Asthma Clinical Research Network

The Addition of Regular-Use to Intermittent Rescue B-Agonist for Patients with Mild Asthma

STUDY PROTOCOL

Version 3.1

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1.Background and Hypothesis to be Tested

A. Introduction

Asthma constitutes a major health problem; within the United States alone there are thought to be 10 million people with asthma. The cost of asthma care and the economic impact of asthma morbidity is estimated to be between 4 and 5 billion dollars per year. Because of the importance of this problem, and the demonstration that asthmatic patients had fewer exacerbations when treated by asthma specialists (1,2), practice guidelines for asthma have been formulated and promulgated (3-5). During the process of guideline formulation, it became clear that there were many issues related to asthma care for which the data base to make firm and scientifically sound recommendations was minimal. In the case of the treatment recommendations for the United States, despite the lack of a comprehensive data base, the Expert Panel of the National Asthma Education Program made their "best guess" at treatment recommendations. Because the prevalence of asthma is so great, treatment errors have the potential to be very costly. There are at least 3 potential costs of treatment to consider:

•Patients who should receive treatment do not receive treatment.

In this case, the cost of asthma care reflects errors of omission, resulting in preventable asthma morbidity including days lost from work or school, as well as hospitalization for asthma that could have been avoided.

- **Patients receive treatment that has no toxicity but also no benefit.**

In this case, health care resources are wasted on useless therapies.

- **Patients receive treatment for their asthma which has demonstrated benefit but which is accompanied by real or potential toxicity.**

This is a difficult case. One has to judge the measured benefits against toxicities which may be difficult to appreciate on the time scale of measured improvement. Furthermore, in a disease such as asthma, it is unclear whether short term benefits in treatment outcome are reflected in long term patient benefits.

Because of these considerations, it is important and economically sensible to obtain the data needed to make recommendations for treatment that have stood the test of rigorous clinical investigation. In this proposal, we address a major problem that faces the family physician, the pediatrician, the generalist and the general internist, as well as the allergist or pulmonary specialist, who treat patients with mild asthma:

What is the appropriate use of inhaled **$***-agonist treatment in the patient with mild asthma?*

In order to appreciate our reasons for choosing this question, it is appropriate to examine the current state of practice for patients with mild asthma.

B. Inhaled Treatment for Mild Asthma

B1. Data supporting that regular use of inhaled $-agonists is deleterious to asthma.

Until recently major textbooks of medicine (6-8) and asthma specialists (9) recommended treating mild-to-moderate asthma with inhaled **$**-agonists given on a regular basis to minimize variability of airway tone. In addition, physicians were advised to prescribe additional inhaled **$**-agonists on an "as needed" basis for the treatment of asthma symptoms. However, the regular use of inhaled **$**-agonists in asthma treatment has recently been called into question. In "landmark" papers, Sears and co-workers (10,11) asked whether individuals who used an inhaled **$**-agonist regularly would have better asthma control than those individuals who used their inhaled **$**-agonists only on an "as needed" basis. They examined the effects of regular use of inhaled fenoterol (a potent **$**-agonist with known **$**-agonist properties that has never been released for asthma treatment in the United States) plus "as needed" **$**-agonists or treatment with "as needed" **$**-agonists alone, in 89 patients wit moderate chronic stable asthma using a double-blind, randomized, placebo-controlled, crossover design. Asthma control was monitored using symptom diaries, AM/PM peak flow rates, airway responsiveness and the requirement for the "as needed" inhaled **$**-agonist or short courses of oral steroids. An asthma control index was derived from the above noted measures. Among the subgroup of patients in whom asthma control was judged to be different on each "arm" of the study, thirty percent of the patients who received regular bronchodilator treatment had improved asthma control when using regular fenoterol when compared to placebo, while 70% of the patients had better asthma control when *not* using inhaled fenoterol on a regular basis. For the group using regular fenoterol, airway responsiveness increased slightly during the fenoterol treatment period. The interpretation of the data offered by the investigators was that regular **$**-agonist use was associated with diminished asthma control and that regular use of powerful and long-acting **$**-agonists could account for increasing world-wide asthma morbidity and perhaps mortality. A similar conclusion was drawn from the data of van Schayck and co-workers (12) who demonstrated that patients with moderate asthma or COPD treated with 1600 ug of inhaled albuterol or ipratroprium bromide on a regular basis had an accelerated rate of decline in lung function compared to the subjects treated with **$**-agonists on an "as needed" basis. Further caution against the use of inhaled **$**-agonists was derived from the studies which showed that with regular use of certain **$**-agonists, the protective effect of **$**-agonist treatment on methacholine-induced bronchospasm was lost after a few weeks to months of treatment (13, 14). These interventional trials were corroborated by the epidemiological observations of Spitzer and colleagues (15) in which it was shown that subjects using high-dose **$**-agonists had an increased risk of death, or near death, from asthma compared with subjects with asthma of similar severity who were not using high-dose **$**-agonists. It is important to note that others have questioned the risk of death, or near death, associated with the use of **$**-agonists (16).

B.2 Data supporting that regular use of inhaled $-agonists is not deleterious to asthma

The conclusion from the studies noted above was that there is a deleterious effect of the regular use of inhaled **$**-agonists in asthma patients. Is this conclusion justified based on currently available data? To address this question it is worthwhile to examine additional data; it is important to point out the data examined was not gathered specifically to address this issue. Haahtela and co-workers (17) reported data from a study in which 103 newly diagnosed mild asthma patients, 15 to 64 years of age, were treated with either 600 ug of budesonide or 325 ug of terbutaline by inhalation twice a day for 2 years. Although the group treated with inhaled budesonide had fewer symptoms and better asthma control than the group treated with inhaled terbutaline, the group which had received chronic **$**-agonist treatment did not have a deterioration in lung function over the two years when compared to the group treated with inhaled steroids. A logical interpretation is that there is not a deleterious effect from chronic **$**-agonist treatment. In a 30 month study of patients with both asthma and COPD, Kerstjens et al (18) demonstrated that the treatment with inhaled terbutaline, 2000 ug daily, was not associated with an accelerated loss of lung function compared to a group of patients treated with both inhaled terbutaline, 2000 ug daily, and inhaled beclomethasone, 800 ug daily. In considering these conclusions one must consider that the "dropout" rates were significantly higher in the groups treated with (3-agonists alone compared to the groups receiving other forms of treatment. Finally, a recent study comparing the use of the long-acting **$**-agonist, salmeterol, to regular use of inhaled albuterol over a 12-week period (19) showed no deleterious effects on asthma control in the patients using either albuterol or salmeterol compared to placebo. Thus, these studies support the conclusion, that chronic use of **$**-agonists does not result in deterioration of airway obstruction. Indeed, in a recent metaanalysis in which the epidemiological data for the risk of death from asthma in patients treated with (**$**-agonists was examined, only a minimal risk could be

documented and only in patients using nebulized **$**-agonists rather than **$**-agonists delivered by metered-dose inhaler (16).

B.3 Treatment of mild asthma with inhaled steroids

An alternative approach to the patient with mild-to-moderate asthma has been to initiate treatment with moderate doses of inhaled steroids. A number of studies have shown benefit in mild-to-moderate asthma patients from treatment with inhaled steroids (17,18,20,21). However, after the medication is stopped the symptoms and physiological changes of asthma return (20,22,23). Are the beneficial effects of inhaled steroids worth the risks of chronic inhaled steroid use? Although there were not significant negative effects of steroids noted in the treatment trials cited above, it has been pointed out (24-30) that there may be long term changes associated with the continued use of these agents in asthma patients. Indeed, there is a feeling among many physicians that steroid treatment is not "worth the risks" in many patients with mild-to-moderate asthma (31-35).

B.4 Summary

These data leave the physician treating the mild-to-moderate asthma patient facing many unresolved questions concerning optimal therapy. Indeed, it is clear that the data on which to base many treatment decisions is not rooted in rigorous, question driven, clinical investigation. We propose in this trial to address one facet of this complex question, namely the role of (**$**-agonists in the treatment of mild asthma. As outlined below, we realize that successful completion of this trial will not resolve all of the questions raised, but it will provide an answer to a significant question about treatment options in a group comprising the largest fraction of the asthmatic population, those individuals with mild asthma.

C. The Hypothesis to be Tested

Population studies (36) demonstrate that the majority of patients with asthma have mild disease. What is the best management for this group? The physician caring for mild asthma patients has to decide among a number of treatment options. Should they treat their mild asthma patients with inhaled **$**-agonists alone or with inhaled anti-inflammatory agents and inhaled **$**-agonists? In either case, should the **$**-agonists be used regularly or only on an "as needed" basis? The treatment options which confront the clinician are shown schematically in Figure 1. Although each of the questions raised is important, they cannot all be addressed at once. Since the likelihood of success of a clinical trial depends on the simplicity of the question posed, we propose the following hypothesis:

In the patient with mild asthma whose only treatment is the use of "as needed" inhaled $-agonists, addition of treatment with inhaled $-agonists on a regular basis will have either a beneficial or a detrimental effect on asthma control.

For statistical considerations in protocol design, this question leads to the following null hypothesis:

Addition of regular inhaled $-agonist treatment to treatment only on an "as needed" basis will result in no effect on asthma control.

D. Rationale for Choosing this Question

Over half the patients who carry a diagnosis of asthma have mild disease. Current treatment guidelines suggest that these individuals should be treated only with inhaled **$**-agonists given on an "as needed" basis (3,5). Since there are approximately 4.5 million people with mild asthma in the United States, even a small impact on the care of this group has the potential for tremendous economic impact. For example, if it can be shown, that patients with asthma benefit from the addition of regular treatment with inhaled (**$**-agonists in terms of asthma control, days lost from school or work, then the individual benefit, when multiplied by the large number of potentially affected patients, results in a substantial overall benefit. Conversely, a demonstration that the use of "as needed" inhaled (**$**-agonist treatment is just as effective as, or perhaps even better than, regular plus "as needed" treatment, there are potential savings of hundreds of millions of dollars in health care costs. Although one could argue that the answer could be predicted by comparing the results of various trials already completed, the tremendous economic and social impact of this issue merits a well designed and dedicated trial in which the question is carefully posed and answered.

Figure 1. Decisions facing the physician treating mild asthma are shown inside the "double-lined" boxes.

Furthermore, among the potential questions which could be addressed (Figure 1) we chose this question for four reasons. First, since most practitioners are currently using inhaled **$**-agonists in their asthma treatment regimens, we should have solid data available to direct their appropriate use. Second, the study by Sears and co-workers, which demonstrated the loss of asthma control with the regular use of inhaled fenoterol, showed the deleterious effect of chronic treatment with inhaled fenoterol even in mild asthma patients who did not require steroid treatment (10,11). Third, the Children's Asthma Management Program (CAMP) trial will address the question of whether inhaled steroids are a viable treatment for mild asthma in a group in whom the side effects of such treatment, like stunted somatic growth, can be easily monitored. Fourth, the trial design, which is of 4 months duration, and includes an analysis of changes in lung function and asthma symptoms at the time of stopping continuous regular treatment with **$**-agonists , will allow detection of persistent and clinically significant changes in these indices.

E. Protocol Overview

This trial will compare the safety and efficacy of regular plus "as needed" use of inhaled albuterol versus the "as needed" use of inhaled albuterol in 250 patients with asthma of mild severity. Albuterol was chosen as the study drug because it is the most commonly prescribed and used intermediate-acting (3-agonist in the United S t a t e s . Furthermore, multicenter studies have been successfully completed in which "regular" and "as needed" use of albuterol have been compared (19), providing a precedent for our proposed trial design. Other inhaled **$**-agonists (including long acting agents) were not considered for the study because they are not likely to be considered as "first line" therapy for patients with mild asthma. In a 6-week single blind run-in period, all patients will be treated with an inhaled placebo, 2 puffs 4 times a day, plus "as needed" inhaled albuterol. Asthma control will be characterized by AM peak flow rates, airway responsiveness, spirometric values, AM/PM peak flow rate difference index, asthma symptoms, quality of life measures, use of rescue medications, and episodes of adverse asthma control. Patients will then be randomly allocated to receive inhaled albuterol, two puffs 4 times a day, or treatment with an identical appearing placebo inhaler. Asthma control will be monitored over the ensuing 16 weeks using the above noted indicators; at the end of this period all patients will be returned to the regular use of a placebo inhaler, 2 puffs 4 times a day, plus the "as needed" use of inhaled albuterol. During the withdrawal period, asthma control will be reassessed as it was during the run-in and active treatment period. Comparisons of asthma control will be made among the run-in, active treatment and withdrawal period and between treatment groups.

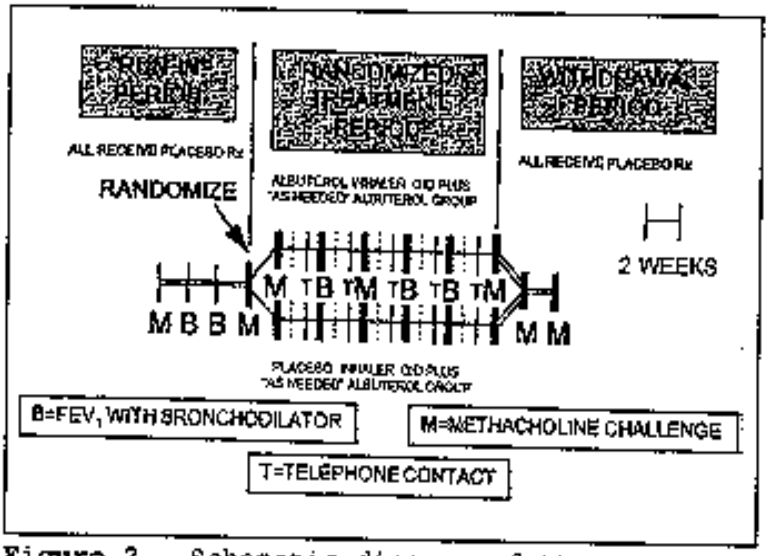

Figure 2. Schematic diagram of the protocol.

The primary outcome indicator to be evaluated will be AM peak flow rate comparing the run-in to the treatment period. This indicator was chosen as the primary indicator because it is a recurrently gathered objective measure that provides a day-to-day index of asthma control. Secondary outcome indicators will be changes in spirometric values, peak flow variability (PM-AM peak flow rate difference normalized by PM peak flow), airway responsiveness, asthma symptoms, quality of life measures, use of rescue medications, and episodes of adverse asthma control over the three periods of the study. Methacholine responsiveness will be used as an index of changes in airway function that occurred over the treatment period; in this case the most important comparison will be between the run-in and withdrawal period.

Each participating center will begin screening patients for possible enrollment beginning in September of 1994. Based on inclusion/exclusion criteria, it is anticipated that 4-5 patients will need to be screened to successfully enter one patient into the run-in period. Each center will attempt to enroll at least 8 - 10 patients per month until the target population is achieved (50 patients/site; 33% minority; no more than 25% being 12 - 18 years of age). The enrollment period will therefore extend over 6 - 9 months. Since each patient will be evaluated over a 26-week time interval, the protocol should be completed at all centers by January of 1996.

II. Inclusion and Exclusion Criteria

A. Inclusion Criteria (at Visit 1)

1. Male and female subjects, without regard to ethnicity, between the ages of 12 and 55 years.

2. Patients with mild asthma, defined as follows: [1]
   "Mild asthma is characterized by mild baseline airflow obstruction in the usual baseline state (FEV, >_ 70% of predicted) and by bronchial hyper-responsiveness.

3. A positive response to inhalation of methacholine by the methods described in the procedure manual (PC_{20} FEV, methacholine less than or equal to 16 mg/ml).

4. Reported use of "as needed" inhaled (3-agonist at least 6 puffs/week or less than 56 puffs/week. If using less than 6 puffs/week, the patient must have a PC_{20} for methacholine of 8 mg/ml or less.

[1] Reversibility of lung function indices will not be considered as a speck enrollment criterion. It is effected that many of the patients enrolled in the trial will have normal or near normal lung function at the time of trial entry. Although reversibility of lung function is not an enrollment criterion it will be monitored during the protocol.

5. Ability to provide informed consent, as evidenced by signing a copy of the consent form approved by the Committee on Human Research of the study institution.

6. If topical nasal steroids will be needed during the study, an ability to take beclomethasone (Sit puffs each sere, bid) during the entire study.

B. Exclusion Criteria for Enrollment into Study (at Visit 1)

1. 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.
2. Medication use: Chronic use of any medication other than study (3-agonists, except oral contraceptives, estrogens for post-menopausal women, vitamins, nasal beclomethasone (ii puffs each nare, bid), acetaminophen, non-steroidal anti-inflammatory medications (e.g. aspirin, ibuprofen), thyroid replacement medication, terfenadine, anti-cholesterol medication, medium and low potency topical steroids.

Table 1. Drugs to be withheld throughout the study	Washout prior to Visit 1
Oral steroids	26 weeks
Inhaled steroids for asthma	26 weeks
Cromofyn/Nedocromil for asthma	26 weeks
Oral beta-adrenergic agonists	21 week
Monoamine oxidase inhibitors	24 weeks
Tricyclic antidepressants	24 weeks
Beta-blockers	24 weeks
Inhaled beta-adrenergic agonists (intermediate-acting eg. albuterol, terbutaline, metaproterenol, pirbuterol	28 hours
Salmeterol	248 hours
Anticholinergics	26 weeks
Short-acting theophyiline (eg, Slophyllin tablets)	212 hours
Long-acting theophylline (eg, Theo-Our, 51o-bid)	224 hours
Ultra long-acting theophylline (eg, Theo-24, Uniphyl)	248 hours
Antihistamines (except Astemizole)	272 hours
Astemizole	280 days
Drugs withheld prior to pulmonary function and/or methacholine testing per MOP	Specified lima period
Terfenadine'	248 hours
Methybcanthine-containing foods or beverages (e.g. coffee, tea)	28 hours
Alcohol-containing foods or beverages	28 hours
'Terfenadine 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.	

3. Lung Disease other than asthma.
4. Significant medical illness other than asthma.
5. History of a respiratory tract infection within the past 6 weeks.
6. History of a significant exacerbation of asthma in the past 6 weeks (See "Adverse Events Related to Asthma Exacerbation" for definition of a significant exacerbation).
7. Current initiation of hyposensitization therapy or receiving immunization therapy not on an established maintenance regimen.
8. Inability, in the opinion of the investigator or clinical coordinator, to coordinate use of a metered dose inhaler (MIDI).
9. History of life-threatening asthma requiring treatment with intubation and mechanical ventilation within the past 5 years.
10. Changes of ischemic heart disease or arrhythmia on screening electrocardiogram (not excluded for occasional [3/min] atrial or ventricular premature contractions).
11. If the patient is between 12 and 18 years of age and the clinical center has enrolled 12 patients in this age group.
12. FEV, less than 70% of predicted.

13. Pregnancy, either at enrollment or during the trial. If potentially able to bear children, not using an acceptable form of birth control (see Manual of Operations, Section 9.2.12).

14. Subjects must be non-smokers of pipes, cigarettes or cigars for at least 1 year; a maximum smoking history of 5 "pack-years" is permitted.

C. Inclusion Criterion During Run-in Period (prior to randomization at Visit 4, week 6)

1. Use of "as needed" inhaled albuterol at least 6 puffs per week and less than 56 puffs/week during the last four weeks of the run-in period. If using less than 6 puffs a week, the patient must have a PC2o for methacholine of 8 mg/ml or less.

D. Exclusion Criteria During Run-in Period (prior to randomization at Visit 4, week 6)

1. Significant asthma exacerbation (See "Adverse Events Related to Asthma Exacerbation" for definition of a significant exacerbation and discussion of steps to be followed for treatment and possible re-enrollment). Note that therapy with all anti-asthma medications other than the inhaled study medications must be discontinued prior to visit one, during the run-in period, and throughout the study.
2. Inability to adhere with regular use of MDI (75% time - at least 42 puffs each week during the last four weeks of the run-in period).

3. Failure to record symptoms in symptom diary on average more than two days/week during the run-in period.

4. Change in status of exclusion criteria in section ILB above.

III. Outcome Measures

The primary outcome indicator to be evaluated will be the weekly average of AM peak flow rate. A longitudinal data analysis will be applied in which a segmented linear model is fit (see section WILE below) and the estimated A.M. peak flow rate at the end of the treatment period will be compared to that at the end of the run-in period. With this type of analysis, all of the data are used in evaluating A.M. peak flow rate. Similar analyses will be applied to the secondary outcome indicators of spirometric values, peak flow variability (PM-AM peak flow rate difference normalized by PM peak flow), airway responsiveness (PC,,, methachoiine), asthma symptom scores, quality of life measures, number of actuations of P-agonist "rescue" MDI, and episodes of adverse asthma control. A categorical data analysis will be applied to compare treatment failure rates.

IV. Protocol

A. Subjects

To have an 80% likelihood of detecting clinically significant changes in morning peak flow and in bronchial reactivity to methacholine (See "Statistical Analysis), we estimate that a total of 250 patients with mild asthma will have to be recruited. This large number of subjects must be appropriately distributed by gender and ethnicity (50% women, 33% ethnic minority) to permit generalizability of the findings to the patient population of interest and must also be recruited rapidly for the study to be completed in a timely manner. Both heterogeneity of the study group and rapidity of recruitment are greatly facilitated by the involvement of several geographically dispersed study centers in a multi-center collaboration. Patients will be recruited from the "standing" populations of the participating centers, by advertisement, and by referral from participating physicians. Patients will meet the inclusion criteria specified herein and not possess any of the exclusion criteria. Every attempt will be made by each center to enroll approximately equal numbers of patients of either gender and to include in their enrolled patients at least 33% (up to 16 patients) from underrepresented minorities.[2] The Data Coordinating Center (DCC) will distribute monthly accrual reports for each clinical center, listing patients entered by age, gender, and ethnicity. This routine monitoring will allow early identification and resolution of problems in achieving demographic goals.

B. Recruitment

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

Harvard Clinical Center

1. Need

Approximately 60 patients with mild asthma are needed to fulfill the recruitment needs of this study at this center. We propose to use the population at Harvard Community Health Plan to achieve our 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 a least 3 months, who were between 12 and 45 years of age, who had pharmacy benefits and who had received prescriptions for P-agonist plus inhaled steroids were selected. Such individuals were also retained in this category if they received concurrent prescriptions for one other asthma medication such as theophylline, cromolyn or nedocromil. Severe asthma was operationally defined as being extant in those individuals who had received prescriptions for (3-agonist plus 2 or more asthma drugs where one of these agents was oral or inhaled steroids. Prescription frequency was not considered when assigning severity categories between moderate and severe patients; failure to consider this may have resulted in an inappropriate assignment of severity category.

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

We will contact a fraction of the 7,588 individuals identified as having mild asthma by the pharmacy search by letter. In this solicitation attention will be paid to postal zip code to achieve the needed minority patients. If we can successfully enroll 1 out of every 100 eligible individuals we should have no difficulty meeting our goals.

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[2] Under-represented minorities include Native Americans, Asian-Pacific Islanders, Blacks and Hispanics.

National Jewish Center/Denver

Research subject recruitment has been very successful for all types of asthma patients at the National Jewish Center for Immunology and Respiratory Medicine. The total of 60 subjects with one-half being female and one-third minority population will come from the following areas.

1. National Jewish Center Outpatient Clinic. The adult clinic saw 1,079 new asthmatic patients 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 patients, but at least 15% are in the mild category. The pediatric clinic saw 490 new asthmatic children with 352 being from the Denver metropolitan area. Again these patients were of varying severity, but about 10-15% are in the mild category. Ninety-seven additional children were seen in follow-up. The National Jewish Center has changed markedly over the last decade. We have evolved from a primary inpatient facility with a small clinic to a very active outpatient service. Thus, we are seeing many more asthmatic patients of all degrees of severity.

2. National Jewish Center asthma research pool. There are over 200 asthma patients (not followed in the NJC outpatient clinic) that have participated in our research studies. Many of these subjects have been through various medication studies and bronchoscopies with lavagelbiopsies. Their FEV1 range from 30-110% of predicted.

a. Denver General Hospital - Dr. Thomas Neff, Head of Pulmonary Medicine, is supporting our efforts by helping us to recruit from the asthmatic patient population at Denver General. This is a large county hospital whose patient population comprises mainly Hispanic and African-American people.

b. Denver Veterans Administration Hospital. Dr. David White, Head of Pulmonary Medicine, will support this grant. The V.A. hospital has a large outpatient clinic of patients 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 March have been actively involved in supporting research at NJC in the past by referring us patients. Their groups will continue to play an active role.

d. Dr. Jay Markson is a pediatrician in a large inner city clinic and will support this grant by recruitment of patients.

University of Wisconsin-Madison

The Allergy Research Program of the University of Wisconsin maintains a file of potential subjects with mild asthma (FEV1 >70%) 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. This file of subjects will be used as the primary source of recruitment for the ACRN beta-agonist 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 patient population. Recruitment of women and minorities from the available pool will be emphasized.

Thomas Jefferson Medical College

All patients with a diagnosis of asthma currently cared for in the outpatient 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. Terminals located at each clinic site are linked to the ACRN file server located in the study coordinator's office. Patients fulfilling every criteria for a given study will be identified by the data-base 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 patient agrees, they will return to the study center to verify entry qualifications and further discuss the study.

University of California/San Francisco

Our basic approach to recruiting subjects with mild asthma for research studies is to place advertisements in editions of the San Francisco Chronicle and Examiner, to place advertisements in small neighborhood

newspapers, and to place fliers on bulletin boards at the UCSF campus and at the campuses of other colleges and universities in the Bay Area. We also place fliers on the bulletin boards of pulmonary medicine and allergy practices at the major teaching hospitals of UCSF (Moffitt-Long, San Francisco General, Ft. Miley VA Hospital, and Mt. Zion Hospital). Responses to these advertisements are made to a dedicated telephone number equipped with an answering machine. We have hired a half-time research assistant to respond to each inquiry and to obtain basic information about the subjects' demographics and about the severity, duration, required treatment, and frequency of symptoms of their asthma. Subjects who pass this telephone screen and who are interested in proceeding are scheduled for a screening appointment in the laboratory. We have obtained permission from our institutional review board to perform basic, simple screening tests on potential research subjects, and these tests include a focused medical history, spirometry, prick skin testing with allergen mixes common to Northern California, and methacholine challenge.

To date, we have entered over 250 subjects in our database. Slightly over 50% of our subjects are women, so we anticipate no problem with meeting the ACRN's needs for both subject number and for gender balance in our studies.

C. Drug Supplies

Drug supplies for this study will consist of albuterol and placebo MDI (200 actuations per inhaler) supplied by Schering-Plough Research Institute. The supply will be forwarded to the DCC for labeling and distribution to the study centers. Albuterol MDI's will deliver 90 pg of drug per actuation. Labelling and masking of MDI's will be the responsibility of the DCC. (See section VIIIB below).

D. Compliance and Monitoring

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

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

2 The Chronolog device will be used to monitor inhaler actuation. The Miniwright peak flow meter with diary recording will be used to record peak flow.

The limitation of the Chronolog is that the subject can activate the MDI without inhaling the medication, but this is better than other forms of measured compliance. Feedback will be given to the subject in regard to appropriate use.

3. Weighing the "regular use" canisters will not be used because placebo and active drug produce different weights for any given number of activations. Thus, once the canisters are weighed blinding of the study will be broken.

"Rescue" canisters will be weighed at each clinic visit and compared to diary records. Clinic coordinators will use these data to aid in compliance assessments with patients at each clinic visit.

E. Study Procedures

Visit 0, Prescreening

Subjects will be interviewed prior to protocol entry (either by phone or in person), as to their asthma and medical history. Specifically, the current status of asthma control, use of asthma and non-asthma medications, and health status in the previous 6 weeks will be determined (refer to Section B, Exclusion Criteria for Enrollment into Study). An overview of the study's goals and visit/procedure requirements will be presented. If the patient appears to fulfill entry criteria, is interested in study participation, ~n is not on oral/inhaled steroids, inhaled nedocromil/cromolyn, salmeterol MDI, or theophylline, Visit 1 may be scheduled. If the patient is on one of these regular asthma medications, a pre-study visit must be scheduled, informed consent obtained, and the patient evaluated by the study investigator as to the appropriateness of drug withdrawal for the 6 weeks prior to Visit 1. If warranted, the investigator may request additional pre-study visits for evaluation of asthma stability during this 6 week period.

Visit 1, Week 0

Patients will visit their clinical center after having had verbal contact with one of the study investigators, or their representatives, concerning the general goal and outline of the trial. On this first visit, written Informed Consent will be obtained using a document which has been approved by the ACRN as well as the local IRB. A medical history, physical examination, allergy skin testing, vital signs, spirometry, and 12-lead electrocardiogram will be obtained. Urine will be obtained for a pregnancy test in females. (See "Timetable for Visits and Data Collected"). If the individual qualifies based on these data, a methacholine challenge will be performed and the Quality of Life questionnaire administered.

If, based on this information, the patient meets the specific inclusion criteria and has the appropriate sensitivity to methacholine (i.e. 8 or 16 [see Section ILC.] mg/ml or less), he/she will be entered into the trial. The patient will be given a "coded" inhaler to be used, 2 puffs 4 times a day, a peak flow recording device, and an albuterol "open label" inhaler to be used for rescue treatment and instructed in their use. Patients will be instructed to use their "regular use" inhaled medications at no less than 3-hour or more than 6-hour intervals. In specific, patients will be instructed to use their "regular" inhaler upon arising (after measuring AM peak flow rate), circa noon, circa 5 PM and at bedtime (after PM peak flow is measured). Prior to distribution, the peak flow meter reading will be checked against that of the spirometer. Only peak flow meters whose readings are within a specified range of the spirometer will be distributed. Patients will be instructed to measure their peak flow twice daily over the course of the entire study. Peak flow will be measured immediately upon arising[3], **before** the use of any inhaled medications, and once between 2000 and 0100 hours. Patients will be instructed not to record peak flow values recorded less than 2 hours after use of inhaled P-agonist. The use of diary cards will be explained and an appropriate supply given for recording asthma symptoms. Patients will be instructed to return to the study center in 2 weeks time.

Skin testing, methacholine challenge testing, spirometry, and the Quality of Life questionnaire will be administered according to protocols outlined in ACRN Manual of Operations and recorded electronically or on forms supplied by the ACRN.

Visit 2, Week 2
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; computer data will be downloaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording; guidelines will be reviewed as needed. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. P-agonist responsiveness will be determined. New "regular use" medications will be dispensed; open label P-agonist will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks time.

Visit 3, Week 4
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; computer data will be downloaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording; guidelines will be reviewed as needed. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. (**$**-agonists responsiveness will be determined. New "regular use" medications will be dispensed; open label **$**-agonists will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks time.

Visit 4 , Week 6
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including urine test (females), pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed; computer data will be downloaded.

If at this time, in the opinion of the clinical center personnel, the patient understands and can follow the protocol adequately to participate in the study, the Quality of Life questionnaire will be administered and a methacholine challenge will be conducted. If the patient continues to meet the entry criteria for the study and does not have any of the exclusion criteria, the ACRN DCC will be contacted and the patient will be randomized to receive either active **$**-agonists or placebo, 2 puffs 4 times a day. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. Based on this randomization patients will receive new "regular use" medications; open label (3-agonist will be issued as needed. New diary cards will be issued and the patient instructed to return to the laboratory in 2 weeks.

Telephone Call - Week 7
The patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, answer any questions that may arise, and assure that their asthma is

[3] For data analysis purposes data from individuals arising before 0500 or after 1000 hours, local time, will not be included.

under adequate control, as assessed by the patient. Specific arrangements will be made for the patient to return to the clinic in 1 week.

Visit 5 - Week 8
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including urine test (female), pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; computer data will be downloaded. The Quality of Life questionnaire will be administered and a methacholine challenge will be conducted. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording; guidelines will be reviewed as needed. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. **$**-agonists responsiveness will be determined. New "regular use" medications will be dispensed; open label (**$**-agonists will be issued as needed. Patients will be instructed to return to the clinical center in 3 weeks time.

Telephone Call - Week 9
The patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, answer any questions that may arise, and assure that their asthma is under adequate control, as assessed by the patient. Specific arrangements will be made for the patient to return to the clinic in 2 weeks.

Visit 6 - Week 11
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; computer data will be downloaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording; guidelines will be reviewed as needed. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. P-agonist responsiveness will be determined. New "regular use" medications will be dispensed; open label P-agonist will be issued as needed. Patients will be instructed to return to the clinical center in 3 weeks time.

Telephone Call - Week 12
The patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, answer any questions that may arise, and assure that their asthma is under adequate control, as assessed by the patient. Specific arrangements will be made for the patient to return to the clinic in 2 weeks.

Visit 7- Week 14
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including urine test (females), pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; computer data will be downloaded. The Quality of Life questionnaire will be administered and a methacholine challenge will be conducted. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording; guidelines will be reviewed as needed. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. (3-agonist responsiveness will be determined. New "regular use" medications will be dispensed; open label P-agonist will be issued as needed. Patients will be instructed to return to the clinical center in 3 weeks time.

Telephone Call - Week 15
The patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, answer any questions that may arise, and assure that their asthma is under adequate control, as assessed by the patient. Specific arrangements will be made for the patient to return to the clinic in 2 weeks.

Visit 8, Week 17
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones

dispensed; computer data will be downloaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording; guidelines will be reviewed as needed. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. (3-agonist responsiveness will be determined. New "regular use" medications will be dispensed; open label (3-agonist will be issued as needed. Patients will be instructed to return to the clinical center in 3 weeks time.

Telephone Call - Week 18
The patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, answer any questions that may arise, and assure that their asthma is under adequate control, as assessed by the patient. Specific arrangements will be made for the patient to return to the clinic in 2 weeks.

Visit 9, Week 20
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; computer data will be downloaded. Clinical center personnel will review the appropriateness of the timing of medication use, peak flow recording and symptom recording; guidelines will be reviewed as needed. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. P-agonist responsiveness will be determined. New "regular use" medications will be dispensed; open label P-agonist will be issued as needed. Patients will be instructed to return to the clinical center in 3 weeks time.

Telephone Call - Week 21
The patients will be contacted by the clinic coordinator to assure that they are continuing to participate appropriately in the study protocol, answer any questions that may arise, and assure that their asthma is under adequate control, as assessed by the patient. Specific arrangements will be made for the patient to return to the clinic in 1 week.

Visit 10, Week 22
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including urine test (females), pulse rate and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; computer data will be downloaded. The Quality of Life questionnaire will be administered and a methacholine challenge will be conducted.

The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. At this time all patients will receive new "regular use" medications which will be a coded placebo; open label P-agonist will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks time.

Visit 11, Week 24
Patients will return to the clinical center at the same time of day as on week 0. A brief physical examination including urine test (females), pulse rate, and respiration rate will be performed. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed and new ones dispensed; computer data will be downloaded. The Quality of Life questionnaire will be administered and a methacholine challenge will be conducted. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. All patients will receive new "regular use" medications (coded placebo); open label a-agonist will be issued as needed. Patients will be instructed to return to the clinical center in 2 weeks time.

Visit 12, Week 26
Patients will return to the clinical center at the same time of day as on week 0. A physical examination will be performed. A urine pregnancy test will be done in females. Spirometry will be obtained. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed; computer data will be downloaded. The Quality of Life questionnaire will be administered and a methacholine challenge will be conducted. All patients will turn in their "regular use" medications and recording devices.

F.

4 Informed consent may be obtained at any time prior to visit one depending on the medication adjustments that need to be made prior to entrance into the run-in period.

5 These procedures may be performed after informed consent has been obtained but prior to day 1.

Protocol in Tabular Form

P=Placebo MDI; **$**=Albuterol MDI

Variable		Run-h			Double Blind Treatment						Withdrawal	
T	1	2	3	4	5	6	7	8	9	10	11	12
Week	0	2	4	6	8	11	14	17	20	22	24	26
Window	-	T3 da	t3 da	t3 da	t3 da	+-1 wk	+- 1wk	+-1 wk	+-1 wk	t3 da	t3 da	t3 da
'Regular'(ie. qid) Treatment	P	P	P	P	**$** or P	**$** or P	**$** or P	**$** or P	**$** or P	**$** or P	P	P
"As needed' Treatment	**$**	**$**	**$**	**$**	**$**	**$**	**$**	**$**	**$**	**$**	**$**	**$**
Randomization				X								
Informed Consent[4]	X											
History	X											
Physical Exam	X											X
Allergy Skin Test[5]	X											
Auscultation	X											X
Blood pressure Pulse	X											X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X
gad ECO with ...rthm strips	X											
Pregnancy test	X			X	X		X			X	X	X
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	X	X
Download Peak Flaw Data		X	X	X	X	X	X	X	X	X	X	X
Dispanae/R.viaw Diary Cards	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Medications	X	X	X	X	X	X	X	X	X	X	X	
13-agonist Response		X	X			X		X	X			
Methacholine Challenge	X			X	X		X			X	X	X
Quality m Life Questionnaire	X			X	X		X			X	X	X

F. Protocol in Tabular Form

G. Risks/Benefits

This is a comparison of two different approved usage strategies for a currently approved pharmaceutical. The risks associated with regular versus “as needed” use of albuterol are minimal and include a small increase in airway responsiveness and a minor loss of asthma control. There are no direct benefits to the individual subjects; there is a potential benefit to patients with asthma in general as a more rational basis for therapy is devised.

V. Adverse Events

A. Definition

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

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 investigator or if the patient is no longer able to effectively participate in the study. Patients 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 judgement of the responsible 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 the illness
- Treatment of illness (medications, doses, dates)
- Whether hospitalization or emergency treatment was required
- Treatment outcome

C. Adverse Events Related to Asthma Exacerbations

C.1 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" (**$**-agonist use of >_8 puffs per 24 hrs over baseline use (baseline defined as average daily use over first 2 weeks of run-in period) for a period of 48 hours or >_16 total puffs per 24 hrs for a period of 48 hrs

- A fall in PEFR of >_35% from reference levels reference level will be defined as the best 3 day (AM and PM) average during the "run-in" section of the protocol).

Patients developing asthma exacerbations during the double-blind treatment period and during the off-treatment period will be managed according to the following rescue algorithms. Patients developing asthma exacerbations during the run-in period will be removed from the study. Once the exacerbation has been resolved the patient may be considered for re-enrollment, starting again with Visit 1.

C.2 Rescue Algorithms

Rescue algorithms will be applied in cases where an exacerbation as defined in Section C.1 fails to resolve or PEFR is not improved to >65% of reference level within 48 hours after increasing PRN albuterol use.

Rescue algorithms are based on recommendations from the NAEP Guidelines for Diagnosis and Management of Asthma (NHLBI Publication No. 91-3042, 1991). Albuterol and oral prednisone are the principal medications for rescue management and patients will be instructed in their use for home management. For severe acute episodes of asthma, treatment will be administered according to the best medical judgment of the treating physician.

C.2a Home Care

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

- Patients who recognize increased symptoms and/or a fall in PEFR #65% reference level will use albuterol by MDI, 2-4 puffs, every 20 min up to 60-90 min if needed and then every 4 hours, or less, if needed. Patients will be instructed to use the "PRN MDI" for treatment.

- If the PEFR does not increase to >60% reference level or if symptoms are not improved after the first 60-90 min of therapy, the patient should contact the investigator, their primary physician or seek care in the emergency department.

- Failure of albuterol to control or maintain PEFR >60% reference level may necessitate the use of steroids (see below).

C.2b Physician's Office or Emergency Room Treatment

- Patients will be assessed by history, physical examination, and by physiological monitoring including spirometry or PEFR. If the patient's PEFR or FEV, are less than 25% predicted or if the patient shows evidence of altered mental status, cyanosis, labored breathing, or use of accessory muscles, sampling of arterial blood for respiratory gas analysis is indicated with appropriate action taken depending on the results obtained.

- When treated in the physician's office or the hospital emergency room, patients should initially be given albuterol by nebulization (0.5 cc of 0.5% solution) every 20 min over the first 60-90 min.

- If the PEFR increases to >60% reference level after the first 60-90 min, the patient can be discharged to continue treatment at home. Prednisone may be administered at the discretion of the physician to augment therapy; see C.2.c

- If symptoms persist and PEFR remains <60% reference level, nebulized albuterol should be continued as often as every hour and further treatment with oral or parenteral corticosteroids should be considered (60 mg prednisone orally; methylprednisolone 60 mg iv bolus). Monitoring of PEFR or spirometry should continue every hour. Within 4 hours of treatment, a decision should be made regarding patient disposition.

- If PEFR increases to >60% reference level within 4 hours, the patient can be discharged to continue treatment at home. Home treatment should include a 8day course of prednisone (see below).

- If PEFR remains >40% but <60% reference level, an individualized decision should be made to hospitalize the patient for more aggressive therapy or to continue therapy at home with a course of prednisone.

- If PEFR is <40% reference level after repeated albuterol treatments, the patient should be admitted to the hospital unless in the physician's best judgment alternative treatment could suffice.

C.2.c Prednisone treatment

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

- For follow-up management after discharge from the physician's office, emergency room, or hospital for an acute exacerbation.
- For home management if the patient is taking **$**16 puffs albuterol per 24 hours over a 48 hour period and, despite this therapy, PEFR remains <60% reference level before albuterol use and the daily sum of the symptom scores in the same period is > 8 (See Patient Diary Card in Appendix 1).
- For home management when the daily sum of the symptom scores is > 10 for 48 hours or longer and the patient is taking **$**16 puffs of albuterol.
- When PEFR falls <50% reference level despite albuterol treatment.

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

D. Adjustment of Trial Medications During Asthma Exacerbations

Trial drugs will be continued during exacerbations unless the treating physician considers it appropriate to suspend such therapy until the exacerbation resolves. Reinstitution of trial medications will occur when the exacerbation has resolved at the discretion of the investigator. A record of all medications, dosages, and frequency of occurrence will be kept during exacerbations.

E. Clinical Center Visits Following Exacerbations

If the patient receives steroids for an exacerbation regular follow-up evaluations will continue according to original protocol.

F. Criteria For Assigning Treatment Failure Status to Patients Due to Asthma Exacerbations

Patients will be considered treatment failures if asthma exacerbations are of such severity or duration that they are effectively unable to control their asthma with the medications allowed in the protocol. Patients assigned "treatment failure" status will continue to participate in the data gathering aspects of the protocol until the time they would have completed the trial. A patient is placed in this status if one of the following criteria are met:

- Deterioration in asthma requiring treatment with inhaled, oral, or intravenous glucocorticoids.
- Need for intubation and ventilator assistance during any exacerbation.

G. Criteria for Assessing Dropout Status

- Patient becomes pregnant.
- Patient withdraws consent.

H. Adverse Events as Outcome Variables

During exacerbations, the following variables will be recorded and used as outcome measures:

- Hospitalization
- Emergency room visits
- Unscheduled physician/clinic visits

- Number of subjects having an exacerbation as defined by prednisones[4] courses
- Treatment failure

VI. Cost, Liability and Payment

All tests will be performed without cost to the participating patients. Since this is a trial comparing two well-established asthma treatments, liability for patient care costs incurred by patients during the course of the trial will in most cases be borne by the patient 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 patient will be paid an amount determined by their local center. For patients who drop out, payments will be pro-rated for the length of time they stayed in the study, but payment will not be made until the study would have been completed had the patient not dropped out.

[6] Prednisone will be the most commonly prescribed medication, but use of any glucocorticoid will place a patient in this group.

VII. Data Recording

Recording of all data including the informed consent, history, physical examination, results of allergy skin testing, vital signs, electrocardiograms, results of pregnancy, adverse events, confirmation of medication dispensation, methacholine challenge testing, and Quality of Life will be recorded on forms prepared by the ACRN Data Coordinating Center. Initial data entry will be done at each Clinical Center and forms will be forwarded to the DCC for confirmatory entry. Results from pulmonary function tests and the metered dose inhaler will be transmitted electronically to the DCC. All data will be stored and analyzed at the DCC.

VIII. Statistical Design and Analysis

A. Data Collection and Data Management

Each center will have a computer configuration that includes an X-terminal, a postscript 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 backup 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 3 days of the patient visit. The advantage of this distributed data entry system is that the Clinic Coordinators will review the data a second time as they are entering it, which serves as another level of quality control. However, the Clinic Coordinators will not be able to query their own data. The data base management system will have range checks and validity checks programmed into it for a second level of quality control. Forms will then be forwarded to the DCC for the second data entry and filing, which will be performed within 3 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. Data collected from the chronolog device for measuring the dispensation of medication will also be downloaded and transferred electronically.

B. Masking

Careful procedures are required in order to maintain triple-masking of the study participants, clinical center personnel, and DCC personnel as to whether individual patients are taking placebo or P-agonist. The DCC will work with Schering-Plough to ensure that sufficient medication for a single patient is supplied for the duration of the study (approximately 11 canisters). The label on the canister will not indicate its contents. Treatment medication for each patient will be packaged together and labeled with a unique number. The contents of the packages will be known only to the database programmer at the DCC. These packages, and canisters for run-in and withdrawal periods will be delivered to the Clinic Coordinators. Triple-masking, i.e., masking of the DCC personnel in addition to the study participants and clinical center personnel, will be employed so that the statistical analyses are not biased by preconceived notions. Until the time of manuscript preparation, DCC personnel will identify the randomized groups as A and B and only the database programmer within the DCC will know the identity of A and B.

In order to decrease the likelihood of incorrect drug distribution, each coded package designated for a study participant will have a sheet of six removable labels attached to it. When the Clinic Coordinator retrieves a canister for the study participant, he/she will remove one of the labels and attach it to the data collection form prior to mailing the form to the DCC. The Clinic Coordinator will initial across the label to indicate that he/she checked to make sure the appropriate canister was distributed to the participant.

C. Randomization

When a patient 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 patient 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 information has been reviewed carefully and the patient is eligible. If so, the Clinic Coordinator will be given a packet number, from which all medication for that patient will be dispensed. In order to maintain security of the randomization schedules, the data manager of the DCC will receive automatically a notice from the ACRN network server that a patient has been randomized. If no follow-up information is forthcoming on such a patient, the data manager will contact the Clinic Coordinators concerning the status of the patient.

D. Stratification

The randomization scheme will be stratified according to center because differences among clinical centers typically yields a large amount of variability. In addition, each clinical center will be restricted to enroll no more than 12 patients (25% of its target sample size of 50) between the ages of 12 and 18.

Within each clinical center the randomization list will consist of blocks (of random size, say 2, 4, or 6 patients) such that each block will contain equal numbers of each treatment group.

E. Statistical Analysis

The primary question to be addressed by this study is whether the change in AM PEFR between the end of the treatment period and the end of the baseline period differs for the albuterol q.i.d. + albuterol PRN and placebo q.i.d. + albuterol PRN groups. Secondary questions to be addressed involve the same comparison but with respect to the secondary response variables such as spirometric values, peak flow variability (PM PEFR - AM PEFR)/PM PEFR, airway responsiveness (PC2o methacholine), asthma symptom scores, quality of life measures, number of occasions and actuations of P-agonist "rescue" MIDI, and episodes of adverse asthma control. Variables that are measured daily from the patient diary cards, e.g., AM PEFR, peak flow variability, and asthma symptom scores, will be averaged on a weekly basis. Another important response variable is the occurrence of treatment failure.

Because of the repeated measurement of the primary and secondary response variables over time, the most appropriate statistical analysis is longitudinal data analysis. In a longitudinal data analysis all of the data from the study participants are incorporated into the analysis. A variety of longitudinal data models have appeared in the statistical literature. We invoke the random coefficient generalized growth curve (RCGGC) model (37, 38), which is a special case of the mixed-effects linear model (39). For the RCGGC model, it is necessary to specify a function for describing the expectation of the chosen response variable over time. Given the design of this trial, a reasonable "within-patient" expectation function is

$$
\begin{aligned}
E(Y_{ijw}) &= \$_{i0} + (w-2)\$_{i1} && \text{if } 2 \# w \# 6 \\
E(Y_{ijw}) &= \$_{i0} + 4\$_{i1} + (w-6)\$_{i2} && \text{if } 6 \# w \# 11 \\
E(Y_{ijw}) &= \$_{i0} + 4\$_{i1} + 5\$_{i2} + (w-11)\$_{i3} && \text{if } 11 \# w \# 22 \\
E(Y_{ijw}) &= (\$_{i0} + 4\$_{i1} + 5\$_{i2} + 11\$_{i3} + (w-22)\$_{i4} && \text{if } 22 \# w \# 26
\end{aligned}
$$

where the subscript i represents treatment group assignment, subscript j represents patient, and subscript w represents week of the trial. Weeks 2-6 correspond to the last 4 weeks off the run-in period, weeks 6-11 correspond to the first 5 weeks of the treatment period, weeks 11-22 correspond to the last 11 weeks of the treatment period, and weeks 22-26 correspond to the withdrawal period. Because we are allowing for a 2-week stabilization period, the data from the first two weeks of the trial will not be included in the analysis. This particular expectation function is called a segmented or piecewise linear function because it consists of a set of connected lines (see Figure 3 for an illustration).

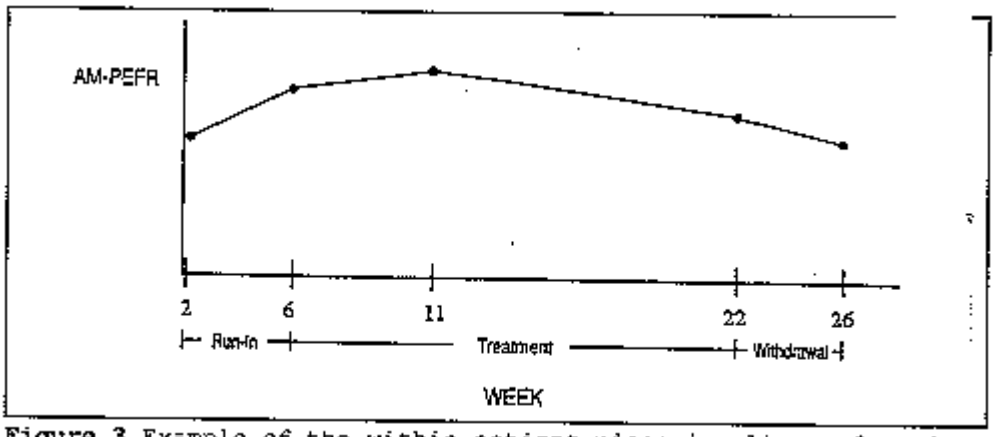

Figure 3 Example of the within-patient piecewise linear function.

The longitudinal data analysis to be applied (37, 38) can be described loosely as follows. The **$**'s are estimated for each patient via least-squares regression. Because each patient yields a different set of **$**'s, this leads to (1) an average set of **$**'s for each treatment group and (2) a 5X5 variance-covariance matrix describing the between-patient variability of the estimates. Thus, in the RCGGC model, there are two sources of variability, namely, the within-patient variability which describes how well (or poorly) a patient's observed data fit the within-subject expectation function, and the between-patient variability which describes how the individual sets of estimated **$**'s vary across patients.

The primary comparison is to determine whether the treatment groups differ with respect to the change between the end of the treatment period and the end of the runin period. This change corresponds to the following contrast of the **$**'s :

$$(5\$_{12} + 11\$_{13}) - (5\$_{22} + 11\$_{23})$$

The statistical approach is to estimate these **$**'s from the data and determine whether the estimated contrast is significantly different from zero. If the estimated contrast is significantly different from zero for a particular response variable, then the conclusion is that treatment groups are significantly different with respect to that response variable and the estimates of $(5\$_{12} + 11\$_{13})$ and $(5\$_{22} + 11\$_{23})$ will indicate the direction of the difference. It should be mentioned at this time that a different set of **$**'s will be modeled for each center so that treatmentxcenter interactions will be explored.

In the balanced and complete RCGGC model, there are no missing data and subject visits are always exactly as scheduled. In reality, there are missed and/or mis-timed subject visits and dropouts in nearly every clinical trial, yielding unbalanced and incomplete longitudinal data. Not only could valuable information be lost if the data from subjects who drop out or miss visits are not included in the analysis, but conclusions based on the statistical analysis could be biased. Therefore, we plan to reduce the bias as much as possible by incorporating all available data in the statistical analysis, regardless of whether a subject has missed some visits, dropped out, or been non-compliant. This is known as the "intent-to-treat" analysis. Subjects will continue to be followed throughout the trial as much as possible and their data will be included in the "intent-to-treat" analysis. A source of bias we will investigate is whether the occurrences of missing values is different for the two groups.

Subjects who are treatment failures actually may exhibit improved lung function when they receive steroids. If one of the groups has a higher rate of treatment failure, then the "intent-to-treat" analysis may indicate that this group has improved lung function significantly more so than the other group. For this reason, as a complement to the "intent-to-treat" analysis, we will exclude all data that are collected after the occurrence of treatment failure.

A secondary analysis to be performed is to account for the compliance of each individual patient in the trial. One way to achieve this is to incorporate the subject's compliance score, as determined from the

diary card or the chronolog data, as a covariate in the model. Finally, other secondary analyses will focus on the subgroup of minority patients.

The occurrence of treatment failure will be analyzed via categorical data analysis, e.g., Mantel-Haenszel statistics or logistic regression. If there is an adequate number of treatment failures (say, 10% of the sample), then time-to-occurrence will be analyzed via survival analysis methods, e.g., logrank tests or proportional hazards regression.

F. Interim Analysis

We plan to conduct an interim analysis of the data midway through the trial (after approximately 100 randomized subjects have completed the trial). In order to adjust the significance level for repeated statistical analyses, we will apply a group sequential procedure which is appropriate for this trial(40). With this approach, the significance level employed at each analysis is adjusted to a value less than the nominal 0.05. In particular, because only one interim analysis and a final analysis will be performed, a significance level of 0.029 will be invoked at each analysis to guarantee that the overall significance level of the trial does not exceed 0.05. Other schemes for assigning significance levels at each analysis have appeared in the literature (41), but the constant significance level across analyses is the most appealing for this trial.

G. Effect Size

Each of the 5 clinical centers will recruit 50 subjects randomized to treatment, providing a total of 250 randomized subjects in the trial. Because of the length of the trial (26 weeks with a 6-week run-in period, a 16-week treatment period, and a 4-week withdrawal period), it is likely that some subjects will not complete the trial and refuse further participation. Therefore, the following calculations are based on the assumption of a 20% dropout rate per center, i.e., 200 randomized subjects completing the trial. Because the centers are limited in terms of recruitment, what is presented below is the effect size for the primary response variable of AM PEFR and the secondary response variable of FEV_1. The effect size is defined as the difference between the treatment groups that can be detected given the sample size, 1-sided or 2-sided test, and the desired level of statistical power.

The primary source for an estimate of variability is a recently-published study on mild asthma (17). This study reported the difference in AM PE FIR and FEV, that occurred between the end of a 2-year treatment period and the end of a 2-week run-in period for two different treatment groups (an inhaled **$**-agonist and an inhaled corticosteroid). This difference is a crude version of the difference between the end of the treatment and run-in periods in the proposed trial, represented by $5\$_{12} + 11\$_{13}$ for treatment group i. Although the cited trial (17) incorporated a 2-year treatment period in contrast to the 16-week treatment period for the proposed trial, it is considered to be the best source of a variability estimate because of similar inclusion/exclusion criteria. The estimate of the effect size for a 2-sided test is

$$\text{Effect Size} = 2\mathbf{F}(z_{1-\mathbf{F}/2} + z_{1-\$})/n^{1/2}$$

where **F** represents the standard deviation of the difference in the response between the end of the treatment and the end of the run-in periods, **"** represents the desired significance level or Type I error rate, **$** represents the desired Type II error rate, $z_{1-\mathbf{F}/2}$ represents the 100(1-**"**/2) percentile and $z_{1-\$}$ represents the 100(1-**$**) percentile from the standard normal distribution, and n represents the total sample size. For the calculations presented below, we use n = 200, **"** = 0.029, and **$** = 0.2, i.e., a 0.029 significance level, 2-sided test with 80% statistical power.

Variable	F	Effect Size	Clinically Significant Difference
AM PEFR (l/min)	55	23.5	25.0
FEV_1 (l)	0.45	0.19	0.20

From this table it is apparent that the target sample size of 250 randomized subjects (with a 20% drop-out rate) is adequate for detecting clinically significant differences. We anticipate that the true effect sizes will

be better (smaller) than those listed in the table because (1) the data from subject withdrawals will be included up to the time of withdrawal and (2) the proposed piecewise regression function should provide better precision (smaller variability) than that reported in the cited trial (17).

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