the DCC computing system over the Internet with the modem as a back-up if the connection is not possible. Though this set-up is installed primarily to allow for distributed data entry into a centralized database on the ACRN project server at the DCC, menu options will also include sending electronic mail, downloading study documents such as forms and reports, and viewing a calendar of ACRN events. A sophisticated security system will limit access to qualified personnel and prevent corruption of the study database.

The DCC will be responsible for generating the data collection forms based on input from the clinical centers. Once the data collection forms have been filled out and reviewed, the Clinic Coordinator will log into the DCC computer system and enter the data within three days of the subject visit. The advantage of this distributed data entry system is that the Clinic Coordinators will review the data a second time as they are entering it, which serves as another level of quality control. However, the Clinic Coordinators will not be able to query their own data. The database management system will have range checks and validity checks programmed into it for a second level of quality control. Forms will then be forwarded to the DCC for the second data entry and filing, which will be performed within three days of receipt. The DCC will be responsible for identifying problem data and resolving inconsistencies. Once the quality control procedures are complete, new study data will be integrated into the primary study database. Results from lung function tests will be sent directly to the DCC via a modem in the computer attached to the spirometer.

B.   Masking

Due to the different doses (requiring various numbers of actuations) this study will be open-label.   The laboratory or laboratories performing the plasma cortisol concentrations and other assays will be blinded. Also, the investigators will be blinded to each subject's results over the course of the trial.

C.   Randomization

When a subject at a particular center is deemed eligible for the study, the Clinic Coordinator will log into the ACRN network server and indicate to the system that a subject requires randomization. After entering the pertinent information with respect to clinical center and eligibility criteria the Clinic Coordinator will be asked to verify that all of the entered information is correct. If so, the Clinic Coordinator will be given a packet number, from which all medication for that subject will be dispensed. In order to maintain security of the randomization schedules, the data manager of the DCC will automatically receive a notice from the ACRN network server that a subject has been randomized. If no follow-up information is forthcoming on such a subject, the data manager will contact the Clinic Coordinator concerning the status of the subject.

D.   Statistical Analysis

In the MICE study several efficacy outcomes are measured, such as FEV_1, methacholine challenge, exercise challenge, nitric oxide and inflammatory cell changes. The cortisol levels in hourly blood draws will be summarized as the area under the curve for each subject's visit. Suppression will be defined at each dose as the area under the curve relative to the area under the curve at baseline.

The focus of the analysis of the MICE data is to estimate the variability of the efficacy/systemic effect relationship. The primary efficacy outcome is FEV_1 and cortisol suppression will measure the systemic effect. In addition, several other efficacy outcomes will be considered to determine which outcome is most sensitive to treatment differences. Also, the efficacy/systemic relationship will be compared between the two steroids.

Longitudinal data analysis will provide the most statistical power and flexibility to accurately model the efficacy/systemic relationship and estimate the variance of this relationship since it uses all the data from each subject visit. Each of the efficacy outcomes, e.g., FEV_1, will be modeled either as a linear or a non-linear mixed effects model (27,28).

The data from the MICE study provide the opportunity to apply various models and assess their fit. Once the most appropriate model is selected, the estimate of the pooled variance will be used to determine the sample size for the main study. If there is little difference between the two steroids, a more conservative variance estimate will be used for the sample size calculation. For example, the upper 95 percent confidence limit of the variance estimate may be used. Based on the pilot results, an appropriate variance estimate will be used for the sample size calculation. In addition, several efficacy outcomes will be investigated to determine which is most sensitive to treatment differences.

The treatment groups will be compared based on testing the model parameters. For example, if the linear mixed model is used, then the slope estimates, which explain the efficacy/systemic relationship in each treatment group, will be compared. If these

estimates are not different statistically, the intercept estimates will be compared. This comparison tests whether the efficacy/systemic relationships are shifted among the treatments.

The statistical model (assuming a linear relationship of efficacy outcome and suppression) appropriate for the treatment period in the main study is:

$$Y_{ijk} = \alpha_{ij} + X_{ijk}\beta_{ij} + E_{ijk}$$

where

i= 1,2 denotes treatment arm

j= 1,...,n_i denotes subject within treatment arm i

k= 1,...p_{ij} denotes Visit number for subject j within treatment arm i

Y_{ijk} = response at Visit k for subject j within treatment arm i

α_{ij} = intercept for subject j within treatment arm i

β_{ij} = slope for subject j within treatment i

X_{ijk}= cortisol suppression at Visit k for subject j within treatment arm i

E_{ijk}= random error at Visit k for subject j within treatment arm i

One of the underlying assumptions for this model is that the responses will behave linearly with respect to suppression during the treatment period. This assumption will be investigated graphically and if it is determined that it is not viable, then the model will be modified to be non-linear.

It is assumed that the [α_{ij} β_{ij}]'s are independent and distributed according to a bivariate normal with mean vector [α_i β_i] and variance matrix with elements $\omega_{\alpha\alpha}$, $\omega_{\beta\beta}$, and $\omega_{\alpha\beta}$. The e_{ijk}'s are independent and identically distributed according to a normal distribution with null mean and variance σ^2. The [α_{ij} β_{ij}]'s and the e_{ijk}'s are mutually independent. The variance components $\omega_{\alpha\alpha}$, $\omega_{\alpha\beta}$, and $\omega_{\beta\beta}$ are inter-subject variances and covariances for the random intercepts and slopes. The variance component σ^2 is the intra-subject variance for the intercept-slope model.

Details for performing restricted maximum likelihood (REML) estimation and empirical generalized least squares (EGLS) estimation of the intercepts, slopes, and variance components are provided elsewhere (27,28). Both REML and EGLS estimation are available in PROC MIXED of SAS (29).

E.   Sample Size

The target sample size is to randomize 12 subjects to each treatment arm (total 24 subjects). Thirty subjects will be enrolled, 15 in each treatment group, to allow for drop outs and missing data. To determine which sample size to select for the study we estimated 95% confidence intervals around a variance estimate of 1.0. Although the variance estimate of 1.0 is arbitrary, the 95% confidence intervals for the variance can be generalized to variance estimates other than 1.0 by multiplying the interval endpoints by the variance estimate. Assuming we use a variance estimate pooled across the two treatment arms, the confidence interval for n=24 is (0.60,2.01) and for

n=36 is (0.65,1.70). The relative savings, regardless of the magnitude of the variance estimate, between a sample of 36 versus 24 are that the lower limit is only 1.08 times higher and the upper limit is only 0.85 times lower. This is a relatively small benefit in precision of the variance estimate compared to the increase in cost required to randomize 36 subjects (which would require enrollment of 48 subjects to allow for dropouts).

The parameter estimates will be compared between the two treatment arms as an exploratory analysis. Given the lack of a valid variance estimate for which to estimate the power of the study to detect a difference between treatment arms, we considered the relative power to detect a difference for a sample size of 18 relative to a sample size of 12 per arm by specifying the ratio of the effect size (i.e., the difference we would want to detect) to the standard deviation. Using 0.25, 0.50 and 0.75 as the specification of the effect size to standard deviation, the relative power of sample size of 18 to 12 per arm is 1.3, 1.4 and 1.2 respectively. These are relatively small increases in power. Therefore, the proposed sample size of 24 allows reliable estimates of the variability and determination of the feasibility of the main study.

F.   Significance

The primary significance of the MICE study is to evaluate the efficacy/ systemic effect relationship of inhaled beclomethasone dipropionate and fluticasone propionate in a range of doses that cause very little to appreciable cortisol suppression. The results of this protocol will allow us to determine whether the response parameters are sufficiently sensitive to assess an efficacy/systemic effect relationship. This will provide the core information necessary to limit the number of efficacy measurements in the full MICE protocol where several inhaled corticosteroids will be compared. Furthermore, the data obtained will provide valuable information for the determination of the number of subjects necessary to conduct the full MICE protocol.

There are several distinct advantages to pursuing the areas of research encompassed by the DICE and MICE studies. First, comparative safety and efficacy of inhaled corticosteroids is a clinically relevant issue for the majority of subjects with asthma. Second, both studies, DICE and MICE, will be the first comprehensive, comparative examinations of the systemic (analysis of cortisol suppression in DICE) and beneficial effects of inhaled corticosteroids (specific efficacy parameters determined from MICE). Third, the results may point out the limitations of inhaled corticosteroids in addressing the scope of inflammation involved in asthma of comparable severity to the study subjects. Finally, these models could become the standard for comparing the safety and efficacy of inhaled corticosteroids, and at the least can be used to compare future steroid-inhaler combinations.

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