COLCHICINE IN MODERATE ASTHMA (CIMA) TRIAL

STUDY PROTOCOL

Version 4.0

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I. Background and Hypothesis to be Tested

A. Introduction

Recent investigations have broadened our understanding of the pathogenesis of asthma and have brought to light the importance of airway inflammation in this disorder. Evidence that asthma involves inflammatory mechanisms derives chiefly from histopathologic and bronchoalveolar lavage studies in patients with asthma [1-11]. These studies have generally revealed inflammatory cell infiltration of airway tissues and air spaces, disruption of epithelial surfaces, submucosal edema, and enhanced mucus production. Although inflammatory cell infiltrates consist primarily of eosinophils, other cells including lymphocytes, mast cells, and neutrophils also appear to be important. The role of chronic inflammatory processes involving alveolar macrophages or other accessory cells and activation of a specific cytokine-driven eosinophilic inflammation of the airways is just now gaining appreciation. These processes are thought to involve activated helper (CD4+) T-lymphocytes and cytokine products including interleukin (IL-) 2 and members of the IL-3, IL-4, IL-5 and GM-CSF cytokine family [12,13]. Also noted is the importance of adherence glycoproteins and how they facilitate cellular traffic in the lung [14-17]. Thus, asthma, a disorder manifested clinically by acute episodes superimposed on chronic airway obstruction, displays histologic features of both acute (eosinophilic) and chronic (lymphocytic) inflammation.

Because inflammatory processes play such an important role in asthma pathogenesis, recommended chronic therapy for asthma now places greater emphasis on agents that interfere with inflammatory pathways than agents designed to relax airway smooth muscle. The salutary effects of corticosteroids have been recognized for years and are generally ascribed to their broad but undefined "anti-inflammatory" properties. The Expert Panel Report of the NAEP indeed recognized the benefits of corticosteroids and recommended inhaled steroids as standard treatment of patients with moderate asthma [18]. Because of the perceived importance of inflammation in asthma pathogenesis and because of the potential risks associated with long-term corticosteroid use, there is great interest in finding alternative anti-inflammatory agents for asthma therapy.

A number of novel anti-inflammatory compounds are in varied stages of drug development, some of which have already been shown in clinical trials to have beneficial effects [19,20]. Lacking approval for general use for any of these novel agents, increasing attention has focused on the potential benefits of already-approved anti-inflammatory drugs that are currently used in the treatment of other disease states, such as rheumatoid arthritis, psoriasis, gout, and allograft rejection.

Because of the complex array of putative inflammatory mechanisms postulated to be involved in asthma, there has been hope that agents such as gold salts, methotrexate, cyclosporin and others could prove effective in asthma. A number of studies [21-39] have been carried out to examine their effects and, despite considerable variation in study design in terms of controls, blinding procedures, and numbers of patients tested, it is reasonable to conclude that none of these compounds has shown a risk-benefit profile that would justify its widespread use as an alternative to corticosteroids, especially inhaled corticosteroids. Toxic side effects, especially abnormalities of renal function, overshadow the lung function benefits achieved with gold salts and cyclosporin [21-25;33-35]. Controlled studies using methotrexate have yielded discordant results, suggesting that the benefits of this drug are not universal and perhaps of questionable significance,

particularly in light of the potential for significant adverse reactions to methotrexate [26-32]. The beneficial effects of fish oils, chloroquin, and hydroxychloroquine also remain unproven [36-39].

Colchicine is another widely used anti-inflammatory drug with proven efficacy in the treatment of a variety of chronic inflammatory disorders including familial Mediterranean fever, gout, Behçet's Disease, and primary biliary cirrhosis [40-43]. The potential benefits of colchicine in asthma are largely unexplored. This protocol therefore addresses the following question:

Does colchicine offer therapeutic benefit in the management of moderate asthma?

B. Rationale for Investigating Colchicine in Asthma

Interest in colchicine as a potential form of asthma therapy is largely based on its pharmacodynamic properties and its lack of significant adverse effects with long term use. Colchicine binds to the protein tubulin to alter microtubular polymerization, thus affecting processes dependent on cytoskeletal function. It has numerous putative anti-inflammatory activities including interference with human leukocyte mobilization, chemotaxis, and secretion [44-46]. Of particular interest are studies showing decreased generation of 5-lipoxygenase products from activated human leukocytes after colchicine pretreatment [47-49]. Colchicine also inhibits histamine secretion from immunologically challenged human basophils and sensitized lung fragments [50,51]. Additional studies have shown that colchicine augments cyclic AMP responses after beta-adrenergic stimulation in leukocytes and macrophages, a response that could limit secretion of inflammatory mediators [52,53]. Other potentially important immunomodulatory effects of colchicine that have been reported include alterations in cytokine production by macrophages and lymphocytes [54-57]; altered expression of cytokine receptors in monocytes and lymphocytes [57,58]; increased con-A-induced suppressor cell function in patients with familial Mediterranean fever and primary biliary cirrhosis; and increased con-A-induced suppressor cell function with decreased numbers of circulating monocytes in patients with asthma [59-62].

There is limited information concerning the potential clinical benefits of colchicine in asthma. Schwartz et al [63] gave colchicine (0.5 mg, twice daily for 4 weeks) to 10 atopic asthmatics and demonstrated improved symptoms with a reduction in beta-agonist use. No improvement in pulmonary function was observed in this study, but it should be noted that the study population had relatively normal lung function at baseline, thus precluding the possibility of attaining any appreciable change as a result of treatment.

In another study, the prevalence of current asthma in patients with familial Mediterranean fever was reported to be significantly lower than in the general population (1.1% versus 6.4%). Investigators reporting this finding suggested that the difference was due to the use of colchicine prophylaxis in these patients [64].

Other studies [65] have examined the effects of colchicine on allergen challenge responses in allergic volunteers. Nine ragweed allergic asthmatics demonstrating both early and late phase airway reactions to inhaled allergen were selected for a single blind crossover evaluation of the effects of colchicine on early and late responses to allergen and changes in methacholine responsiveness after allergen inhalation. Colchicine (0.6 mg twice daily for 7 days) provided pronounced inhibition of the late reaction, evident in terms of both maximum percent fall in FEV_1 (38% inhibition; p=0.008) and area under the curve from 2 to 8 hours after challenge (42% inhibition; p=0.008). There was also a trend toward inhibition of the early reaction, although

the changes were less significant. The maximum early reaction (percent fall FEV_1) after placebo was 50.4 ± 6.9% versus 40.8 ± 5.5% after colchicine, reflecting approximately 19% inhibition (p=0.04). These effects of colchicine on allergen-induced late phase reactions are strikingly similar to the reported effects of corticosteroids in the same human model of asthma [65b]. Allergen-induced increases in methacholine responsiveness were observed with both treatments; for placebo, allergen stimulation produced a 3.2 fold mean (geometric) increase in responsiveness as compared to a 2.2 fold increase after colchicine. While changes in responsiveness were not significantly different under the two treatments (p=0.13), there was a trend towards smaller changes in responsiveness with colchicine.

There is considerable experience with long term colchicine therapy for other conditions and published accounts of this experience indicate that such therapy is safe and well tolerated [66-71]. If colchicine is shown to be beneficial in asthma it has additional cost advantages, as the estimated expense of such therapy is as low as $16 per month.

C. Hypothesis to be Tested

Because colchicine is an anti-inflammatory agent, an examination of its potential efficacy in asthma is best carried out in a population of subjects whose disease is thought to have a significant and yet remediable chronic inflammatory component. Unfortunately, there is no specific test that identifies such patients. However, it is reasonable to assume that patients who use inhaled corticosteroids for control of symptoms and lung function are suitable for such a study. Thus, we propose the following hypothesis:

> ***In patients with moderate asthma who use inhaled corticosteroids for control of symptoms and lung function, colchicine provides therapeutic benefit as measured by maintenance of control when inhaled steroids are discontinued.***

D. Rationale for Protocol

Population studies indicate that the majority of asthmatics have mild to moderate disease requiring use of medications for control of symptoms. A significant but unknown fraction of these patients use inhaled corticosteroids for control. Although regular use of inhaled steroids is now considered standard therapy for such patients, the risks of long term use of such agents are unknown, especially in younger individuals still in growth stages of development and in post-menopausal women who are at risk for accelerated bone density loss. If colchicine furnishes an additional measure of control without side effects to patients on chronic inhaled steroid therapy, it may have a significant impact on asthma morbidity in a large number of patients. Such a finding would warrant further investigation of colchicine's efficacy in patients with severe asthma who, despite chronic oral corticosteroid therapy, continue to experience considerable disability, frequent hospitalizations, and significant morbidity from the disease as well as its treatment.

If colchicine maintains control during inhaled steroid withdrawal, it will represent a useful alternative to inhaled steroids with cost advantages as well as possible advantages in terms of toxicity with long term therap

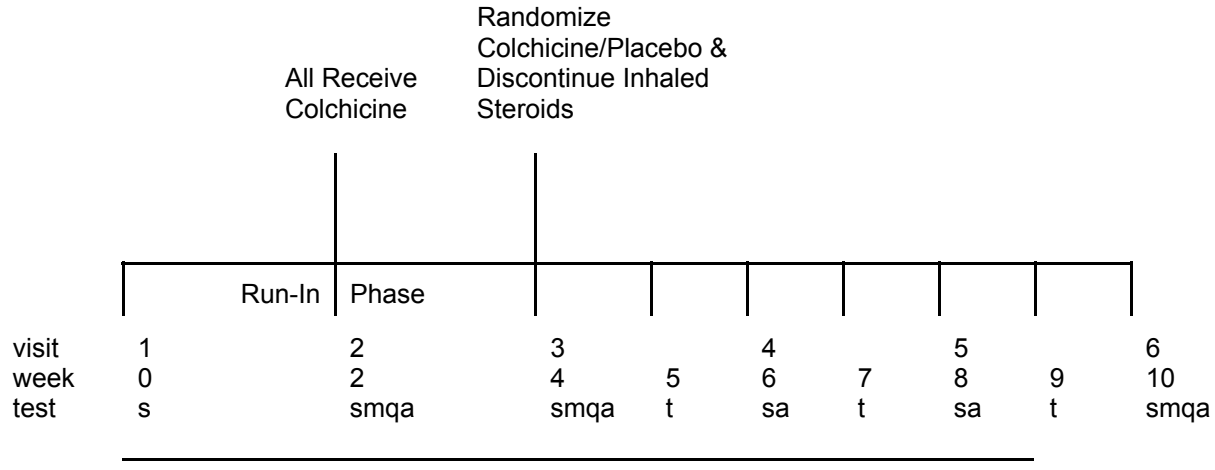
E. Protocol Overview

This trial will examine the safety and efficacy of oral colchicine in 70 patients with asthma of moderate severity who use inhaled corticosteroids for control of symptoms. For entry, patients must use≥ 336 mcgs daily but not more than 1600 mcg daily of any inhaled corticosteroid (e.g., triamcinolone acetonide, beclomethasone dipropionate, or fluonisolide) for symptom control. Patients should be on daily inhaled steroids at a stable dose in the above range for at least 30 days prior to entry and should have a baseline FEV_1 between 55-90% predicted.

During a 4-week run-in phase, patients will be stabilized on triamcinolone acetonide at a dose of 4 puffs twice daily, or 800 mcg daily, and asthma control will be assessed by peak flow rates (AM & PM), asthma symptom scores, as needed inhaled beta-agonist use, airway responsiveness, spirometry, quality of life measures, and episodes of adverse asthma control. For the last two weeks of the run-in period all patients will receive colchicine (0.6 mg, twice daily), in addition to the inhaled corticosteroid, in order to assess their tolerance of colchicine. Patients unable to tolerate colchicine or to maintain $FEV_1 \geq 55\%$ predicted at the end of the run-in phase will be dropped from the study.

Patients who qualify at the end of the run-in will be randomized to continue on colchicine (.6 mg, twice daily) or to take placebo for the last six weeks of the trial. At this time, inhaled steroids will be discontinued but study inhaled beta-agonists will be maintained. Patients will be followed for another six weeks, assessing asthma control as indicated above.

The primary outcome variables will be the time and occurrence of treatment failure after cessation of inhaled steroid therapy (see Section III for treatment failure definition). This variable is chosen because it is thought to best reflect whether colchicine could be used as an alternative to inhaled steroids to maintain asthma control. As a corollary, if there are no differences in treatment failures between groups, it is unlikely that colchicine will be of clinical benefit to a significant number of patients. As a secondary outcome measure, we will compare the FEV_1 change recorded between the end of the run-in period (Visit 3) and the end of the study. The study end is defined as the end of the 6-week observation period after steroid withdrawal (Visit 6) or at the time of patient withdrawal due to treatment failure if such occurs before the end of the stud



peak flow, symptom scores and beta-agonist use kept throughout study

key: s=spirometry; m=methacholine; q=quality of life; a=adverse event; t=telephone contact

Figure 1. Schematic of Protocol

Additional secondary outcome indicators to be used in similar comparisons include AM peak flow, 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. Methacholine responsiveness will be used to assess the effects of colchicine treatment by comparing changes in responsiveness that occur at the end of the first two weeks of the run-in (Visit 2) and after two weeks of colchicine treatment while on inhaled steroids (Visit 3). Changes in responsiveness between Visit 3 and the end of the study will also be compared. In this comparison, only patients completing the 6-week off-steroid phase having a baseline FEV_1 > 55% predicted will be evaluated.

F. Anticipated Results

Several possible outcomes are anticipated from this trial. Based on experience from previous trials[72-75] where inhaled steroids were withdrawn from patients having similar entry criteria as used in this study, it is anticipated that 60% of patients on placebo will qualify as treatment failures within the 6-week final observation period. If colchicine is beneficial using this study design, we would expect to find a significantly lower treatment failure rate (20%) in those receiving medication. We would also expect to find a significantly higher FEV_1 at the final visit in treated versus untreated patients. Based on an enrollment of 14 patients per center, the present protocol design allows us to determine these differences with 80% power.

Because the protocol does not incorporate a positive control (e.g., a steroid continuation arm), it will be difficult to assess how a statistically significant effect of colchicine, if found, would compare to benefits achievable with alternative therapy (e.g., continued use of inhaled steroids). Although this is an acknowledged shortcoming of the present protocol, it is considered acceptable in view of the speculative nature of a study of colchicine's anti-asthma effects and the benefits of limiting expenditure of financial and human resources in such a pilot study. If a significant effect of colchicine can be demonstrated in the present protocol, the Asthma Clinical Research Network (ACRN) could proceed with additional trials to assess the comparative magnitude of the effect and studies to examine the benefits in patients with more severe disease.

It is recognized that the trial may reveal no significant difference between the effects of colchicine and placebo during the steroid withdrawal phase. In this case, it is reasonable to conclude that any difference that might exist is smaller than the difference this study was designed to detect (i.e., 60% treatment failure rate with placebo versus 20% failure rate with colchicine), and that colchicine would not represent an alternative to inhaled steroid therapy in patients with moderate asthma.

This study should provide useful information concerning patients with moderate asthma, regardless of the results obtained. For example, based on previous experience it is anticipated that a number of patients "stabilized" on inhaled steroids will tolerate withdrawal of steroids without deterioration in symptoms or lung function despite taking placebo. What are the differences between moderately severe asthmatic patients who are able to discontinue inhaled steroids without complications versus those who develop exacerbations? It is hoped that this study will enable us to identify factors that will help us better predict who benefits most from steroid therapy and, as a corrollary, who can safely avoid the risks of chronic steroid therapy. Thus, this protocol is expected to provide useful clinical information, even if it proves to be a negative study with respect to the effects of colchicine.

II. Inclusion and Exclusion Criteria

A. Inclusion Criteria (at Visit 1)

1. Male and female subjects between 18 and 60 years of age.

2. Moderate asthma is defined as follows (summarized from the National Asthma Education Program Expert Panel Report, USPHS Publication No. 91-304, p. 71-86) [18]

   "Moderate asthma is characterized by symptoms poorly regulated by episodic administration of a β_2 agonist. Included in this category is asthma causing frequent symptomatic exacerbations (more than twice a week, at night, or with ordinary activities)."

   These patients will have used daily inhaled corticosteroids for control of symptoms for at least 30 days. Patients will have used $\geq$ 336 mcg but not more than 1600 mcg of any inhaled steroid (e.g., triamcinolone acetonide, beclomethasone dipropionate, or fluonisolide) to control their asthma symptoms.

3. Pre-bronchodilator FEV_1 between 55-90% of predicted at Visit 1.

4. Morning cortisol $\geq$ 5 mcg/dL

5. In the preceding 6 months, documentation of $\geq$ 12% FEV_1 response to asthma therapy or a positive response to inhalation of methacholine by the methods described in the procedure manual (PC_{20} FEV_1 Methacholine equal to or less than 8 mg/ml).

6. If topical nasal steroids will be needed during the study, an ability to take beclomethasone ($\leq$ ii puffs each nare bid) during the entire study.

7. 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.

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

1. Use of any drugs listed in Tables 1.A. or 1.B. during the designated washout period prior to Visit 1 or intention to take drugs in Table 1.A. during the study.

Table 1.A. Drugs to be withheld throughout the study.

Drug	Generic Names (may not be inclusive)	Trade Names (may not be inclusive)	Washout Prior to Visit 1
Oral steroids			6 weeks
*Cromolyn/Nedocromil for asthma	cromolyn, nedocromil	Intal, Nasalcrom, Gastrocrom, Tilade	6 weeks
Oral β-agonists	albuterol, metaproterenol, terbutaline	Alupent, Brethine, Bricanyl, Metaprel, Proventil, Ventolin, Repetabs, Volmax	1 week
Monoamine oxidase inhibitors			4 weeks
Antidepressants			4 weeks
Beta-blockers			4 weeks
Short-acting inhaled β-agonists		Primatene Mist, Bronkaid Mist, Duo-Medihaler, Medihaler-Epi	**6 hours**
Intermediate-acting inhaled β-agonists (except study rescue drug)	albuterol, terbutaline, metaproterenol, bitolterol, pirbuterol	Alupent, Brethaire, Brethine, Bronkometer, Maxair, Metaprel, Proventil, Tornalate, Ventolin	**6 hours**
Long-acting inhaled β-agonists	salmeterol	Serevent	48 hours
Anticholinergics	ipratropium bromide	Atrovent	48 hours
Short-acting theophylline	theophylline	Slophyllin, Aminophylline	12 hours
Long-acting theophylline	theophylline	Theo-Dur, Slo-bid	24 hours
Ultra long-acting theophylline	theophylline	Theo-24, Uniphyl	48 hours
Antihistamines (except astemizole, terfenadine chlorpheniramine)	loratidine	Benadryl, Actifed, Claritin,	72 hours
H_1-receptor antagonists	astemizole	Hismanal	80 days
H_2-receptor antagonists	cimetidine, famotidine, ranitidine hydrochloride	Tagamet, Pepcid, Zantac	**48 hours**
Decongestants (except pseudophedrine, oxymetazoline)			48 hours
Quinolone antibiotics	cinoxacin, ciprofloxacin, ofloxacin, norfloxacin, enoxacin, lomefloxacin	Cinobac, Cipro, Floxin, Noroxin, Penetrex, Maxaquin	**3 days**
Macrolide antibiotics	azithromycin, troleandomycin, erythromycin, clarithomycin, dirithromycin, roxithromycin	Zithromax, Tao	6 weeks
Psychotropic drugs		Valium	72 hours

* only allowed for allergic rhinitis if necessary (see MOP for guidelines)

Table 1.B. Drugs/substances allowed during study, but to be withheld prior to pulmonary function and methacholine challenge testing.

Drug/substance	Trade Names	Washout Prior to Visit 1
Study RESCUE Drug	Albuterol	6 hours
Terfenadine	Seldane	48 hours
Chlorpheniramine	Chlor-Trimeton	24 hours
Decongestants (pseudophedrine and oxymetazoline only)	Sudafed, Afrin	24 hours
Methylxanthine-containing food or beverages (caffeinated colas, coffee, tea)	Coke, Pepsi, Mountain Dew, Mello-Yellow	8 hours
Methylxanthine-containing medications	Anacin, Darvon, Esgic, Excedrin, Fiorinal, Fioricet, No-Doz, Norgesic, Vivarin	8 hours
Alcohol-containing foods or beverages		8 hours

Note: Nasal beclomethasone and cromolyn do not need to be discontinued prior to testing , but should be taken the same time prior to the testing, e.g. 4 hours prior to test start.

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

3. Lung disease other than asthma.

4. Significant medical illness other than asthma. Patients with a history of significant renal, hepatic or neuromuscular disease will be excluded.

5. History of having previously experienced untoward side effects from colchicine therapy. Since colchicine is eliminated by urinary and hepatic excretion, patients will also be excluded if they demonstrate evidence of altered renal or hepatic function as defined by abnormalities of the following laboratory tests: BUN, creatinine, total bilirubin, alkaline phosphatase, SGOT, and SGPT (see Section IV.E Laboratory Tests for decision algorithm).

6. History of a respiratory tract infection within the past 6 weeks.

7. History of a significant exacerbation of asthma in the past 6 weeks (see Section V.C. on "Significant Asthma Exacerbations" for definition of a significant exacerbation).

8. Patients who anticipate an allergen immunotherapy dose change during the study.

9. Inability, in the opinion of the investigator or Clinic Coordinator, to coordinate use of metered dose inhaler.

10. History of life-threatening asthma requiring treatment with intubation and mechanical ventilation within the past 5 years.

11. Pregnancy.

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

C. Exclusion Criteria During Run-in Period (Prior to Randomization at Visit 3, Week 4)

1. Patients whose pre-bronchodilator FEV_1 is less than 55% of predicted at Visit 3 on 800 mcg triamcinolone acetonide and colchicine.

2. Evidence of colchicine intolerance.

3. Significant asthma exacerbation (see Section on "Significant Asthma Exacerbations" for definition of a significant exacerbation and discussion of steps to be followed for treatment and possible enrollment).

4. Inability to comply with regular use of steroid metered dose inhaler (use of metered dose inhaler less than twice a day on more than 4 days during the last 2 weeks of the run-in period, as reflected by the medication use record).

5. Inability to comply with the scheduled dose of colchicine at least 80% of the during the last 2 weeks of the run-in period, as reflected by the remaining capsules in the returned

blister card.

6. Failure to record peak expiratory flow rates and symptoms in symptom diary regularly (on average at least five days/week during the run-in period).

7. Change in status of exclusion criteria in Section **II.B.** above.

III. Outcome Measures

The primary outcome indicators to be evaluated will be the time and occurrence of treatment failure. For this protocol, treatment failure will be defined as the occurrence of one or more of the following:

1. FEV_1 value $\leq$ 80% of the value recorded at Visit 3.

2. $FEV_1 \leq$ 40% predicted.

3. A fall in pre-bronchodilator PEFR to $\leq$ 65% of baseline (baseline defined as average AM or PM pre-bronchodilator PEFR recorded during study week 4, just prior to steroid withdrawal) on two out of three consecutive scheduled am or pm measurements.

4. An increase in as needed beta-agonist use of 8 puffs per 24 hours over baseline use (baseline defined as average daily use during the second week of the run-in phase) for a period of 48 hours or $\geq$ 16 puffs/24 hrs for 48 hrs.

5. Refusal to continue with study drugs due to lack of satisfaction with treatment regimen.

All FEV_1 and PEFR readings are pre-bronchodilator, unless otherwise noted. As a secondary outcome measure, we will compare the FEV_1 recorded at the end of the run-in (Visit 3) to that recorded at the end of the study. The study end is defined as the end of the 6-week observation period after steroid withdrawal (Visit 6) or at the time of patient withdrawal due to treatment failure if such occurs before the end of the study (see above for treatment failure definition).

Additional secondary outcome indicators include comparisons at study end of changes in AM peak flow, peak flow variability ((PM-AM peak flow rate difference normalized by PM peak flow), airway responsiveness, asthma symptoms, quality of life measures, and use of rescue medications. Methacholine responsiveness will be used to assess the effects of colchicine treatment by comparing changes in responsiveness that occur at the end of the first two weeks of the run-in (Visit 2) and after two weeks of colchicine treatment while on inhaled steroids (Visit 3). Changes in responsiveness between Visit 3 and the end of the study will also be compared. In this comparison, only patients completing the 6-week off-steroid phase having a baseline FEV_1 > 55% predicted will be evaluated.

IV. Protocol

A. Subjects

To have an 80% chance of detecting statistically significant differences in treatment failure rates, we estimate that a total of 70 patients with moderate asthma will have to be recruited (35 patients per treatment group; accounting for a 10% drop-out rate after randomization). The same number of subjects will allow detection of significant changes in FEV_1 that we consider of clinical importance with the same power (see section VII.E). 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 5 patients) from under-represented minorities.[1] 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 14-16 patients with moderate 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 at least 3 months, who were between 18 and 60 years of age, who had pharmacy benefits and who had received prescriptions for β-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 β-agonist plus 2 or more asthma drugs where

[1] Under-represented minorities include Native Americans, Asian-Pacific Islanders, African Americans, and Hispanics

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 1,883 individuals identified as having moderate 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.

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 14 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 50% are in the moderate 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 40% are in the moderate 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 lavage/biopsies. Their FEV_1 range from 30-110% of predicted.
a. Denver General Hospital - Dr. Michael Hanley, Acting 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 in the 18-20 year age range.

University of Wisconsin-Madison

The Allergy Research Program of the University of Wisconsin maintains a database of potential subjects with 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, pulmonary function testing results, childbearing status, atopic status (including results of skin testing if performed previously), concurrent medical history, asthma and non-asthma medications. 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 patient population. Recruitment of women and minorities from the available database 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 data-base. 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 asthma for research studies relies heavily on community advertising. We place advertisements 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. We also place advertisements on two popular radio stations (one "soft rock" station; one "soul" station). Finally, we place fliers in the patient waiting areas of the Pulmonary Medicine and Allergy Clinics 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 voice mail. We have hired a part-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 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 to determine if they qualify for research studies. These tests include a focused medical history, spirometry, prick skin testing with allergen mixes common to Northern California, and methacholine challenge.

To improve our recruitment of ethnic minorities, especially African Americans, we have opened a second, "satellite" research site in space leased by the UCSF General Clinical Research Center (GCRC) at Summit Hospital in Oakland, CA. This site was established by Dr. Curtis Morris, GCRC Director, for a study of the effects of potassium supplementation on hypertension in African Americans. Dr. Morris has generously allowed us to consult with his clinical research staff for identification of the publications, radio stations, physician practices, community health centers, and census tracts where they have been most successful in recruiting people of minority ethnicity for research studies. People who call to express interest are screened by telephone and by a characterization visit, as described above, except that all procedures are performed at the satellite research site.

To date, we have screened well over 500 subjects for our database. Of those screened at the Moffitt-Long site, less than 10% are members of ethnic minorities. Over 60% of those screened at the Oakland satellite are of this category.

C. Drug Supplies

Drug supplies for this study will consist of colchicine and placebo capsules as well as metered dose inhalers containing Azmacort® and albuterol rescue medication supplied to the DCC for distribution to the Clinical Centers. The Azmacort® and albuterol (Ventolin®) inhalers will be graciously supplied by Rhône-Poulenc Rorer and Glaxo respectively. Labelling and masking of colchicine/placebo capsules will be administered by the DCC.

D. Compliance and Monitoring

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

1. To monitor compliance with colchicine therapy, patients will be instructed to return medication packets (blister packs) at each clinic visit for counting of unused medication.

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

3. "RESCUE" albuterol MDI 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. Laboratory Tests

Blood tests including AM cortisol, BUN, creatinine, bilirubin, alkaline phosphatase, SGOT, and SGPT will be measured at Visit 1 and as appropriate when gastrointestinal side effects are reported (see Section VI). These tests will be analyzed in the clinical laboratories of each ACRN center. A copy of the laboratory certification and list of normal ranges for the above values for each center will be kept on file at the DCC.

Pregnancy tests will be performed using urine pregnancy kits from Abbott Laboratories.

The following laboratory value decision algorithm will be used for enrollment with respect to BUN, creatinine, bilirubin, alkaline phosphatase, SGOT, and SGPT values:

1. If all test results are within normal limits, enroll patient.

2. If test result is outside normal range, repeat the test.

3. Upon repeat, if result is normal, enroll patient. If the repeat test value is again abnormal, but results are within limits for being without clinical significance, the patient may be enrolled

The following limits will be applied:
BUN and creatinine: > 1.25 x upper normal limit

Bilirubin, alk phos, SGOT, SGPT > 1.5 x upper normal limit
(Patients with Gilbert's Disease will not be excluded.)

F. 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 II.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, and is not on oral 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. If documentation of $\geq$ 12% FEV_1 response to asthma therapy or PC_{20} $FEV_1 \leq$ 8 mg/dl in the last 6 months does not exist, these tests may be done as part of prescreening.

Visit 1, Week 0

Patients will visit their Clinical Center after prescreening or 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, and spirometry will be obtained. β-agonist responsiveness will be determined. Urine will be obtained for a pregnancy test in females. (See "Timetable for Visits and Data Collected"). A blood sample for AM cortisol[2], BUN, creatinine, bilirubin, alkaline phosphatase, SGOT and SGPT will be obtained.

If, based on this information, the patient meets the specific inclusion criteria, he/she will be entered into the trial. The patient will be given a steroid inhaler (Azmacort®) to be used as 4 puffs twice daily. The inhaled steroid shall be taken prior to 10:00 AM and between 9:00-12:00 PM. The patient will also be given a peak flow recording device, and an albuterol "open label" inhaler to be used for rescue treatment and instructed in their use. 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. The patients will be instructed to measure 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 taken less than 2 hours after use of inhaled beta-agonist on diary cards. If a peak flow value $\leq$ 65% of baseline is recorded, the patient will be instructed to use rescue therapy as recorded in Section V.B. 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.

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

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[2] If a patient's visits are not in the morning a special AM visit will be necessary to obtain AM cortisol.

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

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 will be performed. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed.

The Quality of Life questionnaire will be administered. Spirometry will be obtained and a methacholine challenge will be performed for patients who have an FEV_1 value $\geq$55%. The patient's peak flow meter will be replaced if its reading is inconsistent with that of the spirometer. Patients will be given active colchicine (0.6 mg twice daily) and maintained on inhaled steroids as given during the previous two weeks. New diary cards will be issued and the patient will be instructed to return to the study center in 2 weeks.

Patients may experience colchicine-related side effects such as abdominal cramping, diarrhea, or nausea after starting therapy. These symptoms should not be treated with any medication, over-the-counter or prescribed. If these symptoms are intolerable, patients may skip the next scheduled dose of colchicine. However, therapy should then be resumed for the next scheduled dose after the skipped dose. If intolerable symptoms persist, the patient may be terminated prior to randomization. Only a single dose of colchicine can be skipped during the run-in between Visits 2 and 3.

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 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 for the appropriateness of medication use timing, peak flow recording, and symptom recording. Guidelines will be reviewed, as needed.

Patients having an FEV1 value < 55% predicted at this visit or demonstrating colchicine intolerance will be excluded from further participation.

If at this time, in the opinion of the Clinical Center personnel, the patient understands and can follow the protocol adequately, 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 inconsistent with that of the spirometer. 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 colchicine or placebo, 0.6 mg twice daily, for the remainder of the trial. Study medication will be dispensed and the patient will be instructed to discontinue use of inhaled steroids. Patients will be instructed to return to the Clinical Center in 2 weeks or to contact the study center if they fulfill treatment failure criteria in the interim.

Telephone Call-Week 5

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. The coordinator will attempt to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue beta-agonist use, peak flow measurements and symptoms. If it is determined that the patient fulfills criteria for treatment failure, they will be advised to visit the study center within 24 hours for evaluation and initiation of treatment as specified by ACRN protocol (see Section V). Otherwise, arrangements will be made for the patient to return to the clinic in 1 week.

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 pulse rate and respiration will be performed. Spirometry will be obtained. β-agonist responsiveness will be determined. The patient's peak flow meter will be replaced if its reading is not consistent with that of the spirometer. Adverse events and evidence of treatment failure will be sought and noted using the protocol outlined by the ACRN to manage asthma exacerbations. 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. New study medications will be dispensed and inhaled beta-agonists will be issued as needed. Patient will be instructed to return to the Clinical Center 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 under adequate control, as assessed by the patient. The coordinator will attempt to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue beta-agonist use, peak flow measurements and symptoms. If it is determined that the patient fulfills criteria for treatment failure, he/she will be advised to visit the study center within 24 hours for evaluation and initiation of treatment as specified by ACRN protocol (see Section V). Otherwise, 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 pulse rate and respiration will be performed. Spirometry will be obtained. β-agonist responsiveness will be determined. The patient's peak flow meter will be replaced if its reading is inconsistent with that of the spirometer. Adverse events and evidence of treatment failure will be sought and noted using the protocol outlined by the ACRN to manage asthma exacerbations. Diary cards will be reviewed and new ones dispensed. 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. New study medications will be dispensed and inhaled beta-agonists will be issued as needed. Patients will be instructed to return to the Clinical Center in 2 weeks.

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. The coordinator will attempt to determine whether the patient is showing signs of treatment failure. Specifically, the coordinator will inquire about rescue beta-agonist use, peak flow measurements and symptoms. If it is determined that the patient fulfills criteria for treatment failure, he/she will be advised to visit the study center within 24 hours for evaluation and initiation of treatment as specified by ACRN protocol (see Section V). Otherwise, arrangements will be made for the patient to return to the clinic in 1 week.

Visit 6, Week 10

Patients will return to the Clinical Center at the same time of day as on week 0. A physical examination will be performed. Spirometry will be obtained. All patients whose FEV_1 is $\geq$55% predicted will undergo methacholine challenge testing. The patient's peak flow meter will be tested to confirm that it is consistent with the spirometer. A pregnancy test will be done in females. Adverse events will be sought and noted using the protocol outlined by the ACRN. Diary cards will be reviewed. The Quality of Life questionnaire will be administered. All patients will turn in unused study medications and recording devices. At this time, patients will be replaced on the inhaled steroid regimen they were taking at the initiation of the study. If the patient fulfills criteria for treatment failure or if, in the judgement of the physician, the patient requires additional therapy to achieve stability, treatment may be given in accordance with ACRN protocol (see Section V).

Treatment Failure Visit

In the event of a "treatment failure" (see Section III), patients will be instructed to come into the Clinical Center as soon as possible, preferably within 72 hours and ideally within 24 hours. At this time the patient will undergo spirometry with a test of β-agonist responsiveness and a physical exam with adverse events assessment. The patient's peak flow meter will be tested to confirm that it is consistent with the spirometer. Diary cards will be reviewed and new ones dispensed. The Quality of Life Questionnaire will be administered. Any non-study drugs taken prior to spirometry testing at this visit will be documented. Patients will continue to follow the protocol with respect to PEFR measurements, maintaining diaries, and keeping scheduled visits to the Clinical Center, but will not undergo methacholine challenge testing and will be removed from the double-blind treatment phase and placed on a regimen to achieve asthma control. The study drug will be collected and new rescue inhaler distributed if necessary. Based on pulmonary function and other measures, the treating physician will place the patient on an appropriate treatment program.

G. Protocol in Tabular Form

Procedure	Run-In			Double Blind w/o steroids			Treatment Failure Visit
Visit	1	2	3	4	5	6	---
Week	0	2	4	6	8	10	---
Window		±2da	±2da	±2da	±2da	±2da	
Dispense Medications							
Colchicine		X					
Study Drug*			X	X	X		
Inhaled Steroids	X	X					
Rescue Inhaler	X	X	X	X	X		X
Randomization			X				
Informed Consent**	X						
History	X						
Physical Exam	X					X	X
Pulse/Respiration	X	X	X	X	X	X	X
Allergy Skin Tests	X						
Spirometry	X	X	X	X	X	X	X
β-agonist response	X			X	X		X
Methacholine Challenge		X	X			X	
Peak Flow Meter QC	X	X	X	X	X	X	X
AM Cortisol	X						
CBC,Diff,BUN, Cr,Bili, SGOT,SGPT***	X						
Pregnancy Test	X					X	
Adverse Events Assessment		X	X	X	X	X	X
Dispense/Review Diaries	X	X	X	X	X	X	X
Quality of Life Survey		X	X			X	X

* Placebo or Colchicine

** Informed consent may be obtained at any time prior to visit 1 depending on the medication adjustments that need to be made prior to entrance into the run-in period.

*** As needed when gastrointestinal side effects reported (see Section VI)

H. Risks/Benefits

Oral colchicine is considered safe when used according to well established therapeutic practices. However, like theophylline, colchicine has a low therapeutic index and is known to have significant toxicity if recommended doses are exceeded. The clinical toxicity of colchicine and its management have recently been reviewed by Putterman et al [73].

Colchicine intoxication due to intentional or accidental overdose may be fatal. A recent review of the literature by Putterman [73] indicates that ingestion of more than 0.8 mg/kg colchicine almost always results in death, while ingestion of less than 0.5 mg/kg produces serious but usually reversible toxicity. However, there are exceptions where fatal toxicity has been reported at lower doses. The lowest reported oral doses causing fatal reactions have been 7 mg given over three days to a 39-year old male in a case described as colchicine hypersensitivity [77] and single doses of 7.5 and 11 mg given respectively to an 18 year-old female [78] and a 13-year old male [79]. Fatal reactions are less likely to occur with oral than intravenous administration, since gastrointestinal side effects are an early sign of toxicity with oral administration and serve as a warning to discontinue dosing. Acute colchicine intoxication is a multisystem disorder characterized by shock, multisystem organ failure, ARDS, and disseminated intravascular coagulation. Complications also include sepsis due to bone marrow hypoplasia and leukopenia [76].

Studies of patients taking usually prescribed oral doses for prevention of symptoms of familial Mediterranean fever or treatment of cirrhosis (0.5 or 0.6 mg twice daily) reported only mild gastrointestinal effects, such as reversible abdominal cramps and diarrhea, occurring in 16-25% of patients [43,80].

There are reports of oral colchicine causing azoospermia and male fertility problems [69,81]. For example, 4 of 19 males taking 0.5-2.0 mg colchicine daily experienced fertility problems, including one case of azoospermia. These effects reversed after drug discontinuation. Studies have failed to demonstrate adverse effects of colchicine on female fertility, ovulation, miscarriage rates or healthy births [68,73,82].

Neuromuscular side effects including muscle weakness and peripheral neuropathy have also been reported [83], but only in patients with renal impairment. These effects remitted within a month of discontinuation of therapy.

To avoid risks associated with colchicine toxicity in this study, the following measures will be taken: (1) Medication will be distributed in lots of 36 pills every 2 weeks so that patients will possess a maximum total dose of only 21.6 mg at any one time[4];
(2) Medications will be packaged in "blister packs" to avoid accidental consumption of excessive drug;
(3) Since colchicine is eliminated by both biliary and urinary excretion, patients with abnormal renal or liver function or a history of significant renal or liver/biliary disease will be excluded. In addition, drugs affecting drug metabolism (e.g., cimetidine, macrolide and quinolone antibiotics, etc.) will not be allowed during the study; and (4) Patients will be thoroughly counseled concerning the risk of accidental or intentional overdose and proper dosing prior to study entry.

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[4] Distribution of 36 pills provides additional medications for up to 96 hrs in the event the patient is unable to keep a scheduled appointment.

Apart from risks associated with colchicine therapy, there is additional risk related to withdrawing inhaled corticosteroid therapy. Specifically, asthma may worsen as a result of withdrawing inhaled corticosteroids. This is an expected result of this trial, since the primary outcome measure is the time and occurrence of treatment failure (see Section III). In order to protect patients from undue harm, the following safeguards are provided: (1) patients will be informed of the risks of asthma exacerbation and provided with methods to identify when exacerbations are occurring (see Sections III and V.A); (2) patients will be given cards describing names and means of contacting study personnel on a 24 hr/day basis; (3) patients will be given a supply of prednisone to take as instructed by a study physician; (4) specific protocols for treatment of exacerbations are provided in the protocol (see Section V.B).

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. Significant Asthma Exacerbations

A. Definition

The criteria for "treatment failure" status due to poor asthma control are defined in Section III. Poor asthma control leading to "treatment failure" status may, depending on severity, also require intervention for patient safety. The following is a description of procedures for medical intervention during an asthma exacerbation. 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:

1) An increase in "as needed" beta-agonist use of 8 puffs per 24 hrs over baseline use (baseline defined as average daily use during the second week of run-in period) for a period of 48 hours or ≥16 total puffs per 24 hrs for a period of 48 hrs

2) A fall in pre-bronchodilator PEFR to ≤ 65% of baseline (baseline defined as the average AM or PM pre-bronchodilator PEFR recorded during study week 4, just prior to steroid withdrawal[5])

Patients developing an exacerbation during the run-in period (prior to randomization) will be dropped from the protocol and treated according to the judgment of the investigator or primary physician. After the exacerbation has resolved, the patient may be re-enrolled in the protocol if eligibility criteria are met and if, in the judgment of the investigator, the patient can maintain asthma control with 800 mcg triamcinolone acetonide and as needed beta-agonists.

Patients developing asthma exacerbations during any phase of study will be managed according to the following rescue algorithms.

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[5] Prior to this time baseline will be defined as the average AM or PM pre-bronchodilator PEFR recorded during the second week of the run-in period.

B. Rescue Algorithms

Rescue algorithms will be applied in cases where an exacerbation as defined in Section A fails to resolve or PEFR is not improved to >65% of baseline (baseline defined as the average AM or PM pre-bronchodilator PEFR recorded during study week 4, just prior to steroid withdrawal) within 48 hours after increasing as needed 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.

B.1 Home Care

Asthma exacerbations will be recognized by an increase in symptoms and by a corresponding drop in PEFR below baseline (baseline defined as the average AM or PM pre-bronchodilator PEFR recorded during study week 4, just prior to steroid withdrawal). 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 to $\leq$ 65% baseline 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 "Rescue MDI" for treatment.

If the PEFR does not increase to >60% baseline 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% baseline may necessitate the use of steroids (see below).

B.2 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_1 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.

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% baseline 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.

If symptoms persist and PEFR remains <60% baseline, 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% baseline within 4 hours, the patient can be discharged to continue treatment at home. Home treatment should include a 8-day course of prednisone (see below)

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

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

B.3 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 in 48 hours and, despite this therapy, PEFR remains <60% baseline before albuterol use and symptom scores in the same period are > 8

For home management when symptom scores are > 10 for 48 hours or longer and the patient is taking ≥ 16 puffs of albuterol.

When PEFR falls <50% baseline 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.

C. Discontinuing Patients From Blinded Treatment Phase and Clinical Center Visits Following Discontinuation

All "treatment failures" will be removed from the double-blind treatment phase and placed on a regimen (unblinded) to achieve asthma control. Patients discontinued from the blinded treatment phase due to

treatment failure or any adverse events will continue to follow the protocol with respect to spirometry, PEFR measurements, maintaining diaries, and keeping scheduled visits to the study center.

D. Significant Asthma Exacerbations as Outcome Variables

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

Hospitalization

Emergency room visits

Unscheduled physician/clinic visits

Treatment failure

VI. Adverse Events

A. Definitions

Both clinical and laboratory adverse events will be documented and reported. A laboratory adverse event is any clinically important worsening in a test variable which occurs during the course of the study, whether or not considered to be drug-related. A clinical adverse event is any unintended worsening in the structure (signs) or function (symptoms) of the body, whether or not considered to be drug-related. This includes any side effect, injury, or sensitivity reaction, as well as any intercurrent event. Only conditions that appear or become worse after study entry will be recorded.

B. Procedures and Reporting

All possible adverse events related to drug administration will be explained to the patient verbally and in the written consent form. Patients reporting gastrointestinal side effects such as abdominal cramping or diarrhea that is considered mild and to present no risk of dehydration to the patient will be asked to continue therapy. If symptoms increase in severity or persist for longer than 4 days, the patient will be asked to return to the study center for evaluation by a physician and to obtain the following laboratory tests:

serum BUN and creatinine
serum total bilirubin
serum alkaline phosphatase, SGOT, SGPT

Patients demonstrating evidence of significant abnormalities (see Section IV.E and Appendix A) of the above tests or clinical signs of colchicine toxicity will be given supportive therapy and study drug will be terminated. These patients will be placed on their baseline dose of inhaled corticosteroids from Visit 1 and will be followed through the end of the study and until drug-related adverse events are resolved.

Clinical adverse events due to intercurrent illnesses 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 judgment of the responsible physician.

Documentation of an adverse event will be recorded on the Clinical or Laboratory Adverse Event Report Form and will include the following information:

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

VII. Cost, Liability and Payment

All tests will be performed without cost to the participating patients. 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. Patients dropped from the study for adverse events will receive full payment at the time they would have completed the trial.

VIII. Data Recording

Recording of all data including the informed consent, history, physical examination, results of allergy skin testing, vital signs, 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 DCC. 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 will be transmitted electronically to the DCC. All data will be stored and analyzed at the DCC.

IX. 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 CIMA Forms Subcommittee. 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 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. 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

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 colchicine. The DCC will work with the pharmaceutical supplier to ensure that sufficient medication for a single patient is supplied for the duration of the study. 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 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 removable labels attached to it. When the Clinic Coordinator retrieves a package 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 package 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, 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 and whether a patient is taking $\leq$ or >800 mcg of inhaled steroid at Visit 1. Center is an important stratifying variable in multi-center trials because differences among Clinical Centers typically yield a large amount of variability. Inhaled steroid dosage is an important stratifying variable in this protocol because it indicates the level of patient reliance on inhaled steroids.

Within each Clinical Center and Visit 1 inhaled steroid group, the randomization list will consist of blocks (of random size, say 2 or 4 patients) such that each block will contain equal numbers of each treatment group.

E. Statistical Analysis

The primary response variables in this study are time and occurrence of treatment failure, where treatment failure is defined in Section III. Kaplan-Meier survival curves will be constructed for the placebo and colchicine groups. Statistical tests, such as the logrank test and the generalized Wilcoxon test, will be applied to compare the survival curves of the groups.

In addition, a proportional hazards regression analysis will be applied, which allows for comparing the survival curves of the groups in the presence of other covariates. In this type of analysis the hazard function at time t is modelled as

$$h(t; \mathbf{x}) = h_0(t)\exp(\mathbf{x}^T\boldsymbol{\xi})$$

where
$h_0(t)$ is the unspecified baseline hazard,
$\mathbf{x} = [x_1 \ldots x_k]^T$ is a vector of explanatory variables, and
$\boldsymbol{\xi} = [\xi_1 \ldots \xi_k]^T$ is a vector of unknown parameters.

The vector $\mathbf{x}$ will include indicator variables for treatment assignment, Clinical Center, and treatment × center interactions. The assumption of proportional hazards is important for the logrank test and the proportional hazards regression. This will be assessed via graphical procedures (comparing log survival plots) and statistical tests (including time-dependent covariates in the proportional hazards regression and testing for significance).

A secondary response variable of interest is the change in FEV_1 between the end of the trial (either at treatment failure or at Visit 6) and the end of the run-in (Visit 3). Other secondary responses include changes in AM peak flow, airway responsiveness, asthma symptoms, quality of life measures, and use of rescue medications. For most of these response variables, analysis of variance and repeated measurements analysis will be applied.

F. Sample Size

Schoenfeld [84] described a formula for sample size calculations based on a proportional hazards regression. For a two-sided test in a two-armed trial, the total number of failures required is

$$4(z_{1-\beta} + z_{1-\alpha/2})^2/\{\log(\Delta)\}^2$$

where
z_γ represents the 100γ percentile from the standard normal distribution,
α is the Type I error rate,
β is the Type II error rate, and
Δ is the hazard ratio of the two treatment groups.

If exponential distributions are assumed for the placebo and colchicine groups, then the corresponding hazard functions and their ratio is constant and not a function of time. Letting θ_p and θ_c denote the proportion of failures in the placebo and colchicine groups, respectively, and letting T denote the length of the trial, then the hazard functions are $-\log(1-\theta_p)/T$ and $-\log(1-\theta_c)/T$, respectively, and the hazard ratio is $\Delta = \log(1-\theta_p)/\log(1-\theta_c)$. From previous trials of this duration (see section I.F), the estimates of θ_p and θ_c are 0.6 and 0.2, respectively, so that $\Delta = 4.106$. For a 5% significance level test with 80% statistical power ($\alpha = 0.05$ and $\beta = 0.20$), Schoenfeld's formula yields that a total of 16 failures are needed. Because the failure rates are 0.2 and 0.6 within the placebo and colchicine groups, respectively, then 16/(0.1+0.3) = 40 patients are needed. Allowing for a 10% drop-out rate yields a final sample size estimate of 45 randomized patient

For the secondary response variable of change in FEV_1 between the end of the trial (either at treatment failure or at Visit 6) and the end of the run-in (Visit 3), a previous trial of similar duration (see Section I.F) revealed a mean change for the placebo group of -0.32 L (S.D. = 0.41, n = 69) and for the treated group of 0.10 L (S.D. = 0.42, n = 77). For the effect size of an FEV, change of 0.3L with a 10% withdrawal rate, and a two-sided 5% significance level test with 80% statistical power, the required sample size is 70 randomized patients.

It is then necessary to have a target sample size of 70 patients, 14 per Clinical Center. Because of the relatively small sample size and the short duration of this trial (10 weeks for each patient), an interim analysis is not planned.

APPENDIX A
ADVERSE EVENTS GRADING SCALE

TEST	GRADE 0 (NONE)	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE-THREATENING OR DEBILITATING)
BUN	≤1.25 x N*or B*	1.26-2.5 x N*or B*	2.6-5 x N*orB*	5.1-10 x N*orB*	>10 x N* or B*
Creatinine	≤1.25 x N*or B*	1.26-2.5 x N*or B*	2.6-5 x N*orB*	5.1-10 x N*orB*	>10 x N* or B*
Bilirubin	≤1.25 x N*or B**	1.26-2.5 x N*or B**	2.6-5 x N* or B**	5.1-10 x N* or B**	>10 x N* or B**
SGOT/SGPT	≤1.25 x N*or B**	1.26-2.5 x N* or B**	2.6-5 x N* or B**	5.1-10 x N* or B**	>10 x N* or B**
Alkaline Phosphatase	≤1.25 x N*or B**	1.26-2.5 x N* or B**	2.6-5 x N* or B**	5.1-10 x N* or B**	>10 x N* or B**

N*= upper limit of normal

B*= baseline level at entry if baseline level is > 1 but < 1.25N*

B**= baseline level at entry if baseline level is >1 but <1.5 x N*

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