Childhood Asthma Management Program (CAMP)

Protocol

Repository:
CAMP Coordinating Center
The Johns Hopkins Center for Clinical Trials
615 North Wolfe Street
Baltimore, Maryland 21205
(410) 955-8175
(410) 955-0932

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Abstract

The childhood asthma management program (CAMP) is a multicenter, masked, randomized, placebo-controlled clinical trial carried out in children with asthma. The trial is designed to determine the long-term effects of 3 treatments (two classes of anti-inflammatory agents [budesonide or nedocromil] and placebo) on pulmonary function as measured by normalized FEV_1 over a 5-6½ year period. Every patient will use an intermittent (as needed) short-acting O_2-agonist (albuterol).

Nine hundred sixty children, aged 5 to 12 (one third from ethnic minority groups), who have had asthma with chronic symptoms for at least 6 months during the past year (as indicated by symptoms at least twice per week, at least twice weekly use of bronchodilators, or daily asthma medication), and a PC_{20} FEV_1 (methacholine) of 12.5 mg/ml or less, will be randomized to one of three treatment groups and followed for a minimum of 5 years (3 visits per year) after enrollment into the trial.

The treatment groups will be compared with respect to lung function (FEV_1). In addition, comparisons will be made with respect to bronchial responsiveness (PC_{20} FEV_1) to methacholine, frequency of self-reported asthma symptoms, days of limited activity, and days lost from school. Physical growth and development (growth rate and bone density), psychological growth and development (neurocognitive functioning and social adjustment), and side effects will also be compared.

1. Background

Asthma represents the most common chronic respiratory disease of childhood. As defined by the National Asthma Education Program of the NHLBI, asthma is a lung disease characterized by: (1) airway obstruction that is at least partially reversible, (2) airway inflammation, and (3) increased airway responsiveness to a variety of stimuli (NHBLI, 1991). There are 3 million asthmatics under the age of 18. Asthma accounts for 2.2 million pediatrician visits per year and 28 million restricted activity days (Gergen et al, 1988). It is the most commonly cited reason for school absence, and is the most frequent cause of hospitalization at most acute care pediatric hospitals. In addition, asthma hospitalizations are increasing among children (Evans et al, 1987). Between 1979 and 1987 the hospital discharge rate for asthma for children < 15 years old rose 43 percent from 19.8 to 28.4/100,000 population (Mak et al, 1982). The rate of hospitalization has increased by 300 percent in the last two decades (Halfon and Newacheck, 1986). The overall cost for childhood asthma exceeds 1 billion dollars per year.

Blacks in the United States appear particularly disadvantaged with respect to asthma, enduring (1) higher prevalence rates and greater severity of disease, (2) greater emergency department utilization as the primary source for asthma care, (3) increased hospitalization rates, and (4) higher mortality rates. Similarly, the poor suffer an increase in asthma prevalence, emergency department utilization, and hospitalization rate. An analysis of Maryland hospital discharge data for the period 1979-82 (Mullally et al, 1984) revealed that some or all of the increased risk of hospitalization experienced by the black children may be related to poverty rather than race. On the other hand Schwartz, et al (1990) in the second NHANES survey of children 6 months to 11 years of age, observed a prevalence of frequent wheeze of 9.3% in blacks compared to 6.2% in whites. In a logistic model for asthma, risk factors were black race (relative odds (RO) = 2.5), male gender (RO = 1.4), younger maternal age (RO = 1.4), residence in inner city (RO = 1.6), and low family income (RO = 1.7).

These findings suggest that blacks are still at increased risk after adjustment for poverty. The reasons for this are unknown but theoretically may include lack of access to, or delay in reaching, appropriate medical care, deleterious sociological attitudes to present medical institutions, and excess environmental exposures including allergens and direct and passive cigarette smoke inhalation. Specifically, families and individuals with both lower socioeconomic status and educational level appear to smoke more, breast feed less, and require day care services sooner for their children, all factors which may influence asthma morbidity. These data clearly establish asthma as a major health care problem for children, with substantial morbidity that disproportionately affects the poor and minority populations.

The impact of asthma on any individual is highly dependent on the control of the disease that can be achieved by elimination of precipitating factors and medical therapy. The trends described above have occurred in spite of improved understanding of the pathophysiologic mechanisms of asthma and availability of more effective medications for its use. Both published and anecdotal information indicates that many of the hospitalizations occur because of improper or under utilization of medication. Even though medications are available for long-term treatment of the inflammatory component of asthma, they are not often used, especially not on a chronic basis, by the children who have high degrees of morbidity and mortality (Birkhead et al, 1989). These observations are perhaps even more relevant for the less dramatic but still important morbidity issues, such as ability of the

children to play and participate in school. There is a growing concern in the medical community that asthma should be treated more aggressively. This concern is the principal reason for this trial.

1.1 Epidemiologic model of growth and decline of lung function

In addition to substantial morbidity, childhood asthma may have important influences on growth and development. Consideration of this possibility requires some knowledge of how childhood events influence adult lung function.

An epidemiologic model for growth and decline in lung function has been developed from limited longitudinal data in children and adults (Figure 1) (Sparrow and Weiss, 1989). The model suggests that the development of chronic obstructive lung disease (line d) may result from an abnormally rapid rate of decline in lung function. Events that occur in childhood, however, alone or in conjunction with constitutional factors, could influence adult pulmonary function in several ways. First, childhood factors might diminish the maximally attained level of lung function in early adult life and increase the likelihood that, with a fixed rate of decline in adult life, some individuals would be more likely to develop disease. Alternatively, childhood events might act directly or interact with the effects of active smoking to increase the risk of earlier and/or more rapid decline in pulmonary function in adult life. Among several childhood factors considered in a multivariate analysis, asthma was shown to have a strong effect on pulmonary function growth in childhood, resulting in an estimated deficit of 5 to 7 percent in FEV_1 by age 14 for females who developed asthma at age 7 (Weiss et al, 1992). In addition to relieving morbidity, treatment of childhood asthma may improve growth of lung function, thus preventing or minimizing adult obstructive lung disease. This is the underlying rationale for this randomized controlled trial.

1.2 Natural history of asthma

There are relatively few cohort studies that examine the natural history of asthma. Most of the studies that have been performed have been conducted in children with follow-up into early adulthood. The methodologic problems presented by these investigations are relevant to their interpretation. All but one of these studies (McNicol and Williams, 1973A; McNicol and Williams, 1973B) are hospital- or clinic-based, thus leading to possible bias in selection of the more severely ill cases. Many (Barr and Logan, 1964; Buffum and Settipane, 1966; Ogilvie, 1962; Ryssing and Flensborg, 1963) are retrospective in design, thus raising important questions about loss to follow-up. None of the trials incorporates a physiological test of airways reactivity, although several examine the question of atopic allergy (Buffum and Settipane, 1966; Ogilvie, 1962; Ryssing and Flensborg, 1963; Kraepelien, 1963). No clear, currently accepted definition of asthma is given in most of the studies (Barr and Logan, 1964; Buffum and Settipane, 1966; Ogilvie, 1962; Ryssing and Flensborg, 1963; Kraepelien, 1963; Rackemann and Edwards, 1952). The criteria for skin test positivity are

unclear in some (Buffum and Settipane, 1966; Ryssing and Flensborg, 1963; Kraepelien, 1963; Rackemann and Edwards, 1952), and none have examined serum IgE levels. Perhaps most importantly, only one trial (McNicol and Williams, 1973B; Martin et al, 1980) utilizes population-based controls. Only two studies (Ogilvie, 1962; Williams and McNicol, 1969) examine the role of respiratory infection, and no trial considers the potential role of cigarette smoking, either personal or parental. No trial considered all risk factors, and none utilized multivariate techniques. In spite of these limitations, some conclusions about the natural history of asthma can be made, albeit tentative.

Roughly 50 percent of children with asthma improve or become symptom-free by early adulthood. On the other hand, significant disease persists in roughly 40 percent of patients. Because all children have growth in lung function in childhood and there is a loose correlation between symptoms and level of lung function, the loss of symptoms may provide a false sense of security. Even in asymptomatic children pulmonary function deficits may persist and put patients at risk for disease in adulthood (Figure 1, line c). Age of onset has a complicated relationship to disease prognosis. While children have a greater chance of remission than adults who develop the disease, within children an earlier age of onset carries a worse prognosis (McNicol and Williams, 1973B, Williams and McNicol, 1969). Whether the presence of atopy increases disease severity after controlling for age is unknown. When McNicol and Williams (1973B) stratified their sample of children by age and examined the relationship of skin test reactivity to disease severity, they found atopy associated with increased severity of disease.

There are no reliable data that relate respiratory infection, allergen exposure or cigarette smoking exposure to childhood asthma prognosis. Given these uncertainties this clinical trial will provide unique information on the natural history of asthma in childhood and its influence on growth and development, information that is badly needed by clinicians to enable them to accurately predict the risks and benefits of treatment.

1.3 The role of asthma in modifying lung growth

There is little information on pulmonary function of asthmatic children followed for several years. Martin and coworkers (Martin et al, 1980) followed a subgroup of the Williams and McNicol cohort and assessed their pulmonary function at age 21 years (14 years after trial onset). Although statistically significant differences were found between the patients when grouped by initial disease severity, the means for all groups were within the 80 to 120 percent of predicted FEV_1 range and therefore are considered normal by clinicians and physiologists. For the most severely ill group, the mean was closer to 80 percent predicted than the 100+ percent predicted of the controls. This difference could have important implications for decline in adult life, as the maximal attained level of lung function may be an important predictor of rate of decline (Fletcher et al, 1976).

Airway inflammation is the most likely mechanism by which asthma might be related to altered growth of lung function; IgE mediated immune responses are potential stimulators of an inflammatory response. The variety of proteases, prostaglandins, superoxide anions and leukotrienes that are released can induce a significant inflammatory response, as evidenced by the airway pathology of patients dying of asthma and bronchial biopsy of mildly symptomatic patients (Kay, 1987). In this regard, clinical studies of small numbers of selected asthmatics have shown that the peripheral eosinophil count correlates with clinical severity of diseases (Ellul-Micallef et al, 1974). Cross-sectional epidemiologic studies have documented that peripheral blood eosinophilia is correlated with level of lung function in children (Iijima et al, 1985) and an increased persistence of respiratory symptoms independent of the effect of cigarette smoking (Taylor and Luksaz, 1987). However, existing reports are all cross-sectional in nature, and no report relates eosinophils to both indices of atopy and airways responsiveness. If airway inflammation is important in asthma and its effect on lung growth, anti-inflammatory medication may decrease morbidity in childhood and maximize the potential for normal growth.

The role of airway responsiveness in asthma and its relationship to asthma severity is controversial (Josephs et al, 1989). Increased airway responsiveness is seen in virtually all cases of active asthma in children (Weiss et al, 1984). A variety of cross-sectional studies have documented the relatively common occurrence of increased levels of airway responsiveness in asymptomatic, nonasthmatic children in community based studies (Weiss et al, 1984; Hopper et al, 1991). One trial has demonstrated that such children are at increased risk of developing asthma if followed prospectively (Hopper et al, 1991). What remains unclear is whether the degree of increased bronchial responsiveness correlates with disease severity and prognosis. Only a longitudinal trial of asthmatic children with serial measurements of airway responsiveness can address these issues.

Also important are known environmental factors which can exacerbate the clinical course of asthma and its response to therapy. There are three factors which are worth mentioning: cigarette smoking, respiratory illness and allergens. Two cross-sectional studies have documented an association between passive cigarette smoke exposure and asthma symptoms (O'Connor et al, 1987; Murray and Morrison, 1986). A third report (Martinez et al, 1988) also has found a relationship between passive cigarette smoke exposure and airway responsiveness in a population sample of 9 year old children. Community surveys in Michigan and Massachusetts suggested that between 18 and 34 percent of asthma in children under 17 years of age was attributable to maternal cigarette smoking (Gortmaker et al, 1982). Furthermore, asthmatic children whose mothers smoked had more symptoms, required more medicine, and had greater bronchial hyperresponsiveness during the winter months (Murray and Morrison, 1988). These cross-sectional studies do not assess the interrelationship of cigarette smoking (active or passive) with airway responsiveness on lung growth nor do they assess the possibly modifying role of atopy on these relationships. Because of the close interrelationship between cigarette smoking, atopy and respiratory illness (Weiss et al, 1989), longitudinal investigations offer the best hope of determining the role, if any, of these factors on

abnormal lung growth in asthmatic children. It seems important to collect information on these factors in this clinical trial as they may influence treatment effects. The influence of environmental factors will also be important. Exposure of children to wood burning stoves (Honiky et al, 1985) and to unvented gas stoves (Samet et al, 1987) has also been reported to be a risk factor for respiratory disease.

1.4 Present status of asthma therapy

The goal of asthma therapy is multiphasic: 1) to relieve bronchospasm, 2) to protect the airways from irritant stimuli, 3) to prevent the pulmonary and inflammatory response to an allergen exposure, and 4) to resolve the inflammatory process in the airways leading to improved pulmonary function with reduced airway hyperresponsiveness. The individual medications may be described with regard to their capacity to improve pulmonary function by bronchodilation, to protect the airways from allergen or histamine challenge, and to resolve airway hyperresponsiveness via anti-inflammatory properties (Table 1).

The NHLBI Guidelines for the Management of Asthma (1991) and the International Paediatric Asthma Consensus Group (Warner et al, 1992) emphasize the need to incorporate anti-inflammatory medications as first-line therapy in the treatment of patients with moderate asthma. The available bronchodilator and anti-inflammatory medications have identified benefits with definite limitations in the treatment of asthma. Newer medications, such as budesonide, nedocromil, salmeterol, and formoterol, may offer significant advantages over those presently available. The following section will summarize the present status of available medications.

1.4.1 Non-bronchodilator anti-asthma medications

In the United States, only two classes of inhaled anti-inflammatory asthma medications are available at the present time: inhaled glucocorticoids and cromolyn sodium. In separate controlled studies, use of inhaled glucocorticoids or cromolyn led to improvement in: 1) asthma symptoms (Burrows et al, 1977; Schwartz, 1984; Kerrebijn, 1990; Salmeron et al, 1989; Dutoit et al, 1987; Shapiro and König, 1985), 2) pulmonary function (Burrows et al, 1977; Schwartz, 1984; Kerrebijn, 1990; Salmeron et al, 1989), 3) non-specific bronchial hyperactivity (Kerrebijn, 1990; Shapiro and König, 1985; Cockcroft and Murdock, 1987; Barnes, 1990; Bierman and Shapiro, 1989), 4) emergency room relapses (Burrows et al, 1977; Shapiro and König, 1985), and 5) hospitalizations (Burrows et al, 1977; Salmeron et al, 1989). Expeditious use of oral glucocorticoids appears to reduce asthma hospitalizations of children evidencing worsening asthma or asthmatics discharged from the emergency room (Bierman and Shapiro, 1989; Harris et al, 1987; Storr et al, 1987; Shapiro

et al, 1983; Weinberger, 1988). Compared to chronic use of the inhaled O_2-agonist terbutaline, the inhaled glucocorticoid budesonide administered to mild asthmatics significantly reduced one cellular degranulation product, eosinophil cationic protein (ECP), levels in bronchoalveolar lavage (BAL) fluid (Adelroth et al, 1990). In an earlier trial, cromolyn preadministration in a dosage of 40 mg *qid* daily for 4 weeks significantly reduced eosinophils within BAL fluid as well as improved asthma symptoms (Flint et al, 1985).

1.4.1.1 Inhaled glucocorticoids

Glucocorticoids represent the most potent anti-inflammatory agents available for the treatment of asthma.

Inhaled glucocorticoids demonstrate clinically important improvements in bronchial hyperresponsiveness which 1) appear dose related (Kraan et al, 1988) 2) can occur as early as a few weeks after initial administration but take months to attain maximal effect (Woolcock et al, 1988) and 3) prevent increases after seasonal exposure to allergen (Lowhagen and Rak, 1985) as summarized recently (Woolcock and Jenkins, 1990). When administered prior to an allergen challenge in a sensitized patient, they block the late phase pulmonary response and the development of airway hyperresponsiveness (Cockcroft and Murdock, 1987). Continued administration is also effective in reducing the immediate pulmonary response to an allergen challenge. They are also more effective than O_2-agonists, theophylline and cromolyn in reducing airway hyperresponsiveness during maintenance treatment (Dutoit et al, 1987; Kerrebijn et al, 1987; Svendsen et al, 1987). All of these studies were conducted over a maximum trial period of six months. Thus, there is a critical need to evaluate the efficacy of selected agents over a prolonged period of time. Some of the anti-inflammatory effects attributed to glucocorticoids include 1) reduction of eosinophil quantity and function, 2) inhibition of late phase reactions, 3) inhibition of membrane phospholipase A_2 activity through induction of lipomodulin and macrocortin, which reduces leukotriene medicated inflammatory effects, 4) reduction in basophilic cells and function, 5) stabilization of cell membranes, and 6) increase in O-adrenergic effectiveness.

Budesonide is the most carefully characterized inhaled glucocorticoid. It is a non-halogenated glucocorticoid with high topical anti-inflammatory potency and low systemic bioavailability. Studies (Toogood et al, 1989) suggest that a 1 mg per day dose of budesonide produces an anti-asthmatic effect equivalent to approximately 35 mg per day prednisone in patients previously receiving steroid therapy and 58 mg per day in patients who have not received steroids. This dose of inhaled budesonide also produces a systemic effect on serum cortisol concentration equivalent to 8.7 mg per day prednisone. Budesonide doses exceeding 1.84 mg/day in adults may produce systemic effects on cortisol levels and eosinophil counts that are equivalent to approximately 15 mg per day prednisone. The latter dose is associated with steroid complications, such as osteoporosis.

Budesonide is also very well characterized in regards to deposition. Following intravenous administration of budesonide in healthy male volunteers, the plasma budesonide half-life was 2.8 ± 1.1 hrs (mean ± S.D.) and plasma clearance was 1395 ± 458 ml/min/1.73 m^2 (Ryrfeldt et al, 1982). The plasma protein binding for budesonide was 88.3 ± 1.5% with negligible binding to transcortin. Following oral budesonide administration, only 10.7 ± 4.3% is absorbed, consistent with extensive first pass metabolism, likely in the liver. From *in vitro* studies with human liver, two major metabolites were isolated, 6O-hydroxybudesonide and 16O-hydroxyprednisolone. These metabolites have 1/100th the biological activity of budesonide (Dahlberg et al, 1984). The disposition of these metabolites is not known. Budesonide is a 1:1 mixture of two epimere that provides a relative binding affinity approximately 7 times greater than dexamethasone. In glucocorticoid receptor binding and biological activity measurements in skeletal muscle, differences were noted in the binding affinity and activity of the two epimere. The 22R-epimere was twice as active as the 22S-epimere, 4 times greater than triamcinolone, and 14 times greater than dexamethasone (Dahlberg et al, 1984).

1.4.1.2 Cromolyn

Given the potential for systemic effects of inhaled glucocorticoids, even at low doses, it is important to identify nonsteroid anti-inflammatory medications. At the present time, cromolyn is the only medication that fits into this category. This medication blocks both the early and late phase pulmonary response to allergen challenge as well as preventing the development of airway hyperresponsiveness (Cockcroft and Murdock, 1987). Although the precise mechanism of action is not known, several mechanisms have been proposed including mast cell stabilization, as well as some suppressive effects on other inflammatory cells. Other proposed mechanisms include inhibition of excitatory responses via vagal reflex mechanisms. There are also suggestions that cromolyn may have a direct action on relaxing smooth muscle or potentiating other bronchodilator agents (Murphy, 1987).

A few longer term studies of chronic cromolyn use in a placebo controlled format evidenced small reductions in non-specific bronchial hyperactivity to histamine (Dickson and Cole, 1979). Cromolyn sodium by metered dose inhaler (MDI) was shown to be highly effective as measured by significant improvements in 1) controlling asthmatic symptoms, 2) improving lung function, and 3) decreasing the need for concomitant bronchodilators (Blumenthal et al, 1988). In another large scale multicenter trial (Eigen et al, 1987) of 397 adult and childhood asthmatics inadequately controlled with inhaled O_2-agonists or theophylline, cromolyn treatment for 10 to 12 months in a double-blind placebo controlled investigation led to significant improvements in asthma severity, morning and evening peak expiratory flow rates, and days of disrupted normal activity.

1.4.1.2 Cromolyn

Cromolyn's primary advantage is the minimal incidence of adverse effects, making it a safe medication for all age groups including young children. The beneficial effects of cromolyn relate to its prophylactic effect on allergen and exercise-induced asthma. There are no studies available that show cromolyn, or for that matter any other chronic medication, alters the natural history of the disease.

It is well recognized that only a percentage of patients respond and it has the highest probability of being effective in patients with mild asthma. As the severity of asthma increases, the beneficial effects of cromolyn are less obvious.

1.4.1.3 Nedocromil

Nedocromil is being proposed as a nonsteroidal anti-inflammatory medication with properties very similar to cromolyn, but having the advantage of being effective on a wider array of inflammatory cells, with a marked and sustained effect on reducing airway hyperresponsiveness.

Nedocromil inhibits histamine release in human lung mast cells (Leung et al, 1986) and the antigen-induced release of histamine, leukotriene C_4 and prostaglandin D_2 from bronchoalveolar lavage cells of macaques sensitized to Ascaris sum and is approximately 200 times more potent than cromolyn in this model (Eady, 1986). Rebuck et al evaluated the effect of nedocromil 4 mg four times per day (n=127) versus placebo (n = 61) in adult asthmatic patients with a double-blind, parallel trial over a 3-month treatment period. They reported a slight but significant benefit of nedocromil based on diary card symptom scores, morning and evening peak expiratory flow rates, and inhaled O_2-agonist use (Rebuck et al, 1990).

In a similar trial design Bel et al (1990) compared inhaled nedocromil sodium 4 mg per dose (n=9) and beclomethasone dipropionate 100 Og per dose (n=8) and placebo (n=8) administered four times per day for four months in nonatopic adult asthmatic patients. Compared to the pretreatment value, methacholine PC_{20} FEV_1 did not change in the placebo group, but increased significantly by a factor of 3 after 8 weeks of treatment with beclomethasone or nedocromil. FEV_1 did not change after placebo or nedocromil, but increased after 4 weeks of treatment with beclomethasone. Maximal and partial expiratory flow volume curves (M/P ratio) were obtained via deep breath measured during methacholine-induced bronchoconstriction. Geometric mean M/P ratio increased from 1.98 to 2.66 after 4 weeks of beclomethasone but not after nedocromil or placebo. Therefore, nedocromil and beclomethasone attenuated airway hyperresponsiveness, but through different mechanisms.

1.4.1.3 Nedocromil

Svendsen et al (1989) compared the effects of nedocromil sodium, 4 mg twice daily, and beclomethasone dipropionate, 200 Og twice daily, in a double-blind, double dummy, crossover trial of 39 adult asthmatic patients with 6 weeks for each trial drug. Both treatment groups demonstrated improvements from baseline in clinical assessment of lung function performed after the first 6 weeks of treatment. No significant differences were observed when the effects of treatment were compared on FEV_1, FVC, and peak expiratory flow. Bronchial reactivity to histamine (PC_{20} FEV_1) decreased significantly with beclomethasone compared to the effect of nedocromil. Asthma severity, symptom score, and inhaled bronchodilator use demonstrated significantly better results with beclomethasone. After crossover of treatment, the group transferring from nedocromil to beclomethasone continued to improve, whereas the group crossing from beclomethasone to nedocromil tended to demonstrate a major deterioration during the first 3 weeks, after which a stabilization or an increase in FEV_1, FVC, and in PC_{20} FEV_1 appeared to occur. It was concluded that nedocromil was effective, but the inhaled glucocorticoid had a greater effect on clinical response and pulmonary function. While nedocromil appears to offer advantages in the treatment of asthma, additional studies are needed to confirm its long term efficacy.

1.4.2 Bronchodilators

In some respects, these medications are viewed as supplementary to the nonbronchodilator anti-asthma medications. The frequency of use could be an indicator of the need for additional anti-inflammatory therapy.

1.4.2.1 Theophylline

Although a weak bronchodilator when compared to O_2-agonists, the main advantage of theophylline is the long duration of action, 10 to 12 hours with the use of sustained-release preparations, especially useful in the management of nocturnal asthma (Joad et al, 1987). Theophylline has moderate bronchoprotective effects in regard to exercise and histamine challenge, and also attentuates the early and late phase pulmonary response to an allergen challenge (Pauwels et al, 1985). This may be related to potential anti-inflammatory properties, since it decreases microvascular leakage and macrophage activity.

Theophylline demonstrates only a very small protective effect on bronchial reactivity to methacholine or histamine, does not protect against the increase in bronchial hyperactivity following antigen challenge, and in long term treatment reduced bronchial hyperactivity to a small extent (Elizabeth et al, 1990). From these data, combined with the necessity to determine blood levels to optimize theophylline efficacy and minimize side effects, theophylline use during a long-term 5 year trial would be inconvenient. Moreover, the recognized narrow window between efficacy and toxicity

demands frequent determinations of serum drug levels. Its questionable action as an anti-inflammatory agent, combined with its potential for significant adverse effects argue for the emergence of a safer first-line maintenance medication for childhood asthma.

1.4.2.2 O_2-agonists

This group of medications has evolved from those that are relatively short acting (epinephrine, isoproterenol) to those of longer duration of action (albuterol, terbutaline, pirbuterol), but still lasting only 4 to 6 hours (Joad et al, 1987). Their greatest advantage is a rapid onset of effect in the relief of acute bronchospasm via smooth muscle relaxation. These medications are the treatment of choice for acute exacerbations of asthma and are indicated for the treatment of episodic bronchoconstriction. They are also excellent bronchoprotective agents for pretreatment prior to exercise, perhaps, related to their effect of blocking release of mediators from mast cells. Prior to allergen exposure, they effectively block the early pulmonary response, but are of insufficient duration of action to prevent the late phase pulmonary response unless administered in high doses (Twentyman et al, 1991). They do not block the development of airway hyperresponsiveness (Cockcroft and Murdock, 1987).

O_2-agonists are often used in the maintenance therapy of mild asthmatics who are considered candidates for continuous therapy (Canny and Levison, 1990; Warner et al, 1989). However, this form of treatment has been criticized based on the results of several recent studies. To date, available studies indicate that adverse effects of O_2-agonists are very limited. These include tremor, tachycardia, and palpitations (Canny and Levison, 1990). At high continuous doses used in the treatment of refractory acute exacerbations, hypokalemia has been reported (Schnack et al, 1989). This has not been observed on routine chronic therapy with conventional doses.

Of greater concern is the apparent failure of chronic O_2-agonist therapy to reduce airway hyperresponsiveness. Indeed, a comparison of an inhaled glucocorticoid, budesonide, with the inhaled O_2-agonist, terbutaline, by Kerrebijn et al (1987) raised the question whether routine use of this medication could result in increased airway hyperresponsiveness. This observation received further discussion with the recent disturbing report of Sears et al (1990). These investigators performed a double-blind, placebo-controlled, randomized crossover trial involving 89 adult asthmatic patients. The patients inhaled fenoterol or placebo four times daily for a period of 24 weeks. The placebo group was allowed to use bronchodilator medication on an as needed basis. Patients were allowed to continue cromolyn sodium or inhaled glucocorticoid if they were previously taking that medication. Of the 64 patients completing the trial, 30% showed better control of their asthma with regular bronchodilator therapy, whereas 70% had better control with the bronchodilator used only as needed. Mean airway responsiveness to methacholine increased slightly during the regular fenoterol treatment period even when glucocorticoids were administered at the same time. Although this was an adult trial with a particular O_2-agonist that is not available in the United States,

it raised very important questions regarding the use of regular O_2-agonist therapy for the treatment of asthma.

Haahtela et al (1991) compared an inhaled O_2-agonist, terbutaline in a dose of 375 Og twice daily, to an inhaled glucocorticoid, budesonide 600 Og twice daily, over a two year trial period in 103 newly diagnosed asthmatic patients, ages 15 to 64 years. This trial was randomized, masked, and parallel in design. While the response to inhaled histamine was improved in the patients receiving inhaled budesonide, it was also improved to a lesser extent in the patients receiving terbutaline. The response to budesonide was greater than that to terbutaline in measurements of morning and evening peak flow expiratory rate. Budesonide was also more effective in reducing asthma symptoms and the use of supplemental O_2-agonist treatment. Interestingly, a slight increase in the use of supplemental O_2-agonist treatment occurred in the terbutaline group. The investigators concluded that "anti-inflammatory therapy with inhaled budesonide is an effective first-line treatment for patients with newly detected, mild asthma, and it is superior to the use of terbutaline in such patients".

One can argue that this observation needs further evaluation. It appears that the traditional and simplistic view that O_2-agonists act simply by dilating airways is insufficient to explain their beneficial effect in the treatment of asthma. O_2-agonists may reduce the exudation of plasma into inflamed airways (Persson, 1991; Assem and Schild, 1969; Persson, 1986). Inhibition of mast cell degranulation, increased mucociliary clearance, and reduced bronchial reactivity to stimuli including exercise and methacholine have also been described (Svedmyr, 1990). However, it has also been proposed that O_2-agonists may inhibit the release of substances such as heparin that contribute to the resolution of inflammation (Page, 1991).

Two newly introduced O_2-agonists, formoterol and salmeterol, produce bronchodilation which persists well beyond 12 hours (Becker and Simons, 1989; Ullman and Svedmyr, 1988). Their prolonged effect overcomes several of the shortcomings of the O_2-agonists presently available. They are particularly effective in preventing nocturnal asthma (Wallin et al, 1990; Ullman et al, 1990). They also block not only the early, but also the late bronchoconstrictor response to inhaled allergen challenge (Twentyman et al, 1990). All of these actions could be anticipated, based on the extended duration of action. In addition, however, the administration of salmeterol preceding allergen challenge also blocked the development of increased bronchial responsiveness to inhaled histamine

measured 24 hours later, after the bronchodilator effect of the salmeterol was resolved (Twentyman et al, 1990).

1.5 The effects of treatment on pulmonary function, airway responsiveness and asthma morbidity

Given the relationships among FEV_1, bronchial hyperresponsiveness, and long-term outcome, one could speculate that treatment which would return FEV_1 and bronchial hyperresponsiveness to normal, rather than just that needed to minimize symptoms, would improve outcome. An additional, powerful incentive for use of medication prophylactically and chronically would be provided by definitive documentation that chronic use of anti-inflammatory medications improves the quality of life of children with asthma and decreases the more severe forms of morbidity. While parents and children are often reluctant to use medication on a chronic basis, several studies have demonstrated that asthma education improves compliance significantly (Wilson-Pessano and Mellins, 1987). In addition, information on toxicity of anti-inflammatory therapy is badly needed to provide clinicians and parents with accurate information on the risks and benefits of treatment. Information of the type likely to be obtained in the proposed trial would be extremely useful in providing ongoing encouragement for chronic medication use, both to physicians who prescribe it and to individuals who use it.

The data on the effects of long term treatment to influence bronchial responsiveness and pulmonary function in children are limited. One uncontrolled published trial in children has demonstrated a significant decrease in bronchial hyperresponsiveness during long term treatment with inhaled glucocorticoids (Kerrebijn et al, 1987). Even within this trial, there was a variability in response among the study population. Some patients showed a gradual sustained improvement in pulmonary function. Others demonstrated no change in bronchial hyperresponsiveness despite 6 months of treatment.

De Baets et al (1990) treated children (ages 7-14 years) with mild asthma (treated with cromolyn on a regular basis and/or bronchodilators on a regular basis or on demand) in a double-blind placebo-controlled trial with budesonide three times daily for two months. Steroid treatment caused a decrease in bronchial responsiveness to both histamine and allergen (house dust mite). These effects reversed rapidly when the treatment was discontinued, indicating either that continued therapy is required or, at least, that therapy of only two months duration is not adequate to produce long-term effects. However, not all patients responded in the same manner.

Since the stimuli for induction of inflammation are likely to be ongoing, it is possible that long-term therapy may be necessary. In a controlled trial Kraemer and coworkers found that beclomethasone significantly reduced airway responsiveness to methacholine compared to disodium cromoglycate and placebo (Kraemer et al, 1987). The Dutch randomized controlled trial has demonstrated a benefit to inhaled glucocorticoid (budesonide 200 Og 3 times a day) versus O_2-agonist (albuterol 200 Og 3 times a day) in childhood asthma (Van Essen et al, 1992).

A number of uncontrolled trials of inhaled steroids primarily in severe asthma demonstrate beneficial effects on pulmonary function and on decreasing oral steroid dose (Brown et al, 1980; Francis, 1976; Godfrey and König, 1974). Other than the Dutch trial in severe asthmatics, no

randomized controlled trial of anti-inflammatory treatment with pulmonary function growth as the primary outcome has been attempted. Hence the importance of this trial. Furthermore, with careful analysis of environmental control and behavioral measures this protocol will permit analysis of features that contribute to response or failure of individual agents.

1.6 The effects of treatment on physical growth and development

The common and uncommon potential side effects of using inhaled glucocorticoids were recently reviewed (Toogood, 1990). Concern has been raised regarding potential systemic effects. Fortunately, these systemic effects are very rarely a problem, and any side effects are unusual when low or moderate doses are used.

1.6.1 Adrenal suppression

Most studies have focused on hypothalamic-pituitary-adrenal axis suppression. These studies show that the 24-hour excretion of free cortisol, 17-hydroxyglucocorticoids, baseline serum cortisol, and responses to ACTH (adrenocorticotropic hormone) and metyrapone administration are not different from those of control patients after long-term maintenance therapy with inhaled glucocorticoids given in doses up to 800 Og per day (Kerrebijn, 1990; Francis, 1976; Kerrebijn, 1976; Godfrey and König, 1974). Adrenal suppression has however been reported in several studies. Tabachnik and Zadik (1991) studied ten children with chronic asthma 10-14 years of age who received beclomethasone dipropionate as a dose of 200 mcg by aerosol twice daily (400 mcg/day) for a three month period. There was a marked reduction in spontaneous diurnal cortisol secretion as measured by the 24 hour urinary excretion of cortisol and a decrease in the diurnal variation of cortisol following three months on beclomethasone. The peak cortisol level in response to corticotropin administration, however, was normal.

The lack of sensitivity of AM cortisol determination and the logistic difficulty with performing the other tests of adrenal function combined with the planned measurement of end organ effects of adrenal function (somatic growth, sexual maturation, and bone metabolism) led to the decision not to include hormonal measurements of the hypothalamic-pituitary-adrenal axis.

1.6.2 Somatic growth

There is normally a rapid linear growth spurt during adolescence with peak growth velocity rates between 10 and 15 years of age, depending on sex and individual factors. Following the peak in

growth velocity, the growth velocity rate declines rapidly to zero at approximately 14 to 18 years of age.

Under certain conditions somatic growth may decrease in children receiving inhaled corticosteroids. An 8 year old child receiving triamcinolone acetonide 300 Og twice daily for 10 months by the inhaled route, and no other steroid therapy, was reported to show growth retardation, obesity, and hirsutism (Hollman and Allen, 1988). Littlewood et al reported growth suppression in 16 children with asthma, aged 8-13 years, receiving beclomethasone dipropionate < 800 Og per day by dry powder inhalation (Littlewood et al, 1988). Several recent studies suggest that high-dose inhaled glucocorticoids may affect growth, serum osteocalcin (a protein synthesized by osteoblasts and associated with bone formation), and skin thickness (Wolthers and Pedersen, 1991; Pouw et al, 1991; Ali et al, 1991; Capewell et al, 1990). A recent trial conducted under the auspices of the American Academy of Allergy and Immunology compared inhaled beclomethasone dipropionate 400 Og per day with theophylline in the treatment of adult and pediatric patients with moderate asthma severity. Of concern was the observation of slower growth rate in the pediatric patients who received inhaled beclomethasone as compared to those receiving theophylline. Whether this reflects merely a delay in maturation with the final growth being normal or a permanent effect on growth is unknown. In contrast to the above, inhaled budesonide at low to moderate doses of 200 to 400 Og daily for 2 months failed to affect mean growth velocity by knemometry in 43 school age children with mild asthma (Wolthers and Pedersen, 1992). Moreover, uncontrolled asthma rather than inhaled corticosteroid treatment was associated with reduction in height velocity in 58 prepubertal children with asthma (Ninan and Russell, 1992). Thus, the long-term effects of better asthma control might outweigh the short-term effects of therapy on growth.

In addition to linear growth, maturation effects are important to consider. Delayed sexual and bone maturation may be seen with systemic corticosteroids, and any effects of growth must be correlated with maturation stage. If maturation is delayed, then the decreased growth seen with inhaled corticosteroids may merely reflect a growth delay but the final growth may not be adversely affected. If, however, maturation is unchanged, the decreased growth due to corticosteroids may result in decreased final growth. Thus, careful long-term growth measurements are critical.

1.6.3 Lung growth

Lung growth normally follows a similar pattern to somatic growth, except for a rightward shift of approximately two years. Following the rapid lung growth, a slow steady decline in lung function begins. The most common measures of lung growth in children and adolescents are standard spirometric measures (FVC, FEV_1, and FEF_{50}). In addition to growth velocity curves, the relationship between somatic and lung growth may be used to evaluate lung growth.

Chronic disease may inhibit normal somatic growth; thus, optimal treatment of the underlying disease, such as asthma, may facilitate maximal growth. Additionally, since asthma is an inflammatory disease, chronic asthma may lead to progressive pulmonary scarring and impaired lung growth and a fixed airway obstruction. This is demonstrated by the fact that, in general, asthmatic children under good control have normal spirometry, while many adult asthmatic patients have a fixed obstructive pulmonary impairment. By decreasing the inflammation involved in childhood asthma, such as by inhaled corticosteroid therapy, optimal growth may be obtained. There is growing concern, however, that anti-inflammatory therapy, specifically inhaled corticosteroid therapy, may alter lung and/or somatic growth in these children.

On the other hand, inhaled corticosteroids may exert a local effect on lung growth independent of the systemic effects. Corticosteroids are known to increase maturation in fetal and developing tissues. Conversely, systemic corticosteroids inhibit growth and delay puberty. A possible local effect of inhaled corticosteroids might be that lung growth is decreased, as manifested by a rightward shift and blunting of the peak lung growth velocity curves compared with patients not receiving inhaled corticosteroids.

1.6.4 Bone metabolism

Numerous studies have also examined the effects of inhaled corticosteroids on bone metabolism. Abnormally low total body calcium levels, drops in hydroxyproline, creatinine ratios, decreased alkaline phosphatase, depressed osteocalcin levels, and decreased bone density have all been documented when using inhaled corticosteroids. These changes are significantly less than those seen with systemic corticosteroids, but are present and may significantly affect a growing child. Once again, these measurements will be difficult to obtain. Instead it is proposed to study any effects on the end-organ, i.e., bone density will be evaluated.

1.7 The effects of treatment on psychological growth and development

Asthma, as with other chronic childhood illnesses, presents the child and his/her family with a significant burden that can interfere with normal psychological adaptation (Cadman et al, 1987; Orr et al, 1984). Behavioral problems have been found to occur with increased frequency among asthmatic children (Mrazek, 1985), and several studies have reported frequent feelings of depression and anxiety among asthmatic children (Austin, 1989; Bender et al, 1988; Kashani et al, 1988). Exacerbation of symptoms may lead to restriction of physical activity, school absence and social isolation, resulting in increased psychological strain and decreased quality of life. Childhood asthma interferes with the child's participation in age-typical social and physical activities, frequently

resulting in impaired physical conditioning (Ludwick et al, 1986). Children with asthma are also absent from school significantly more often than their healthy peers (Parcel et al, 1979).

The protocol for this study will provide a unique opportunity to investigate changes in psychological functioning associated with several long-term pharmacologic treatments. Psychological problems and compromised quality of life which occur among asthmatic children may be expected to improve as a result of successful treatment. In addition, the potential psychological side effects resulting from long-term use of specific asthma medications will also be evaluated for the first time. Finally, patient characteristics which may significantly affect treatment compliance and consequently successful management, including asthma knowledge and the presence of family dysfunction, will increase understanding of treatment response and allow the investigators to control some of the treatment-response variance in order to highlight pharmacologically-based treatment differences.

Important in the study of childhood asthma is the multidimensional assessment of psychological issues that can be affected by asthma and/or its treatment. The review that follows will address the four major psychological issues for children with asthma.

1.7.1 Behavioral/emotional functioning

Children with asthma experience a chronic medical condition that may impact both their physical and psychological well-being. Asthmatic children are at risk for developing symptoms associated with psychological disturbance (Bender et al, 1988; Kashani et al, 1988; Mrazek, 1985; Mrazek et al, 1985). However, not all studies agree that asthmatic children are at increased risk for psychological disturbance (Norrish et al, 1977; Steinhausen, 1982). Furthermore, some studies suggest that asthmatic children with mild to moderate asthma are at less risk for psychological disturbance than those with severe asthma (Graham et al, 1967; McNicol et al, 1973). Other studies, however, have not found severity of asthma to be related to a degree of psychological disturbance (Heilveil and Schimmel, 1982; Panides, 1984; and Kashani et al, 1988). It is likely that the inconsistent findings across studies of asthmatic children are due to a variety of methodological issues such as (1) patient selection (i.e., age, socioeconomic status, sex, severity of asthma), (2) treatment interventions (i.e., hospitalizations and type of medication, etc.), (3) treatment efficacy, (4) definitions of psychological disturbance, (5) measures used to detect psychological symptoms or competence, and (6) family factors.

Two of the more frequently reported psychological problems in asthmatic children are feelings of depression and anxiety (Austin, 1989; Bender et al, 1988; and Kashani et al, 1988). Austin (1989) found increased depression on the Child Behavior Checklist (CBCL) in girls with asthma. Bender et al (1988) reported that 8 to 16 year-old asthmatic children and adolescents on high doses of steroid

medication (61.5 mg/day) reported increased depressive symptoms on the Children's Depression Inventory and increased anxiety symptoms on the Revised Childhood Manifest Anxiety Scale. However, in the Bender et al (1988) study all such symptoms remained below clinical levels for depression and anxiety. Kashani et al (1988) found both the Diagnostic Interview for Children and Adolescent-Parent version (DICA-P) and the CBCL to reveal significantly more depression and anxiety in asthmatic children, regardless of the severity of their asthmatic condition, compared to matched controls.

The findings regarding depression and anxiety must be understood within the larger psychosocial context in which they occur. Therefore the CAMP Protocol will also examine the child's perception of the psychosocial consequences of asthma, defined as social anxiety. This concept is particularly important in the study of a chronic illness such as asthma because there is a relationship between social maladjustment and juvenile delinquency, academic problems, and mental health problems. The Social Anxiety Scale for Children (LaGreca et al, 1988) was developed specifically to assess children's self-reported social avoidance, social distress, and fear of negative evaluation. In addition, measures of family functioning (see Section 1.7.3) will provide a rich context for understanding the psychological consequences of treatment of asthma.

The present study offers a unique opportunity to assess the psychological impact that is associated with mild to moderate childhood asthma. The two major classes of medication being evaluated in the present study (i.e., corticosteroids and O_2-agonists) have the potential to impact mood (Reckart and Eisendrath, 1990; Friedel and Brogden, 1988). The developmental psychological effects of the sustained long-term use of these medications in children have never been studied. We, thus, have the opportunity to evaluate the impact of a chronic medical disorder on psychological symptoms and the effect, if any, of maintaining such chronically ill children on medications known to impact mood.

1.7.2 Neuropsychological functioning

Asthma is the most frequently occurring chronic illness in childhood, yet little longitudinal information has been published about the cognitive, academic and neuropsychological development in children with asthma. Previous studies have yielded inconsistent evidence and conclusions regarding academic impairment in asthmatic populations. Two recent studies have surveyed academic achievement in large groups of asthmatic children, with one concluding that the academic achievement of asthmatic children is no less than that of healthy controls (Lindgren et al, 1982), while the second provides evidence that asthmatic children are twice as likely as controls to demonstrate learning disabilities (Fowler et al, 1992).

The potential presence or absence of specific neuropsychological impairments in asthmatic children has been investigated, and is of particular importance because even subtle

neuropsychological dysfunction may compromise academic performance. Most studies have focused upon the relationship between asthma medications and neuropsychological dysfunction, reporting that theophylline (Rachelefsky et al, 1986), corticosteroids (Bender et al, 1988; Bender et al, 1991B), and beta agonists (Mazer et al, 1990) each produce different subtle neuropsychological changes. Most frequently reported are changes in attention and memory. At least six cases of significant behavioral change in asthmatic children following use of inhaled steroids have been reported (Connett and Lenney, 1991; Meyboom and DeGraff-Breederveld, 1988; Lewis and Cochrane, 1983). However no controlled investigation of mood, behavior, or neuropsychological changes in asthmatic children receiving nedocromil sodium or inhaled steroids have been conducted. The present study will allow us to determine whether longitudinal changes in academic functioning occur in asthmatic children in relationship to their illness, whether previously reported short-term medication related changes in attention, memory, and mood persist over the course of long-term treatment, and whether changes in mood, cognition, or behavior occur in relationship to inhaled steroids or nedocromil sodium.

1.7.3 Family functioning

The literature on chronic illness in children documents an important dynamic: such illness can adversely impact family functioning and, reciprocally, reduced family functioning can create stressful emotions and circumstances that may exacerbate illness symptoms (Cosper and Erickson, 1985). Chronic asthma in a child has repeatedly been shown to have significant impact on family and parental functioning (Cosper and Erickson, 1985; Kohen, 1987; Townsend et al, 1991; Pituch and Bruggerman, 1982). Included among the problems identified are anxiety, guilt, helplessness, frustration, fatigue, restrictions in social life, decreased interaction with significant others, neglect of siblings, and financial and marital stress. Furthermore, families in different ethnic and socioeconomic groups are differentially equipped in terms of financial, social, emotional and instrumental resources with which to deal with chronic disease in youthful members (Wissow et al, 1988; Mitchell et al, 1989). Several studies have shown that children in low income or minority families are less likely to comply with treatment regimens (Shields et al, 1990; Mitchell et al, 1989).

The family measures proposed will assess the effect of the child's chronic illness on the critical complex of interrelationships in their family. The dynamics between the child and their illness and the family unit are essentially reciprocal. It is anticipated, for example, that a more stabilized and confident familial response will in turn be reflected in better control of the illness and, perhaps, reduced adverse symptoms, potentially reducing strain on the family system and a strengthening of family relationships and coping abilities. As can be seen, this process is iterative. The degree to which these dynamics occur over time will be one of the factors moderating outcomes in this five year medication trial.

2. Treatments

The three treatments to be compared are budesonide (initially 400 µg/day with options for tapering to 200 µg/day or to zero), nedocromil (initially 16 mg/day with options for tapering to 8 mg/day or to zero), and placebo (see Table 2 for a design summary). The placebo treated group in this design will be 40% larger than either of the two test treatment groups and will be divided equally between patients assigned to a placebo Turbuhaler® matching that used for budesonide, or to a placebo metered dose inhaler matching that used for nedocromil. The treatments are to be administered to patients either as two 100 µg inhalations (with tapering to one or zero) twice daily from a Turbuhaler® (budesonide or its matching placebo), or four 2 mg inhalations (with tapering to two or zero) twice daily from a metered dose inhaler (nedocromil or its matching placebo). AeroChambers® must be used for administration of nedocromil and its matching placebo.

Tapering of the dose of the assigned study medicine will occur for any patient in any of the three treatment groups who has been at full dose for at least 7.5 months and who has had minimal symptoms and satisfactory lung function for the previous 6 months (50% dose reduction), or who has been at half dose for at least 7.5 months and has had minimal symptoms and satisfactory lung function for the previous 6 months (reduction to 0). Any significant recurrence of symptoms or deterioration in lung function identified at or between four-monthly visits will result in resumption of the initial full dose treatment (see Section 7.4, Adjustment of treatment, for details on the criteria for tapering of doses and resumption of treatment).

Children whose asthma is not adequately controlled by the full dose study medication will have beclomethasone added (four 42 µg puffs twice daily) to their treatment. If the child's asthma still is not adequately controlled, the child will be treated according to physician discretion (see Section 7.4, Adjustment of treatment, for details on the criteria for addition of beclomethasone and treatment by physician discretion).

All patients will use (as needed) an intermittent (*prn*) inhaled O_2-agonist (albuterol) and will receive systemic glucocorticoids (oral prednisone) for acute exacerbations. The albuterol administration protocol will be to use as needed, two 90 µg puffs per usage. Use of an AeroChamber® with the albuterol metered dose inhaler is optional. If an AeroChamber® is not used with albuterol, the child may use either the closed-mouth or open-mouth technique of inhalation.

Besides being at the forefront of current asthma therapy, a major advantage of both budesonide and nedocromil is the convenience of a twice daily dosing schedule. While each of these medications holds promise as first-line therapies for asthma, long-term trials are needed to examine the comparative efficacy and side effect profiles of these agents.

3. Objectives

3.1 Primary objective

To determine the long-term effects of 3 treatments (either of two classes of anti-inflammatory agents [budesonide or nedocromil] and placebo) on pulmonary function as measured by normalized FEV_1 over a 5-6½ year period in children with asthma. Every patient will use an intermittent (as needed) short-acting O_2-agonist (albuterol).

3.2 Secondary objectives

- To determine if the three treatments differ with respect to the long-term effects on bronchial responsiveness to methacholine.

- To determine if the three treatments differ with respect to morbidity as measured by peak expiratory flow rate (PEFR; measured on peak flow meter), frequency and severity of asthma symptoms, days of limited activity, nocturnal awakenings, and use of albuterol and prednisone to control symptoms and stabilize pulmonary function as determined by PEFR.

- To determine if the three treatments differ with respect to use of health care resources such as emergency room visits, hospitalizations, and physician contacts.

- To determine if the three treatments differ with respect to mortality, long-term safety, and side effects.

- To determine if the three treatments differ with respect to physical growth and development as indicated by sexual maturation, growth rates, and bone density.

- To determine if the three treatments differ with respect to psychological growth and development as indicated by measures of neurocognitive functioning and psychological adjustment.

- To determine the influence of environmental and psychological factors and atopic status in response to the different treatments.

4. Patient selection

4.1 Inclusion criteria

In order to be eligible for entry into the trial, children must satisfy the following criteria:

- Age 5-12 years at time of screening
- Chronic asthma as evidenced by one or more of the following historical findings for at least 6 months in the past year:
  - Asthma symptoms at least twice per week
  - Two usages or more per week of an inhaled bronchodilator (usage is defined to be two 90 Og puffs)
  - Daily asthma medication
- Current asthma symptoms either by diary card symptom code at least 1 [Table 5] or am or pm PEFR less than 80% of personal best peak flow on 8 or more days during the *prn* screening period (during this period, treatment to prevent exercise-induced asthma will be recommended)
- Sensitivity to methacholine: PC_{20} FEV_1 less than or equal to 12.5 mg/ml
- Ability of family to comply with trial for 5-6½ years
- Consent of child's guardian
- Assent of child

Personal best peak flow is initially determined at the second screening visit (Visit S2) for purposes of establishing the child's action plan for the 28 day *prn* screening period prior to randomization. The coordinator will choose a personal best value based on observation of the child's technique, the peak flows obtained in the clinic at Visit S2, his/her knowledge of the child, and any Diary Cards completed before Visit S2. At Visit S3 prior to the methacholine challenge, for purposes of determining eligibility, personal best peak flow is redetermined based on one of the following two pools of values:

- The Diary Card peak flow data for the 28 day *prn* screening period and the 3 post-bronchodilator peak flows obtained at Visit S2, provided the child's technique at Visit S2 was acceptable
- The Diary Card peak flow data for the 28 day *prn* screening period if the child's technique at Visit S2 was not acceptable

The personal best peak flow is the **highest value** of those in the pool if there is another observation of that value in the pool or if the second highest value in the pool is more than 90% of the highest value. If the highest value occurs only once (ie, no ties) and if the second highest value is 90% of the highest value or less, personal best peak flow is the **second highest value**.

Personal best peak flow will remain the value used to determine eligibility until a higher post-bronchodilator peak flow with acceptable technique is observed in the clinic. If the post-bronchodilator peak flow observed after the methacholine challenge at Visit S3 is higher than the value used for eligibility and the child's technique at Visit S3 is acceptable, then the personal best peak flow (for followup, not eligibility) changes to the Visit S3 best post-bronchodilator value.

4.2 Exclusion criteria

Children will be ineligible for entry into the trial if any one of the following criteria is met:

- The presence of one or more of the following diseases or problems:
  (see Table 3 for operational disease definitions)

  - Pulmonary disease, including cystic fibrosis, bronchiectasis, tuberculosis, or immunodeficiency leading to recurrent sino-pulmonary infections

  - Any other chronic condition (e.g., physical disability, mental, neurological or psychiatric problems) presumed by the CAMP physician to be likely to interfere with successful completion of the project or confound its interpretation

  - Pulmonary function testing findings suggesting a ventilatory defect other than asthma, or evidence of existing irreversible lung damage

  - Severe chronic sinusitis or nasal polyposis

  - Introduction of, or a change in, allergen immunotherapy within 30 days of screening

  - Nasal steroid use other than 1-4 sprays daily of beclomethasone (children on other nasal steroids may be switched to beclomethasone but must conform to these limitations on dose)

  - Treatment for gastroesophageal reflux

- Current use of metoclopramide, ranitidine, or cimetidine
- Participation in another drug trial (including immunotherapy)
- Pregnancy

- Severe asthma as evidenced by one or more of the following criteria:
  - More than one hospitalization for asthma in the year prior to screening or randomization
  - More than 5 steroid bursts in the year prior to screening or randomization
  - Demonstrated need for continuous use of glucocorticocoids, either oral or inhaled
  - FEV_1 less than 65% predicted when off short-acting inhaled O_2-agonists for more than 4 hours and long-acting inhaled O_2-agonist or theophylline for more than 24 hours
  - Intubation for asthma at any time in the past
  - During *prn* screening period, the need for more than 8 puffs/24 hrs of albuterol for each of 3 consecutive days (not to include preventive use prior to exercise), nocturnal asthma awakenings greater than 1.5/wk on average, average diary card symptom code greater than 2 [Table 5], or requirement of any medicine other than albuterol to control asthma

- Inability to perform three acceptable forced vital capacity maneuvers with two reproducible FEV_1s within 10% of the largest FEV_1 during the pre- and post-bronchodilator spirometry sessions

- Inability to complete the methacholine challenge or a sensitivity to methacholine, PC_{20} FEV_1 greater than 12.5 mg/ml

- Evidence that the patient or family may be unreliable or non-compliant, or may move from the clinical center area before trial completion

4.3 Recruitment

Patients will be recruited from a variety of sources, including emergency rooms, other clinics in the trial institutions, subspecialty practices, pediatricians, general practitioners, family physicians, managed health care groups, school nurses, and the general public by press, radio, and television advertising. Special efforts will be directed at recruitment of minority individuals. The schedule of events for the recruitment and eligibility screening of prospective patients is shown in Table 4.

5. Design

5.1 Randomization

The assignment process includes the following features:

- Assignments arranged in permuted blocks of varying lengths within clinic strata
- Use of a documented generation scheme producing a reproducible order of assignment
- Assignments not released until eligibility determined, consent and assent obtained, and required baseline data collected, recorded, and keyed
- Assignments released in masked fashion and in a manner consistent with masked administration
- Future assignments not predictable from past assignments
- Audit trail for the assignment process

The only stratification variable is clinic. Other baseline covariates, such as severity of asthma, initial pulmonary function status, sex, or ethnic group, were not selected for added stratification since the gain in statistical precision from stratification is virtually nil, given a sample size as large as in this trial, compared with the use of multiple regression techniques to adjust for imbalance in the composition of the treatment groups with respect to their covariates (Grizzle, 1982).

5.2 Masking and bias control

- Patients and clinical staff will be masked regarding assigned treatments but not masked as to whether the treatment is administered via Turbuhaler® or metered dose inhaler
- Prior to any test, pulmonary function technicians will not have access to measurements obtained at earlier visits

6. Outcome measures

6.1 Lung function

Enrolled patients will have forced expiratory spirometry conducted at baseline (Visits S2 and RZ) and at each followup visit (except at the visits when methacholine testing is done) at least 4 hours after the last use of a short-acting bronchodilator and at least 24 hours after the last use of theophylline or a long-acting bronchodilator. Spirometry will be done before and after the administration of 2 puffs of albuterol MDI (at which time the MDI technique will be reviewed). After administering the bronchodilator, the minimum elapsed time before performing the post-bronchodilator tests will be 15 minutes. Testing will be performed with a volume displacement spirometer interfaced to a computer. Transportable equipment will be developed to allow for testing in field centers or at home or school. The equipment specifications and testing protocol meet or exceed ATS standards.

PEFR will be measured using a peak flow meter before medications twice a day, in the morning and in the evening before bedtime. At each of these times the child will be instructed to make the measurement while standing, to take a maximum inspiration, and to note the reading on the instrument. He or she will record the best of three efforts on the trial diary card daily. The children will bring their peak flow meters to each visit. A peak flow measurement will be performed in the clinic before and after bronchodilation.

6.2 Bronchial hyperresponsiveness

One of the secondary objective measures of CAMP is a measure of airway responsiveness to methacholine. The most widely used method for studying airway responsiveness is through the nebulization of a variety of pharmacological agents. Of these agents, the most widely used include histamine and the cholinergic agonists. In the CAMP study, methacholine will be used as the provocation agent, and airway responsiveness will be determined by the FEV_1 response to this agent. Methacholine exerts its bronchoconstrictor effect directly on the muscarinic receptors of the bronchial smooth muscle. The methodology for determining bronchial responsiveness to methacholine is as follows:

- Tidal breathing for two minutes using the Wright nebulizer will be done. The FEV_1 will be determined immediately after each two-minute inhalation of an incremental increase in the dose of methacholine ranging from 0.098 to 25 mg/ml, or until there is a 20% fall in the FEV_1. The methacholine concentration at which the FEV_1 falls by 20% (PC_{20} FEV_1) will be reported

- Airway reactivity will be assessed at Visits S3, F8, F20, F32, F44, F56, and F68

- No determinations of bronchial reactivity will be made
  - within 4 weeks of a cold or upper respiratory tract infection or viral illness
  - within 4 weeks of an asthmatic exacerbation requiring oral steroids
  - within 24 hours of using theophylline or a long-acting bronchodilator
  - within 4 hours of using a short-acting bronchodilator
  - if FEV_1 is less than 70% of predicted

- If the patient has consumed caffeine within 4 hours of the methacholine challenge, the test will be done and the consumption of caffeine will be noted on the form

- Effort will be made to do methacholine challenge testing on any one patient at the same time of day from one testing to the next; the time the test ended will be noted on the form

- Two 90 Og puffs of albuterol will be administered after methacholine challenge testing. The child will not be allowed to leave until the FEV_1 is at least 90% of baseline

6.3 Asthma morbidity

Diary cards will be used to record, in two week increments, daily data on asthma symptoms and treatment including: morning and evening PEFR measurements, use of regular and *prn* medications, indication of any medical contacts initiated, and rating of symptoms and activity limitation on a scale [Table 5]. Patients will be instructed to mail diary cards to trial staff at the end of each two week period. This will serve to monitor adherence and allow intervention or corrective action, if necessary, before the regularly scheduled 4 month visit.

Patient morbidity from asthma will be determined as follows:

- Frequency and severity of asthma symptoms

- Frequency and magnitude of PEFR measurements less than 80% of personal best

- Frequency of albuterol use on an as-needed basis

- Frequency of nocturnal awakenings, days of limited activity, and days of absence from school due to asthma

- Number of courses of oral prednisone (days and dose)

Use of health care resources will be determined as follows:

- Physician contact (trial or non-trial) for management of asthma symptoms by phone or office visits (acute care visits only)
- Emergency room visits
- Hospitalization for asthmatic exacerbations

The associations between community levels of common outdoor air pollutants and respiratory health will be assessed via the CAMP ancillary study, "An air quality-asthma analysis of the CAMP data".

6.4 Physical growth and development

Since the long-term implications of potential adverse effects of inhaled glucocorticoids in actively growing children remain unknown, a critical examination of the effects of asthma and asthma therapy on somatic and lung growth and development, and other systemic effects is fundamental to the evaluation of the treatment protocols of the trial.

The following measures will be collected:

- Somatic growth
  - Linear growth (height) - every four months
  - Weight - every four months
  - Truncal growth (lower segment (leg) length, sitting height, waist and hip measurements (and waist/hip ratio determination)) - annually
  - Sexual maturation (Tanner staging) - annually
  - Body mass index (BMI; Wt (Kg)/[ht (M)]^2) will be determined from the 4 month serial height and weight measurements
- Lung growth: Growth velocity curves for the following will be determined from the serial spirometry determinations (post-bronchodilator values will be used to correct for any ongoing reversible bronchospasm):
  - FVC
  - FEV_1
  - FEV_1/FVC

- Other

  - Physical exam - annually
  - Hematology - WBC, hemoglobin, differential, total eosinophil count, and serum IgE at baseline and at 5 years, with 5 cc serum banked for unspecified studies
  - Bone density (spine) - annually

The impact of the three CAMP treatments on adrenal function will be assessed in a subset of CAMP patients by means of the CAMP ancillary study, "Hypothalamic-Pituitary-Adrenal Axis Function in Children Participating in CAMP".

6.5 Psychological growth and development

There are two major areas of assessment in a battery approach to psychological growth and development. The two areas include: neurocognitive functioning and individual and family functioning.

- **Neurocognitive measures:**

  The following measures are administered to the child in an individual meeting with the psychometrician during screening, and at the 3 year and 5 year visits:

  - Children age 5: Wechsler Preschool and Primary Scale of Intelligence - Revised: The following subtests will be administered to the child: Similarities, Vocabulary, Block Design. From these subtests a Full Scale IQ measure will be derived using a conventional algorithm.

  - Children ages 6-18: Wechsler Intelligence Scale for Children - III (Wechsler, 1991): The following subtests will be administered to the child: Vocabulary, Similarities, Block Design, and Symbol Search. From these subtests a Full Scale IQ measure will be derived using a conventional algorithm.

  - Woodcock-Johnson Psycho-Educational Battery Tests of Achievement-Revised (Woodcock and Johnson, 1990): The following subtests, comprising the Skills Cluster, will be administered to the child: Letter-Word Identification, Applied Problems, and Dictation.

- Wide Range of Assessment of Memory and Learning (Adams and Sheslow, 1990): The following subtests will be administered to the child: Picture Memory, Design Memory, Verbal Learning, Story Memory, Delayed Recall-Verbal Learning, Delayed Recall-Story Memory and Recognition Task - Story Memory. A memory screening index scores will then be derived according to established guidelines.

- Gordon Diagnostic System (Gordon and Mettelman, 1987): The following tasks will be administered to the child less than age 6: Delay and Vigilance. The following tasks will be administered to the child age 6 or older: Delay, Vigilance, and Distractibility. Each task results in several independent measures. From the Delay Task the Efficiency Ratio, Total Responses, and Total Correct will be recorded. From the Vigilance and Distractibility Tasks the Total Commissions and Total Correct scores will be recorded.

▾ **Individual and family functioning measures**

The following measures are completed annually by the child/teen:

- Youth Self Report Form, Ages 11-18 (YSR) (Achenbach, 1991B)
- Children's Depression Inventory (CDI) (Kovacs, 1981)
- Revised Children's Manifest Anxiety Scale (RCMAS) (Reynolds and Richmond, 1985)
- Social Anxiety Scale for Children-Revised (SASC-R) (La Greca and Stone, 1992)

The following measures are completed annually by the parent:

- Child Behavior Checklist (CBCL) (Achenbach, 1991A)
- Family Environment Scale (FES) (Moos and Moos, 1981)
- Impact on Family Scale (IFS) (Stein and Riessman, 1980)
- Medical Outcome Study Social Support Survey (MOS) (Sherbourne and Stewart, 1991)

7. Patient management

7.1 Patient education

The educational protocol includes both group and individual components, and emphasizes monitoring of key skills and management strategies.

The educational component will be administered by all project staff who have direct contact with patients and their families. To enhance coherence of the educational component, one staff member conversant with the topics of most of the curriculum will be present for most of the education sessions.

Training for implementation of the educational protocol will be coordinated at the National Jewish Center for all participating institutions. It is expected that project staff will already have the general educational and counseling skills necessary for the education program. Thus, training will focus on introducing and rehearsing the specific curriculum and procedures developed for CAMP. An educational handbook will be prepared for the educators, and material will be designed for three groups: parents/caretakers, children ages K-3rd grade, and children ages 4-6th grades.

Specific protocols will standardize core educational program content for use of medications, peak flow monitoring, action plans for dealing with symptoms, and environmental control measures. Curricula elements which are most pertinent to the experimental treatment will be covered earliest. "Booster" education materials to review, correct, and reinforce management skills will be distributed every four months throughout the study. Participants will also receive quarterly newsletters which will contain educational material as well as activities and games.

Standardization and quality control will be achieved through training meetings for all clinic staff participating in patient education, initially and annually.

Those aspects of patient education not covered in the screening period will be addressed in one of two ways: (1) curricula elements judged essential to education of all participants will be covered in portions of regularly scheduled visits of the trial during its first year; (2) curricula elements judged desirable but inessential will be included in optional group meetings and activities during the trial, and will be designed both to motivate continued participation in the trial and to provide participants helpful information about asthma and its management.

A principal objective of the patient education protocol is to maximize adherence to CAMP's treatment and evaluation regimens. Key aspects of the protocol to enhance adherence include:

- Emphasis on participants' appreciation of and commitment to the special and important purposes of the trial
- Emphasis on participants' "bonding" to the trial, co-participants, its staff, and the sponsoring institutions
- Monitoring of adherence and prompt, individualized response to indications of waning adherence

- Investment in support of participants by professional staff, including principal investigators, e.g., through participation in social or morale boosting activities, educational activities
- Group activities to enhance bonding among trial participants
- Individualized attention to and support of participants by professional staff, including principal investigators
- Explicit attention to the duration of the trial by planning for variety in activities
- Reinforcement of education accomplishments through a variety of activities throughout the trial
- Reinforcement of trial adherence through certificates and small gifts

Each center will carry out activities to boost morale. The individual clinical centers will have substantial latitude in choosing activities of their own design. Sample activities might include:

- Baseball games or other athletic contests
- Picnics--including athletic activities to emphasize that asthma is compatible with an active lifestyle
- Outings to an amusement park
- Outings to meet with celebrity asthmatics

Where possible, a CAMP committee of participants and their guardians will be established in each center and will be responsible for planning the activities.

Quarterly meetings open to participants and interested family members will be held to maintain contact with the trial and to enhance motivation for cooperation with it.

Because the CAMP study medications should not be taken during pregnancy, girls who have reached Tanner Stage 2 will be queried about sexual activity and counseled about contraception.

7.2 Participation of primary physician

If a physician is to be involved in the asthma care of a CAMP trial patient, then the physician must abide by the protocol delineated below (see Rescue algorithms). Since it is important to have participation of the primary physicians, this option must be offered. Every effort will be made to have the primary care physician intimately knowledgeable about the CAMP protocol. Indications

that the physician is not following the protocol will be followed with re-education and attempts to draw the physician more closely into the trial.

7.3 Rescue algorithms

The approach to rescue medications will be based on the consensus report presented in the recent National Heart, Lung and Blood Institute Guidelines (NHLBI, 1991). Patients will be given an individualized guide for decision making and rescue management (action plan). Two medications, albuterol or oral prednisone, will be employed when increasing symptoms and/or fall in peak flow require treatment. For severe acute asthma, patients will be medicated according to the best medical judgment of the treating physician.

Home care:

The onset of an asthma exacerbation will be recognized by symptoms such as coughing, dyspnea, chest tightness and/or wheezing, or by a decrease in the patient's PEFR. Caretakers and patients will be educated to recognize signs and symptoms early and the significance of falls in the peak flow readings so that prompt rescue treatment may be instituted and morbidity decreased.

Patients who experience symptoms of cough, dyspnea, chest tightness, wheeze, and/or PEFR less than 80% personal best will use albuterol (2 puffs) by MDI or compressor-driven nebulizer (0.25 cc recommended to be similar to 2 MDI puffs) every 20 minutes for up to 1 hour and then every 4 hours if necessary. If the patient cannot achieve PEFR at least 80% of personal best, or if symptoms persist after 3 treatments, the primary physician should be contacted. If the patient’s peak flow reaches 80% of personal best or greater, but the patient requires albuterol every 4 hours for 24 hours in order to maintain a peak flow of at least 80% personal best or if symptoms persist, the child's primary physician should be contacted. A clinic visit may be necessary, as may be initiation of glucocorticoid therapy (Harris et al, 1987; Littenberg and Gluck, 1986).

If symptoms are severe or the child has retractions, indications of cyanosis, or is struggling for air, and/or PEFR is less than 50% of personal best after 2 puffs of albuterol (or 0.25 cc by nebulizer), the patient must seek immediate medical care and should contact the CAMP office.

Physician's office or emergency room:

In the primary physician's office or emergency room, the patient with an acute asthma exacerbation will be treated with nebulized albuterol. The dose of albuterol for the doctor-supervised situation is 0.10 - 0.15 mg/kg up to 5 mg per treatment. Albuterol can be delivered by nebulizer driven with oxygen, and treatments will be given every 20 minutes for up to 3 treatments (Schuh et al, 1990; Schuh et al, 1989; Fanta et al, 1986; Robertson et al, 1985; Nelson et al, 1983; Rossing et al, 1982). If after 3 treatments, the child is not stabilized as described below, the physician may use additional albuterol treatments or other medication as his/her judgment warrants. The child will be assessed for general level of activity, color, pulse rate, use of accessory muscles and airflow obstruction determined by auscultation (Waring, 1983; Galant et al, 1978; Commey and Levison,

1976), and FEV_1 and/or PEFR before and after each bronchodilator treatment. Measurement of oxygenation with a pulse oximeter may also be helpful.

- If the patient has a favorable response to initial albuterol nebulizer treatment (FEV_1 and/or PEFR at least 80% predicted or personal best), the patient will be observed for 1 hour prior to being discharged home with instructions to continue albuterol every 4 hours as needed and to report any fall in PEFR and/or symptom fluctuation promptly.

- If the patient does not improve (FEV_1 or PEFR less than 80% predicted or personal best) after the initial albuterol nebulizer treatment, nebulized albuterol therapy will be continued for at least 2 more times (for a total of 3 times in 1 hour). If the patient's clinical symptoms are stabilized and FEV_1 or PEFR is between 50-80% of predicted or personal best, the patient will be discharged home to continue use of albuterol (2 puffs every 4 hours) and to start a four day course of oral prednisone.

- If the patient's FEV_1 is less than 50% predicted or PEFR is less than 50% of personal best after 3 treatments with nebulized albuterol in 1 hour, the physician may use his/her best medical judgment to treat the patient.

Prednisone courses:

Glucocorticoids will be administered for the treatment of impending episodes of severe asthma when bronchodilator therapy is inadequate (Harris et al, 1987). The decision about initiation or continuation of a course of oral prednisone will be at the physician's discretion.

Guidelines for Prednisone Use (NHLBI, 1991; Charlton et al, 1990). Prednisone should be prescribed if:

- The patient uses more than 12 puffs or 1.5 cc by nebulizer (0.25 cc recommended to be similar to 2 MDI puffs) of albuterol in 24 hours (excluding preventive use before exercise) and has diary card symptom code of 3 [Table 5] or PEFR less than 70% of personal best before each albuterol use, or

- The patient has symptom code of 3 [Table 5] for 48 hours or longer, or

- PEFR drops to less than 50% of personal best despite albuterol treatment.

Upon notification of the CAMP staff by the primary care physician about the need for prednisone, the patient will be encouraged to be seen at the CAMP clinic, though the investigator may use his or her discretion concerning "sick visits." Patients whose severe symptoms persist or whose PEFR remains under 50% of personal best after 3 albuterol treatments should initiate prednisone and call the primary physician immediately.

The recommended prednisone dose for acute exacerbations is 2 mg/kg/day (maximum 60 mg) as a single morning dose for two days followed by 1 mg/kg/day (maximum 30 mg) as a single morning dose for two days. All administered doses should be rounded down to the nearest 5 mg.

7.4 Adjustment of treatment

A patient's initially assigned treatment will be adjusted, if warranted, because of inadequate control of asthma (section 7.4.1), adverse events attributed to the study treatment (section 7.4.2), pregnancy (section 7.4.3), or well-being (section 7.4.4). Treatment for asthma after adverse events attributed to the study medication or during pregnancy will be managed by the child's primary physician. Data collection for patients experiencing adjustment of treatment for any reason will continue according to schedule; patients will continue to complete visits and diary cards.

Many of the criteria for making treatment adjustments depend on Diary Card data. Treatment adjustment because of inadequate control of asthma will utilize whatever diary data are available and assume that missing data imply well-being. Treatment adjustment because of well-being will require 75% or more of the days under consideration to have at least one Diary Card value recorded for adjustment to be considered; if more than 25% of the days under consideration have all data missing, treatment adjustment for well-being will not be allowed. If 25% or less of the diary days have all missing data, all missing data will be assumed to imply well-being. The rationale for these assumptions regarding missing data is: (1) it should be difficult to deviate from the full assigned dose of study medication and easy to return to it, and (2) treatment adjustment because of inadequate control of asthma can be done on the sole reason of physician judgment.

7.4.1 Adjustment of treatment because of inadequate control of asthma

Need for assisted ventilation at any time during followup will mandate treatment by physician discretion, and the child will continue to be treated by physician's discretion for the duration of the study. Otherwise, patients whose asthma is inadequately controlled while on full dose study medication will require the addition of beclomethasone and will continue to take their study inhaler. Patients will be treated with beclomethasone for at least 106 days (3.5 months) before considering withdrawal of beclomethasone.

Criteria for addition of beclomethasone

If the child has been on full dose study drug for less than 365 days (12 months), the criteria for addition of beclomethasone will be the occurrence of any one or more of the following events:

- 6 or more prednisone courses or 31 or more days of prednisone therapy since the last assignment to full dose study drug; **OR**
- 2 or more hospitalizations for asthma since the last assignment to full dose study drug; **OR**
- *Prn* use of more than 300 puffs albuterol/30 days (excluding preventive use before exercise) for any 120 day period since the last assignment to full dose study drug, after investigation of reasons for use and counseling about excessive use; **OR**

- Other asthma worsening that in the CAMP physician's judgment warrants addition of therapy

If the child has been on full dose study drug for the previous 365 days (12 months), the criteria for addition of beclomethasone will be the occurrence of any one or more of the following events:

- 6 or more prednisone courses or 31 or more days of prednisone therapy in the previous 365 days (12 months); **OR**
- 2 or more hospitalizations for asthma in the previous 365 days (12 months); **OR**
- *Prn* use of more than 300 puffs albuterol/30 days (excluding preventive use before exercise) for any 120 day period in the previous 365 days (12 months), after investigation of reasons for use and counseling about excessive use; **OR**
- Other asthma worsening that in the CAMP physician's judgment warrants addition of therapy

If the child is currently on a tapered dose of study drug (half or zero dose), asthma worsening requires resumption of full dose study drug, not addition of beclomethasone (see section 7.4.4).

Treatment with beclomethasone

The patient will be instructed to use four 42 Og puffs of beclomethasone twice daily. At this dose, patients will not receive more than 1 mg of glucocorticoid even if taking full dose budesonide. This dose level should not put the patient at a substantially increased risk for developing systemic side effects. If the patient's asthma is inadequately controlled by beclomethasone with full dose study drug, the child will be treated at the discretion of either the CAMP physician or the patient's private physician.

Criteria for step up to treatment by physician discretion from beclomethasone

If the patient meets any of the following criteria while being treated with beclomethasone, the patient will progress to treatment at physician discretion:

- Prescription of any anti-asthma medication other than the assigned study drug, beclomethasone, and albuterol since initiating beclomethasone as documented on the Diary Cards, as elicited during interview, or as reported by child's primary physician; **OR**
- Hospitalization for asthma since initiating beclomethasone; **OR**
- *Prn* use of more than 300 puffs albuterol/30 days (excluding preventive use before exercise) since initiating beclomethasone; **OR**
- Other asthma worsening judged by the CAMP physician to warrant treatment by physician discretion.

Once a child has been stepped from treatment with full dose study drug and beclomethasone to physician discretion treatment, he/she will be treated according to physician discretion treatment until the physician judges that the child may be treated by full dose study drug only. However, if the

child ever needs assisted ventilation, the child must stay at physician discretion treatment for the duration of the study.

Criteria for withdrawal of beclomethasone

Beclomethasone will be withdrawn and the child will resume treatment with full dose study drug only if the patient meets all of the following criteria:

- Child has used beclomethasone and full dose study drug for at least 106 days (3.5 months); **AND**
- Child has not been prescribed any anti-asthma medication other than the assigned study drug, beclomethasone, and albuterol since initiating the step as documented on the Diary Cards, as elicited during interview, or as reported by child's primary physician; **AND**
- Child has not been hospitalized for asthma since initiating beclomethasone; **AND**
- Child has used 300 puffs or less albuterol/30 days (excluding preventive use before exercise) since initiating beclomethasone; **AND**
- CAMP physician's judgment that asthma has improved such that withdrawal of beclomethasone is appropriate

7.4.2 Adjustment of treatment due to adverse events attributed to CAMP treatment

If a child has an adverse event that is attributed to CAMP treatment that is judged to warrant treatment by physician discretion, the child will be returned to his/her primary physician for asthma treatment management. Treatment will be according to the best medical judgment of the treating physician. The child will continue to complete CAMP visits and diaries. The CAMP study physician will contact the primary physician periodically to see if it is possible for the child to resume his/her assigned treatment.

7.4.3 Adjustment of treatment because of pregnancy

If a patient becomes pregnant, the patient will be returned to her primary physician for asthma treatment management. The patient will continue to complete CAMP visits and diaries. Once the pregnancy terminates, the patient will be asked to resume her assigned CAMP treatment.

7.4.4 Adjustment of treatment because of well-being

Tapering of assigned treatment on the basis of well-being will be done in two steps — an initial taper to half dosage, followed by tapering to zero dose. Tapering will first be considered after the child has been at the assigned dosage for at least 228 days (7.5 months) and will be reconsidered at each 4 month followup visit thereafter. Therefore, the earliest that a patient can be tapered to half

dosage is at the 8 month followup visit (Visit F8), and the earliest that a patient can be tapered to zero dosage is at the 16 month visit (Visit F16).

The initial taper will be from 2 puffs *bid* to 1 puff *bid* for patients receiving budesonide (i.e., 400 Og/day to 200 Og/day) or its matching placebo, and from 4 puffs *bid* to 2 puffs *bid* for patients receiving nedocromil (16 mg/day to 8 mg/day) or its matching placebo. If the conditions for tapering to zero dose are met, use of the assigned drug will be stopped. Diary recordings and use of *prn* albuterol will be maintained regardless of tapering status. Patients will be contacted at 2 and 4 weeks after a tapering of therapy has occurred to verify that their condition has not worsened.

If a patient fails to maintain a state of well-being following a tapering of dosage, treatment will revert to full dosage, which must be continued for at least 228 days (7.5 months) before criteria for tapering can be considered again. Need for prednisone while at a tapered dose will require resumption of full dose study drug.

Tapering of treatment will be considered if less than 25% diary days are completely missing. If fewer than 25% of days are completely missing, all missing Diary Card data will be assumed to imply that the child is well; that is, missing peak flows will be assumed to be at least 80% personal best, blank entries for prednisone pills and use of albuterol will be assumed to reflect non-use, and missing asthma codes will be assumed to be 0. Time periods used in the criteria are specified in numbers of days and will be counted back from the date of the current visit (inclusive).

Criteria for initial taper to half dosage

The criteria for the initial taper (to half dosage) are:

- At least 75% of diary days have at least one value recorded; **AND**
- On full dosage for at least 228 consecutive days (7.5 months); **AND**
- Pre-bronchodilator FEV_1 at least 85% of predicted and pre-bronchodilator FEV_1/FVC ratio at least 85% at the current visit; **AND**
- Four puffs (2 usages) or less per 7 days (1 week) of albuterol for each 7 day period (1 week) in the preceding 183 days (6 months), excluding preventive use before exercise, as documented on the Diary Cards; **AND**
- One day or less per 30 days (1 month) of asthma symptoms that prevent the child from full participation in his or her usual daily activities (symptom code 2 or more), as documented on the Diary Cards for each 30 day period (1 month) in the preceding 183 days (6 months)

Criteria for taper to zero dosage

The criteria for Step 2, tapering to no use of the assigned drug (zero dosage) are:

- At least 75% of diary days have at least one value recorded; **AND**
- On half dosage (Step 1) for at least 228 consecutive days (7.5 consecutive months) preceding Step 2; **AND**

- Pre-bronchodilator FEV_1 at least 85% of predicted and pre-bronchodilator FEV_1/FVC ratio at least 85% at the current visit; **AND**
- Four puffs (2 usages) or less per 30 days (1 month) of albuterol for each 30 day period (1 month) in the preceding 183 days (6 months), excluding preventive use before exercise, as documented on the Diary Cards; **AND**
- One day or less per 30 days (1 month) and fewer than 5 days total of asthma symptoms that prevent the child from full participation in his or her usual daily activities (symptom code 2 or more) as documented on the Diary Cards for each 30 day period (1 month) in the preceding 183 days (6 months)

Criteria for resumption of full dosage

The criteria for failure to maintain a state of well-being following dosage tapering (and thus requiring resumption of full dose assigned treatment) are:

- Pre-bronchodilator FEV_1 below 90% previous best or below 85% of predicted or pre-bronchodilator FEV_1/FVC below 85%; **OR**
- Eight or more days during any 28 day (4 week) period with asthma symptom code 2 or more or mean (am and pm) PEFR below 80% of personal best, as documented on the Diary Cards; **OR**
- 32 puffs (16 usages) or more of albuterol during any 28 day (4 week) period, excluding preventive use before exercise, as documented on the Diary Cards; **OR**
- One or more hospitalizations for asthma since taper
- Need for any anti-asthmatic medication other than albuterol to control an exacerbation, as documented on the Diary Cards, as elicited during interview, or as reported by child's primary physician; **OR**
- Judgment by the study physician that resumption of full dose study drug is warranted

7.5 Environmental assessment

Environmental control:

Specific recommendations and materials will be supplied for appropriate environmental controls, based upon the patient's history of exposure and, where relevant, demonstrated skin test reactivity. These will include:

- Recommendation for mattress covers and pillow covers
- Recommendation for weekly washing of bedding in hot water
- Home-specific instructions in animal dander control aimed preferentially at removing the pet from the home
- Instruction in cockroach control, plus recommendations for pesticide treatment if sightings have occurred

- When there is a smoker in the home, referral to tobacco smoking adjustment classes when feasible
- Instruction in measures for the reduction of mold growth, and
- Recommendations for adjustment of wood and kerosene burning in unvented or poorly vented stoves

Environmental counselling will be repeated annually based on the Home Environment Questionnaire.

House dust specimen collection

At baseline (after randomization but no more than 6 months later), after 3 years, and after moving into a new home, a house dust specimen will be collected by a technician, who will, at the same time, complete an observational survey of the home. Dust specimens will be collected from the child's primary residence and any other residence at which the child spends more than 30% of his/her time.

A mixed house dust specimen (0.5 g) will be obtained using a vacuum cleaner fitted with a filter by specifically vacuuming the upper surface of the patient's mattress (if encased in plastic, the surface of the plastic cover will be vacuumed), bedroom floor or carpet, living room/family room floor or carpet, the kitchen floor, and a major item of upholstered furniture. Sites will be revacuumed if the initial specimen is inadequate in size. The dust specimen will be sieved to obtain fine dust free of large particles and fibers, then quantitatively analyzed for the presence of major allergens of D pteronyssinus, D farinae, cat, and cockroach. An agar plate will be streaked for enumeration of fungus colonies without further identification. An analysis for major allergen of dog will be performed if available; a specimen of the dust will be maintained in a frozen state for future analysis. Monoclonal antibody assays will be employed for all allergen determinations.

The levels of major allergens will be compared wherever possible to suggested levels for risk of sensitization or risk of acute asthma: for Der p 1 and Der f 1, 2 Og/gm of dust and 10 Og/gm of dust respectively (Pollart et al, 1989); for Fel D 1, 8 Og/gm of dust for sensitization (Luczynska et al, 1990); and for cockroach 2 units/gram of dust for significant exposure (Gelber et al, 1990).

7.6 Unmasking

Unmasking of a child's assigned treatment will be detrimental to CAMP. The following policy has been adopted to help assure that unmasking is never necessary:

- If staff are queried as to the child’s treatment assignment, he/she should remind the questioner that the child is either on budesonide [nedocromil] or placebo
- The child will stop the study inhaler if there is concern over its effects

- Staff should contact the Executive Committee if there are further questions

7.7 Chicken pox

Chicken pox is usually a mild disease of early childhood. It is so mild, in fact, that some physicians have questioned the wisdom of widespread use of a vaccine that could delay the appearance of the disease until adulthood. As immunity from the vaccine wanes, mild childhood disease could be replaced with the more severe adult reaction to the virus.

However mild the disease is in the general population, there are approximately 150 deaths due to chicken pox each year in the U.S. Most of these deaths occur in otherwise apparently normal children. Only 25% of these deaths occur in children who are immunocompromised.

Concern has been raised recently over the risk of varicella complications, including death, in asthmatic individuals who have received corticosteroid medication. This concern derives from several case reports of children who have received oral steroids for asthma exacerbations and then developed chicken pox with severe complications and death. The FDA has extended the concern about chicken pox complications to those children with asthma who are taking inhaled steroids.

Based on the handful of case reports and the unproven speculation that inhaled steroids may cause immunosuppression, the FDA has derived a series of recommendations about treatment of children with asthma who are taking these medications and who are exposed to or subsequently develop the viral infection. In reviewing these recommendations it is important to put the concern about chicken pox in the context of the epidemiology of this disease in childhood.

Given 150 deaths per year, it is possible that the 5 case reports in the world's literature of deaths in children who have been treated with oral corticosteroids for asthma do not represent an association between either asthma or oral steroids and chicken pox complications. However, a common disease with rare complications does not lend itself to definitive epidemiological study, particularly when the disease is not reported in the vast majority of children.

Instructions to parents and recommendations for dealing with exposure to chicken pox in CAMP patients are as follows:

All parents:

1. Parents should be notified about the FDA guidelines, placing them in the context of the experience in the literature.
2. Parents of children without a history of chicken pox or with negative antibody titer should be instructed to call the CAMP center if the child is exposed to chicken pox.

Parents of a child who has been exposed to chicken pox and who has received oral steroids within one week of exposure:

1. Administration of varicella zoster immune globulin within 96 hours (4 days) of exposure should be considered. The final decision should take into account the intensity of exposure, the details about oral steroid use, etc.
2. Oral acyclovir should be administered within 24 hours of onset of lesions.
3. The parents should be instructed to contact the doctor if complications of chicken pox become apparent. At this time, the child should be examined and use of intravenous acyclovir considered.

Parents of a child who has been exposed to chicken pox and has not received oral steroids within one week of exposure but who is assigned to budesonide or its placebo:

1. Instruct the parents to call their doctor upon onset of lesions.
2. Oral acyclovir should be administered within 24 hours of onset of lesions.
3. The parents should be instructed to contact the doctor if complications of chicken pox become apparent. At this time, the child should be examined and use of intravenous acyclovir considered.

7.8 Adverse events reporting

Serious, unexpected adverse experiences that are thought to be associated with use of a CAMP study drug (budesonide, nedocromil, or their placebos) must be reported to the holder of the IND for the study drug, who in turn must report the experience to the FDA. Experiences that do not meet all 3 criteria (serious, unexpected, and associated with use of a study drug) should not be reported to the holder of the IND for the study drug; however, some of these events are reportable as CAMP data as described later in this section.

The Code of Federal Regulations (CFR) defines **serious adverse experience** as any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, these include any drug-related event that is fatal or life-threatening, is permanently disabling, requires or extends inpatient hospitalization, or is congenital anomaly, cancer, or overdose. A life threatening event is one that, in the study physician's opinion, the patient was at immediate risk of death from the reaction as it occurred.

Unexpected adverse experience means any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure for the study drug.

Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the drug. Identification of an adverse experience as study drug related is the responsibility of the study physician. All adverse experiences should be presumed to be related to the study drug currently in use unless other evidence, experience or the patient's medical history suggests the contrary. Study physicians should call the Study Chair or Vice Chair for consultation if they think that a serious adverse experience has occurred.

The holder of the INDs for both CAMP study drugs is the NHLBI. The reporting procedure for clinic staff for an adverse experience that is serious, unexpected, and thought to be associated with use of a study drug is:

- Complete the CAMP Adverse Experience Report (Form AE) and a narrative summary of the event.
- Send a copy of Form AE and the summary to the NHLBI Project Officer; she must submit a written report to the FDA within 10 working days of the experience. Mail copies to the CC, and key Form AE to the CAMP data system at your clinic. **PLEASE make sure that individual identifiers are not present in the summary; the patient should always be identified by ID number and name code -- NEVER by name.**
- If the experience is life threatening or fatal, call the NHLBI Project Officer and the CC using the telephone numbers provided on Form AE; the FDA must be notified within 3 working days of the experience. If you cannot reach the NHLBI Project Officer, call the FDA directly.
- Report the adverse experience to your local IRB.
- Complete the CAMP Death Report (Form DR) if applicable.

The NHLBI Project Officer, as holder of the INDs for the CAMP study drugs, will do the following:

- Notify the FDA of the experience. In the written report, all reports previously filed with the IND concerning a similar adverse experience, shall be identified, and the significance of the adverse experience in light of the previously filed reports shall be analyzed.
- Notify all CAMP clinic directors, the CC director, the Study chair, the DSMB chair, and the pharmaceutical company for the drug involved. CAMP clinic directors must report the event to their IRB as directed by the NHLBI Project Officer.

Reporting of other types of adverse experiences is handled as follows:

- Expected adverse experience associated with a study drug: report on the Followup Interview form (Form FI) or Interim Treatment Event Report (Form TE)
- Unexpected adverse experience associated with a study drug that is not serious: report on Form FI or Form TE
- A death that is not associated with use of a study drug: complete the Death Report (Form DR), key it to the CAMP data system, and fax the form to the CC
- All other adverse experiences (ie, those that are neither associated with a study drug nor fatal): not reportable to CAMP or the holder of the IND

Please note that your local IRB may require notification of some of the adverse experiences in the categories described above. You should check with your IRB to make sure that you are in compliance with their requirements.

8. Data collection schedule

The following is a general outline for data collection as shown in more detail in Table 6.

Potential patients will be screened by telephone interview or by communication with referring physicians to determine preliminary eligibility. If initial qualifications are met, the trial candidate will come into the clinic for: (1) screening questionnaires and informed consent and assent procedures; (2) baseline medical, physical, and psychological evaluations; and, if all trial requirements are met, (3) randomization to a treatment regimen. Data collection will continue until a common closeout date 5 years after the end of recruitment. The screening questionnaires will elicit data on demographics, eligibility, and likelihood of adherence. The asthma and allergy history will cover the history of asthma (symptoms and severity), treatment for asthma including hospitalizations, medications, allergy history, and relevant family history. Baseline psychological testing will be administered by a CAMP certified psychometrician.

Starting with the second screening visit, the patients and caretakers will be asked to keep a daily diary in which they will record days of limited activity, days missed from school, frequency of nocturnal asthma awakenings, physician contacts for asthma, albuterol use before exercise and for asthma, use of study medications, prednisone use, peak flow readings, and symptoms. Patients and caretakers will bring this diary with them when they come for the next clinic visit. Throughout the study the diary cards will be mailed to the clinic every 2 weeks.

In addition, patients will have the following procedures carried out with the indicated frequency:

- Physical exam (baseline and annually)
- Spirometry (baseline, 2 months, and every 4 months from baseline except at visits when methacholine challenge testing is done)
- Methacholine challenges (baseline, 8 months, 20 months and annually thereafter)
- Assessment of potential glucocorticoid adverse effects on linear growth (2 months and every 4 months from baseline)
- Allergen skin test testing (baseline and year 5)
- Bone density (baseline and annually)
- Tanner staging (baseline and annually)
- Determination of indoor allergen content (baseline, year 3, and if the patient moves)
- Determination of serum total IgE concentration (baseline and year 5)
- Neurocognitive evaluation (baseline, years 3 and 5)
- Psychosocial functioning (baseline and annually)
- Compliance assessment (2 months and every 4 months from baseline)
  - Review of asthma diaries
  - Weighing of albuterol metered dose inhalers
  - Counts of prednisone pills

9. Biostatistical considerations

9.1 Adequacy of sample size

A combined sample size of 960 patients (288 each for the budesonide and nedocromil groups and 384 for the placebo group) is planned (see Figure 2). The placebo group will be equally divided between 192 patients receiving placebo Turbuhalers® that match those in the budesonide group and 192 patients receiving placebo metered dose inhalers that match those in the nedocromil group. Each of the 8 clinical centers will recruit 120 patients (at least 1/3 of whom are minorities) over an 18 month period. In addition, 16 startup phase patients (2 per clinic, randomized to budesonide, nedocromil, or placebo) will be recruited and followed as part of quality assurance for the trial proper. Data from these startup patients will not be combined with trial data in any analyses.

The outcome measure used in the sample size calculations was change from baseline in FEV_1 percent of predicted, i.e., change in the ratio 100 x [FEV_1 ÷ predicted FEV_1 (based on gender, race, and height)]. The planned sample size gives 90% power to detect a 3.5% difference in mean change between either of the two test treatments vs placebo and a 3.8% difference in mean change for the test treatments compared with each other. Other assumptions used in the calculations were: 11% within group standard deviation for the change in ratio, 2-sided type I error of 0.01, and missing data rate of 10%.

Additional calculations were carried out keeping the two different types of placebos as distinct groups. Under the same assumptions as above, a 4.6% difference in mean change in FEV_1 percent of predicted will be detectable between the two types of placebo patients (192 budesonide placebo Turbuhaler® vs 192 nedocromil placebo metered dose inhalers) and a 4.2% difference will be detectable if comparisons are limited to either test treatment (n=288) and its matching placebo (n=192).

The sample size calculations did not take into account the attenuation of effects due to non-compliance nor did they include formal adjustments for multiplicity (multiple comparisons, multiple looks, or multiple outcomes), although the type I error of 0.01 (rather than 0.05) was chosen out of concern for these issues. Determination of the minimal detectable effects was based on the t-test for comparing means of the individual changes (see Dupont and Plummer, 1990 for formulas and software).

The clinical significance of the detectable effect sizes derived for CAMP can be put into perspective using data from Weiss (1992) and Adkinson (Personal communication, 1992: Childhood Asthma Study, 106 asthmatic children followed from 6 to 60 months), which both yield an approximate 1% per year worsening in FEV_1 as a percent of predicted in children with asthma. Also, the recent Dutch trial (Van Essen-Zandvliet, 1992) on 116 asthmatic children found a highly significant difference of 11% in the change in FEV_1 percent of predicted over a 22 month period following treatment with bronchodilator (salbutamol) plus budesonide compared with bronchodilator plus placebo.

9.1 Adequacy of sample size

The standard deviation (11%) assumed for within group change in FEV_1 percent of predicted (measured from baseline to a single point during followup) was derived from two sources. The Dutch Trial reported an effect size (of 11%) at two months and associated 95% confidence limits (of 7-15%), from which the within group standard deviation (SD) was calculated. An SD estimate of 11% was also obtained from the Childhood Asthma Study data comparing baseline vs 6-month FEV_1 determinations. Although these data may not reflect future experience in CAMP, the 11% SD figure was deemed to be adequate for planning purposes and may in fact be conservative.

It may be conservative because, in contrast to the sample size calculations, which are based on a baseline determination and a single measure during followup, the actual CAMP analyses will use, in effect, weighted averages of individual slopes based on all FEV_1 measures made at baseline and at the four-monthly visits during the 5 - 6½ year period of follow-up. The within group SD for individual slopes derived for children from the Childhood Asthma Study followed from 6 to 60 months was 6%. If similar reductions in SD are achieved in CAMP, when weighted slopes are used instead of simple differences, even smaller effects will be detectable: e.g., (using the other assumptions as above) 1.9% for test treatment vs placebo and 2.1% for the test treatments vs each other in the difference in mean change in FEV_1 percent of predicted.

Detectable effects for other outcome measures, given the planned sample size, will be on the order of 32% SD (i.e., within group SD of the outcome measure) for comparing a test treatment with placebo and 34% SD for comparing the test treatments with each other.

9.2 Interim monitoring

The responsibility for interim monitoring of the accumulating data for evidence of adverse or beneficial effects will rest with the CAMP Data and Safety Monitoring Board (DSMB) that is advisory to the sponsor, NHLBI, and independent of the CAMP Research Group. While no formal statistical stopping rules are proposed for the CAMP trial (see Canner, 1977 and Berry, 1985 for reasons why formal stopping rules may be undesirable), it is anticipated, however, that conditional probabilities of rejection of the null hypothesis (i.e., conditional power and conditional Type I error), given the accumulated data at given interim analyses, will be calculated using stochastic curtailment methods (Halperin et al, 1982).

Interim analyses are intended to assess patient safety, protocol integrity and data quality, and to determine whether the trial objectives are being met. The DSMB will meet regularly (at least twice per year) during the conduct of the trial to monitor the emerging results and to assess the risks and benefits of each mode of therapy, thus insuring the safety of the patients enrolled in the trial. The CC will be responsible for performing all analyses on behalf of CAMP, including those required for both performance and treatment effects monitoring, as well as those required for presentations or

publication of the results of the trial. Members of the DSMB will be primary contributors to the analysis process, but substantial contributions from the SC and from clinical investigators will be encouraged.

9.3 Data analysis

The primary data analyses will focus on comparisons among the 3 treatment groups to identify adverse or beneficial effects that might be attributable to the treatment. Primary analyses will be carried out according to original treatment assignment.

Pooling of patients assigned to Turbuhaler® placebos with those assigned to metered dose inhaler placebos will be done only after checking that, after adjustment for baseline characteristics, the outcome measures are comparable between the two placebo types. If there is a clinically significant difference between the two types of placebos (e.g., mean changes in FEV_1 percent predicted differ by more than 5%) or if the difference between the placebo groups is numerically larger than either of the test treatments vs its matching placebo, the pooled placebo group would not be used. If this situation, which is considered unlikely, should arise, comparisons would be limited to each test treatment vs its matching placebo. Interpretation of direct comparisons of the two test treatments in the presence of such variations in response by type of placebo used would be problematic.

Patients with missing outcome measures at a particular time will be excluded from analyses that require those measures but will not be excluded from other analyses for which data are available. The pattern of missing data will be compared across treatment groups and within the two types of placebos to determine if data are missing at random. Baseline characteristics of patients with missing measures will be compared with those with complete data.

Exploration of the measurements and other responses collected will employ robust statistical methods to reduce the influence of extreme responses: trimmed means or trimeans for estimating means, median absolute deviations to estimate standard deviations, stem and leaf charts, letter value displays (5-value summary), identification of outliers, and determination of transformations of scale, if needed (Hoaglin et al, 1983).

The primary outcome for the CAMP trial will be change in level of FEV_1 percent of predicted over five years, to be measured in a masked and standardized fashion from serial FEV_1 measurements on patients at baseline and 2 times per year following randomization. Secondary outcomes will include 1) other spirometric measures (e.g., FVC and FEV_1/FVC) and change in airway responsiveness (PC_{20} FEV_1 from the methacholine challenge), 2) self reports of morbidity, 3) self

reports of the frequency of use of health care resources, 4) self reports of the frequency of side effects, and 5) measures of psychological growth and development.

All primary analyses will be based on original treatment assignment. The simplest analysis for treatment effects will focus on contrasts in estimated rates of change in FEV_1 percent of predicted determined by regressing individual slopes, obtained from fitting a straight line to each patient's serial FEV_1 measures (including baseline) vs. time, on treatment group and baseline covariates (age at entry, height, and ethnic group, gender, etc.) using weights inversely proportional to the estimated variance of the slope for each patient. For FEV_1 percent of predicted and for the other outcome measures, a more efficient general approach to the regression analysis of dependent (i.e., correlated), continuous or discrete responses will be used (Liang and Zeger, 1986). Continuous outcome methods which are based on a random effects model will also be employed (Laird and Ware, 1982). Assessments of the fit of resulting models will be made using residual plots and other measures of fit (McCullagh and Nelder, 1989).

10. CAMP organizational units

- **Clinical Centers and Directors**

ASTHMA, Inc, Seattle, WA
Gail G. Shapiro, MD

Brigham & Women's Hospital, Boston, MA
Scott T. Weiss, MD, MS

Hospital for Sick Children, Toronto, Ontario
Henry Levison, MD, FRCP(C)

Johns Hopkins Asthma and Allergy Center, Baltimore, MD
N. Franklin Adkinson, Jr, MD

National Jewish Center, Denver, CO
Stanley J. Szefler, MD

University of California, San Diego, CA
Robert S. Zeiger, MD, PhD

University of New Mexico, Albuquerque, NM
Bennie C. McWilliams, MD

Washington University, St. Louis, MO
Robert C. Strunk, MD

- **Resource Centers**

Central Laboratories (CL)

Dust & IgE Laboratories
JHU DACI Reference Laboratory
Robert Hamilton, PhD

Serum Repository
JHU DACI Reference Laboratory
N. Franklin Adkinson, Jr, MD

Chairman's Office (CO)
National Jewish Center
Reuben M. Cherniack, MD

Coordinating Center (CC)
The Johns Hopkins University
James Tonascia, PhD
Curtis L. Meinert, PhD

Drug Distribution Center (DDC)
Ogden BioServices Corporation
Mark Walls

Patient Education Center (PEC)
National Jewish Center
Stanley Szefler, MD

Pharmaceutical Suppliers (PS)
Astra Pharmaceutical Products, Inc.
Donation of budesonide (Pulmicort®) and matching placebo Turbuhaler®

Fisons Pharmaceuticals
Donation of nedocromil (Tilade®) and matching placebo metered dose inhalers

Glaxo Inc. Research Institute
Donation of albuterol (Ventolin®)

Project Office (PO)
National Heart, Lung, and Blood Institute
Virginia Taggart, MPH

▾ **Steering Committee (SC) - Phase I**

Reuben M. Cherniack, MD, National Jewish Center, Chairman
Robert C. Strunk, MD, Washington University, Vice-Chairman
N. Franklin Adkinson, Jr, MD, Johns Hopkins Asthma & Allergy Center
Robert Annett, PhD, University of New Mexico
Bruce Bender, PhD, National Jewish Center
Thomas DuHamel, PhD, ASTHMA, Inc
Henry Levison, MD, FRCP(C), Hospital for Sick Children
Bennie C. McWilliams, MD, University of New Mexico
Curtis L. Meinert, PhD, The Johns Hopkins University
Sydney R. Parker, PhD, National Heart, Lung, and Blood Institute
Gail G. Shapiro, MD, ASTHMA, Inc
Stanley J. Szefler, MD, National Jewish Center
James Tonascia, PhD, The Johns Hopkins University
Scott T. Weiss, MD, MS, Brigham & Women's Hospital
Robert S. Zeiger, MD, PhD, University of California, San Diego

▾ **Steering Committee (SC) - Phase II** *(effective: recruitment of start-up patients)*

Reuben M. Cherniack, MD, National Jewish Center, Chairman
Robert C. Strunk, MD, Washington University, Vice-Chairman
N. Franklin Adkinson, Jr, MD, Johns Hopkins Asthma & Allergy Center
Robert Annett, PHD, University of New Mexico*
Bruce Bender, PhD, National Jewish Center*
Thomas DuHamel, PhD, ASTHMA, Inc*
Henry Levison, MD, FRCP(C), Hospital for Sick Children
Bennie C. McWilliams, MD, University of New Mexico
Curtis L. Meinert, PhD, The Johns Hopkins University
Marian Sharpe, BSN, ASTHMA, Inc.†
Gail G. Shapiro, MD, ASTHMA, Inc.
Stanley J. Szefler, MD, National Jewish Center
Virginia Taggart, MPH, National Heart, Lung, and Blood Institute
James Tonascia, PhD, The Johns Hopkins University
Scott T. Weiss, MD, MS, Brigham & Women's Hospital
Barbara Wheeler, RN, BSN, Johns Hopkins Asthma & Allergy Center†
Robert Wise, MD, The Johns Hopkins University
Robert S. Zeiger, MD, PhD, University of California, San Diego

*3 behavioral scientists are represented for Phase II of the SC; 2 will attend the SC meetings; but only one vote will be cast

†2 center coordinators are represented for Phase II of the SC; both will attend the SC meetings; but only one vote will be cast

▾ **Executive Committee (EC)**

Reuben M. Cherniack, MD, Chairman
Curtis L. Meinert, PhD, Coordinating Center
Robert C. Strunk, MD, Vice-Chairman (renewable 3 year term)
Virginia Taggart, MPH, Project Office
James Tonascia, PhD, Coordinating Center

▾ Data and Safety Monitoring Board (DSMB)

Members:

Howard Eigen, MD, Riley Hospital for Children, Chairman
Michelle Cloutier, MD, University of Connecticut Health Center
John Connett, PhD, University of Minnesota
Clarence E. Davis, PhD, University of North Carolina
David Evans, PhD, Columbia University College of Phys & Surgs
Meyer Kattan, MD, Mount Sinai Medical Center
Sanford Leikin, MD, Children's National Medical Center
Rogelio Menendez, MD, Asthma and Allergy Research Center of El Paso
Estelle R. Simons, MD, Children's Hospital of Winnipeg

Non members:

Reuben M. Cherniack, MD	CAMP Chairman
Curtis L. Meinert, PhD	CC representative
Robert C. Strunk, MD	CAMP Vice-Chairman
Virgina Taggart, MPH	Project Officer, NHLBI
James Tonascia, PhD	CC representative
Margaret C. Wu, PhD	Statistician, NHLBI

11. Patient rights and responsibilities

11.1 IRB approval

Local IRBs will review and approve the final protocol, including the prototype consent statement (see Appendix) which contains all of the legally required elements of the informed consent and is to be used as a model by each clinical center for their IRB submission. Any substantive protocol issues raised by local IRBs will have to be adjudicated with the Steering Committee.

11.2 Patient confidentiality

All patient data will be kept in a secure location at each clinical center. Access to patient identification data will be limited to direct-care clinical personnel and the clinic coordinator. Patient identification data will not be transmitted to the Coordinating Center. Other patient data will be identified by trial ID codes only; a patient ID number and name code will be assigned at registration. Clinical data will be released to the patients, the Coordinating Center, and may be released, without personal identifiers, to the pharmaceutical sponsor or the FDA for monitoring purposes without consent of the patient. Clinically relevant information may be placed in the patient's medical record. Release of data to any other persons or organizations will require the written consent of the patient.

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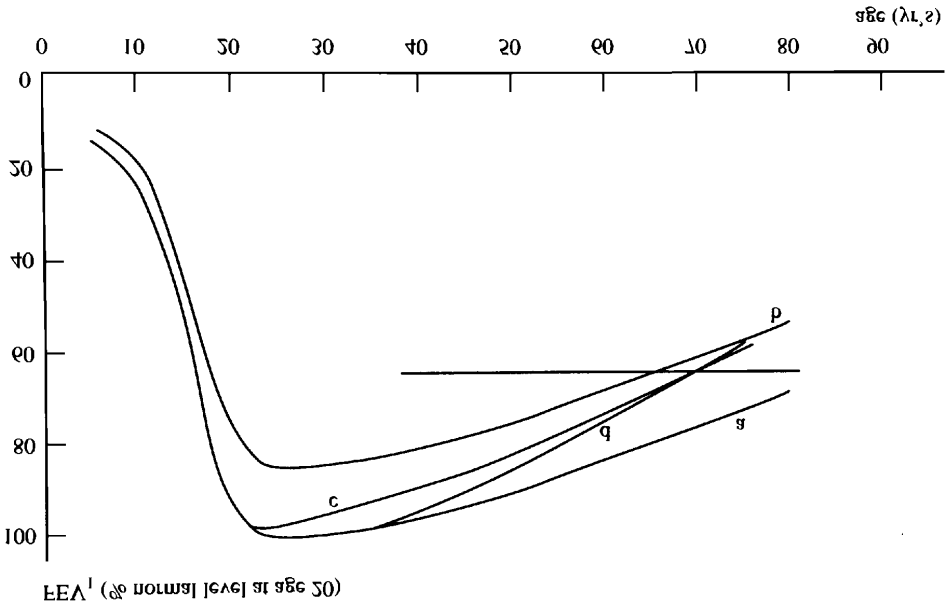
CAMP Protocol

Figure 1. An epidemiologic model for growth and decline in lung function



A general theoretical model of growth and decline of lung function with time; adapted from Sparrow and Weiss, Airway Responsiveness and Atopy in the Obstructive Lung Diseases. Raven Press N.Y. 1989 p13. Line a represents patients with normal growth, plateau phase and decline. Line b represents patients with submaximal growth in childhood, a normal plateau phase and a normal rate of decline. Line c represents patients who have normal growth, an attenuated plateau phase and have an earlier onset of decline, although the rate of decline is normal. Line d represents patients with normal growth, normal plateau phase but an accelerated rate of decline in lung function. The horizontal line at 60% of predicted FEV_1 represents the development of obstructive airways disease.

CAMP Protocol

Figure 2. Treatment groups

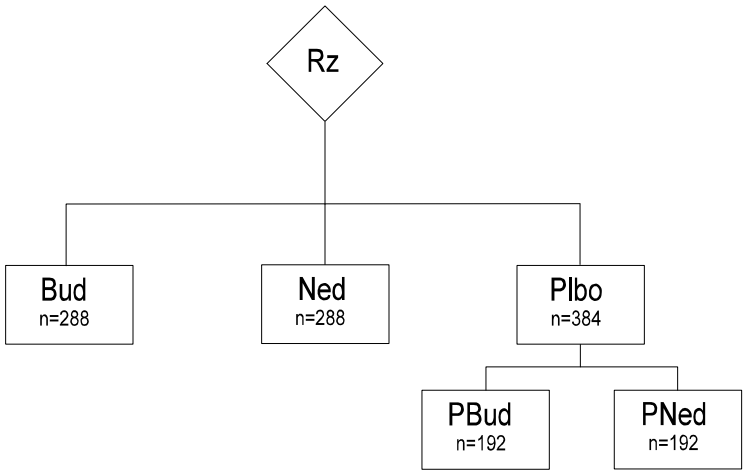


Table 1. Comparative efficacy of available anti-asthma medications and those proposed for this clinical trial

Medication	Bronchodilator	Protection to: Allergen	Protection to: Histamine	Resolution of inflammation*
Available agents				
Bronchodilators				
O_2-agonist	+++	I	+++	-
Theophylline	++	I,L	+	+
Anticholinergic	+	-	ND	-
Non-bronchodilator anti-asthma medications				
Cromolyn	-	I,L,AR	-	++
Glucocorticoid	-	L,AR	-	+++
CAMP				
Budesonide	-	I,L,AR	-	+++
Nedocromil	-	I,L,AR	-	+++

+++ marked effect; ++ moderate effect; + some effect; - no effect; ND no data available
Single dose of medication blocks immediate (I) or late (L) pulmonary response to allergen challenge, or consequent airway hyperresponsiveness (AR)
*Resolution is defined as a reduction in airway hyperresponsiveness with chronic therapy

CAMP Protocol

Table 2. Design summary

Objective

- The Childhood Asthma Management Program (CAMP) is a clinical trial carried out in children with asthma. The trial is designed to determine the long-term effects of 3 treatments (budesonide, nedocromil, or placebo) on pulmonary function as measured by normalized FEV_1 over a 5-6½ year period.

Type of study

- Multicenter, masked, placebo-controlled, randomized
- Population: 960 (288 each in budesonide and nedocromil groups and 384 in placebo group) children aged 5-12, of whom at least **a** are minority

Stratification

- Clinic

Treatments [abbreviation]

- **[Bud]** Inhaled glucocorticoid (budesonide) + intermittent O_2-agonist (albuterol)
- **[Ned]** Inhaled nonsteroidal anti-inflammatory (nedocromil) + intermittent O_2-agonist (albuterol)
- **[Plbo]** Intermittent O_2-agonist (albuterol) +
  - [PBud]: budesonide placebo
    or
  - [PNed]: nedocromil placebo

Treatment administration

- Budesonide (Pulmicort®), two 100 Og puffs *bid* + two 90 Og puffs albuterol (Ventolin®) *prn*
- Nedocromil (Tilade®), four 2 mg puffs *bid* + two 90 Og puffs albuterol *prn*
- Two 100 Og puffs budesonide placebo *bid* + two 90 Og puffs albuterol *prn*
  or
  Four 2 mg puffs nedocromil placebo *bid* + two 90 Og puffs albuterol *prn*
- Tapering of doses from 100% to 50% to 0% for patients who have sustained minimal symptoms and satisfactory lung function
- Addition of beclomethasone (four 42 Og puffs *bid*) for patients whose asthma is inadequately controlled while on full dose study medication and albuterol

Masking

- Masked with respect to active drug or placebo [masked Turbuhaler® (budesonide or matching placebo), masked meter dose inhaler (nedocromil or matching placebo)]
- Unmasked use of intermittent O_2-agonist (albuterol)
- Unmasked Data and Safety Monitoring Board

Table 2. Design summary

Inclusion criteria

- Age 5 to 12 years at time of screening
- Chronic asthma of as evidenced by one or more of the following historical findings for at least 6 months during the past year:
  - Asthma symptoms at least 2 times per week
  - 2 or more usages per week of an inhaled bronchodilator
  - Daily asthma medication
- Current asthma symptoms either by diary symptom code of 1 or greater (Table 5) or am or pm PEFR less than 80% of personal best post-bronchodilator value by diary, on 8 or more days during the *prn* screening period
- Methacholine sensitivity: estimated PC_{20} FEV_1 less than or equal 12.5 mg/ml
- Consent of guardian and assent of child
- Ability to comply with trial for 5-6½ years

Exclusion criteria

- Presence of one or more of the following confounding or complicating problems:
  - Any other active pulmonary disease
  - Any chronic condition presumed to interfere with the successful completion of the project or confound its interpretation
  - Pulmonary function testing findings suggesting a ventilatory defect other than asthma, or evidence of existing irreversible lung damage
  - Severe chronic sinusitis or nasal polyposis
  - Introduction of or a change in allergen immunotherapy within the past month
  - Use of more than 4 sprays of nasal steroids daily (only beclomethasone allowed)
  - Pregnancy
  - Current use of metoclopramide, ranitidine, or cimetidine
  - Treatment for gastroesophageal reflux
  - Participation in another drug study
- Evidence of severe asthma as indicated by one or more of the following:
  - Two or more hospitalizations for asthma in the past year
  - Six or more steroid bursts in the past year
  - Demonstrated need for continuous use of glucocorticoids, either oral or inhaled
  - When off inhaled O_2-agonist for more than 4 hrs and theophylline for more than 24 hrs, FEV_1 less than 65% predicted
  - Intubation for asthma at any time in the past
  - Need for 9 or more puffs/day of albuterol for each of 3 consecutive days (excluding preventive use prior to exercise), or nocturnal asthma awakenings more than 1.5 times per week on average, or average diary card symptom code greater than 2 (Table 5), or requirement for other medications to control asthma, during *prn* screening period

Table 2. Design summary

Exclusion criteria (cont'd)

- Inability to perform 3 acceptable FVC maneuvers of which at least 2 reproducible FEV_1s are within 10% of the largest FEV_1
- Inability to complete the methacholine challenge or methacholine PC_{20} FEV_1 greater than 12.5 mg/ml
- Evidence that patient or family may be unreliable or non-compliant or may move from the metropolitan area before trial completion

Recruitment

- To sample size goal
- 18 months

Duration of followup

- To common closing date 5 years after end of recruitment phase (5 - 6½ yrs.)

Outcomes

Primary:

- Lung function (FEV_1)

Secondary:

- Bronchial responsiveness to methacholine
- Need for beclomethasone due to asthma symptoms
- Termination of assigned treatment due to cessation of symptoms
- Asthma morbidity
  - Frequency and severity of asthma symptoms
  - Frequency and magnitude of PEFR measurements less than 80% of personal best
  - *Prn* use of supplemental inhaled albuterol
  - Nocturnal awakenings, days of limited activity and absences from school
  - Courses of steroids (days and dose)
- Mortality, long term safety, and side effects
- Physical growth and development
  - Somatic growth measures (linear growth, weight, body mass index, truncal growth, sexual maturation)
  - Steroid effects (bone density)
  - Lung growth (spirometry)
- Psychological growth and development

Table 2. Design summary

Secondary outcomes (cont'd)

- Neurocognitive function (Wechsler Preschool and Primary Scale of Intelligence, Wechsler Intelligence Scale for Children III, Woodcock-Johnson Psycho-Educational Battery Tests, Wide Range of Assessment of Memory and Learning, Gordon Diagnostic System)
- Individual and family functioning measures (Youth Self Report, Children's Depression Inventory, Revised Children's Manifest Anxiety Scale, Social Anxiety Scale for Children, Child Behavior Checklist, Family Environment Scale, Impact on Family Scale, Medical Outcome Study Social Support Survey)

- Use of health care resources
  - Emergency room visits
  - Hospitalizations
  - Physician visits/contacts

Treatment adjustment for inadequate control of asthma (addition of beclomethasone)

- Six or more prednisone courses in the previous 12 months
- Thirty-one or more days of prednisone use in the previous 12 months
- Two or more hospitalizations for asthma in the previous 12 month period
- Excessive use of albuterol (more than 1.5 canisters/month *prn* use for 4 months)
- Other asthma worsening judged to warrant addition of beclomethasone

Treatment adjustment because of adverse reaction to study drug, pregnancy, need for assisted ventilation, or asthma worsening after addition of beclomethasone

- Treatment at the discretion of the CAMP and/or private physician

Treatment tapering for well-being

- Adjustment of treatment downward to be considered after 7.5 months on protocol and at 4 month intervals thereafter
- Treatment drug dose down 50% from full dose if all of the following conditions are met
  - On full dosage at least 7.5 consecutive months; and
  - Pre-bronchodilator FEV_1 at least 85% predicted and pre-bronchodilator FEV_1/FVC ratio at least 85%; and
  - Four puffs (2 usages) or less per week of albuterol during each week in the preceding 6 months, excluding preventive use before exercise; and
  - One day or less per month of asthma symptoms curtailing daily activities (symptom code at least 2 [Table 5]) in the preceding 6 months

Table 2. Design summary

Treatment tapering for well-being (cont'd)

- Treatment drug tapered to no use if all of the following conditions are met
  - On half dosage for at least 7.5 consecutive months; and
  - Pre-bronchodilator FEV_1 at least 85% of predicted and pre-bronchodilator FEV_1/FVC ratio at least 85%; and
  - Four puffs (2 usages) or less per month of albuterol during each month in the preceding 6 months, excluding preventive use before exercise; and
  - One day or less per month (and fewer than 5 days total) of asthma symptoms curtailing daily activities (symptom code at least 2 [Table 5]) in past 6 months
- Resumption of full dose trial medication if any of the following occurs:
  - Pre-bronchodilator FEV_1 less than 90% previous best or less than 85% of predicted, or pre-bronchodilator FEV_1/FVC less than 85%; or
  - 8 or more days during any 4 week period with asthma symptoms curtailing daily activities (symptom code at least 2; [Table 5]) or mean daily PEFR less than 80% of personal best; or
  - At least 32 puffs (16 usages) of albuterol during any 4 week period, excluding preventive use before exercise; or
  - Other anti-asthmatic medications required for control of asthma symptoms; or
  - Judgment by physician that resumption of full dose study drug is appropriate
- If adjustment fails, the full dose trial medication would be resumed for 7.5 months, after which the adjustment criteria will be applied again

Data collection schedule

- Baseline: 5 visits
  - -7 wks, -6 wks, -2 wks, -1 wk, and 0 wks
- Followup:
  - At 2 months and every 4 months from baseline for duration of trial

Treatment comparisons and detectable changes in FEV_1

- (FEV_1 % = Detectable differences in FEV_1 percent of predicted, assuming a 2-sided Type I error of 0.01, a power of 0.9, and an 11% within group SD for the change in FEV_1 percent predicted)
- Bud vs Ned (FEV_1 % = 3.8%)
- If PBud vs PNed (FEV_1 % = 4.6%) combinable
  - Bud vs Plbo (FEV_1 % = 3.5%)
  - Ned vs Plbo (FEV_1 % = 3.5%)
- If PBud vs PNed not combinable
  - Bud vs PBud (FEV_1 % = 4.2%)
  - Ned vs PNed (FEV_1 % = 4.2%)

Table 2. Design summary

Data analysis and monitoring

- Review of data by Data and Safety Monitoring Board (DSMB) at semiannual meetings
- Early termination of the trial or protocol modifications made by the DSMB (no formal stopping rules)
- Primary analyses by original treatment assignment
- All events or measurements made after randomization will be included in primary analyses

CAMP Protocol

Table 3. Operational disease definitions

	Disease or condition	Indices of clinical suspicion	Source of definitive diagnosis
1.	Cystic fibrosis (CF)	Recurrent pneumonia; greasy foul-smelling stools; family history of CF	Sweat chloride test
2.	Bronchiectasis	Chronic productive cough with purulent sputum and recurrent episodes of pneumonia	CT scan of chest
3.	Immunodeficiency	Recurrent sinopulmonary infection with fever	Serum immunoglobulins (IgG/usually with IgM/IgA); complete blood count with differential
4.	Chronic sinusitis	Recurrent marked nasal stuffiness and/or purulent nasal discharge; need for antibiotic therapy ▾ 6 times per year	Sinus x-rays
5.	Nasal polyposis	Persistent nasal obstruction; chronic sinusitis	Physical exam and/or sinus x-ray
6.	Aspiration, chronic	Coughing after eating	Barium swallow
7.	Bronchopulmonary dysplasia	Premature at birth; need for assisted ventilation in neonatal period; need for O_2 supplements in 1st year of life	Treating phsyician
8.	Upper airway obstruction	Episodes of stridor; atypical dyspnea	Flow-volume loops
9.	Interstitial lung disease	Dyspnea at rest; erythrocytosis, persistent tachycardia or tachypnea	DLCO (Diffusion Lung Carbon Monoxide); chest x-ray
10.	Treatment for gastroesophageal reflux	Treatment with anti H_2 blocker (e.g., cimetidine, ranitidine) and/or regular use of metoclopramide	Treating physician
11.	Tuberculosis	Patient history	Treating physician

Patients with one or more indices of clinical suspicion must be excluded unless the test indicated for definitive diagnosis is performed and the results do not support the diagnosis.

CAMP Protocol

Table 4. Screening process schematic

Tel contact	-7 weeks* Visit S1 (2 hrs)	-6 weeks** Visit S2 (3 hrs)†‡▾	-2 weeks Visit S3 (3 hrs)	-1 week Visit S4 (2.5 hrs)	0 weeks Visit RZ (3 hrs)
Exclusions Age Asthma hxCurrent trt Hosp adm Intensive care Pulmonary hx	Exclusions Hosp hx Medications Other diseases Trt hx	Exclusions Spirometry	Exclusions Meth challenge Interview answers Peak flow recording Diary card review Symptoms off meds	Exclusions Judgement by clinic staff that patient should not be enrolled	Exclusions Judgement by clinic staff that patient should not be enrolled
Data None	Data Locator info Initial eligibility interview Asthma and allergy hx Registration form	Data Adherence interview Home environment questionnaire Baseline medical hx Signed consent Spiro (before & after bronchodilator)** Peak flow (before & after bronchodilator)	Data Bone density Confidence interview Hematology Meth challenge Family interviews Phys exam Skin test Tanner staging	Data Psychological (child and caretaker)	Data Spiro (before & after bronchodilator) Peak flow (before & after bronchodilator)
Education Length of study # of visits Purpose & benefits of study	Education Practice spiro Practice peak flow Practice diary card Study design slide show Handouts: What is CAMP What is asthma Asthma signs PF monitoring	Education Education notebook Environmental counselling Review: What is asthma Asthma signs PF monitoring Peak flow Handouts: Rescue inhaler Action plan	Education Environmental counselling Review: Diary card Rescue inhaler Action plan	Education Review diary card	Education Handouts: Pretest for exercise Study inhaler How to take CAMP medicine Things that make asthma worse Environ control handouts Review: Action plan Diary card
Action Mail study brochure	Action None‡	Action Sign consent material‡ Stop all meds except *prn*‡	Action Consent review Stop all meds except *prn*	Action Stop all meds except *prn*	Action Reaffirm consent Randomize Distribute meds
	Take home Appointment Consent material Education handouts Home environment questionnaire Diary card Peak flow meter	Take home Appointment Asthma handbook and action plan Rescue inhaler Med use instructions Practice inhalers Diary card Education notebook	Take home Appointment Diary card Action plan Rescue inhaler	Take home Appointment Diary card Action plan Rescue inhaler	Take home Appointment Diary card Action plan Medications Mattress and pillow covers

Note: *Weeks indicate time to randomization; hours indicate length of visit; maximum of 4 months for screening.
†Candidate needs to withhold theophylline and long-acting O_2-agonist for 24 hrs and short-acting O_2-agonist for 4 hrs
**Do not do spirometry until tapering is complete
‡If tapering meds, a visit between S1 and S2 spirometry is needed to sign consent, give rescue inhaler and action plan, and initiate tapering, so that tapering is finished when S2 spirometry is done
▾Telephone contact between Visits S2 and S3

CAMP Protocol

Table 5. Definition of Diary Card asthma symptom codes

An asthma episode is a single period of 1 or more asthma "stop signs", such as wheezing, coughing, chest tightness, or shortness of breath.

0 = No asthma episodes

1 = 1-3 asthma episodes, each lasting 2 hours or less - all mild

2 = 4 or more mild asthma episodes, or 1 or more asthma episodes that temporarily interfered with activity, play, school, or sleep

3 = 1 or more asthma episodes lasting longer than 2 hours, or resulting in shortening normal activity, or seeing a doctor for acute care, or going to a hospital for acute care

CAMP Protocol

Table 6. Data collection schedule

	Baseline	2 month	Yearly 4 month	Yearly 8 month	Yearly 12 month
Baseline specific					
Initial phone contact	X				
Registration	S1				
Location information	S1				
Eligibility	S1,S2,S3				
Adherence and understanding assessments	S2,S3				
Randomization	RZ				
Followup specific					
Followup questionnaire		X	X	X	X
Compliance assessment		X	X	X	X
Pulmonary function					
Spirometry	S2,RZ	X	X		X
Methacholine challenge	S3			X	
Asthma morbidity					
Asthma and allergy history	S1	X	X	X	X
Diary card	S2 and every day thereafter				
Nocturnal awakenings					
Limitation of activity					
Absenteeism from school					
Use of *prn* albuterol					
Use of study medication					
Use of prednisone					
Morning and nightly peak flow					
Physician contacts					
Diary card review	S3,S4,RZ	X	X	X	X
Asthma symptoms while on *prn* albuterol	S3	X	X	X	X
Medication side effects	S2,S3	X	X	X	X
Utilization of health care resources	S2,S3	X	X	X	X

CAMP Protocol

Table 6. Data collection schedule

	Baseline	2 month	Yearly 4 month	Yearly 8 month	Yearly 12 month
Physical growth and development					
Medical history	S2				X
Chest ascultation	S3				X
Physical exam	S3				X
Height	S3,RZ	X	X	X	X
Weight	S3,RZ	X	X	X	X
Truncal growth	S3				X
Tanner staging	S3				X
Bone density	S3				X
Psychological growth and development					
Neurocognitive functioning	S4				Yr. 3,5
Individual and family functioning	S4				X
Allergy testing and hematology					
Skin test	S3				Yr. 5
Hematology	S3				Yr. 5
Serum IgE	S3				Yr. 5
Serum banking	S3				Yr. 5
Environment					
Home environment questionnaire	S1				X
House dust specimen collection	X†				Yr. 3‡

†No more than 6 months after randomization
‡Also collected whenever the child moves to a new home

Appendix: Patient consent/assent statements

SAMPLE CONSENT FORM

The Johns Hopkins University
School of Hygiene and Public Health
Committee on Human Research

Title of Research Project: Childhood Asthma Management Program (CAMP)

Purpose of Study

To determine which of three drug treatments is best for long term use in children with moderate asthma. If your child has moderate asthma and is 5 to 12 years of age, he or she may qualify for this study.

Study Procedures

1. Initiation

To qualify for the study, your child must pass certain screening tests. The tests will include (1) two standard types of breathing tests: spirometry and methacholine inhalation; (2) allergy testing by skin tests; (3) physical examination including height, weight, and sexual maturation; (4) a blood test (1 tablespoon, 15 cc); (5) bone density measurements to determine bone thickness; and (6) tests of intelligence, attention, memory, and academic achievement and interviews about behaviors and feelings. The interview about behaviors and feelings will include such questions as "do you feel lonely", "do you get teased a lot", "do you think about hurting or killing yourself".

You will also fill out questionnaires about (1) your child's behavior (eg, does your child argue a lot, deliberately harm him/herself, hear voices, set fires, or talk about killing him/herself); (2) family characteristics and relationships (eg, True/False: family members sometimes get so angry that they throw things; there is a feeling of togetherness in our family); and (3) how your child's asthma affects your family life (eg, Agree/Disagree: the illness is causing financial problems for the family; I think about not having more children because of the illness).

These screening tests will be performed over several visits. During this screening period, we will ask your child to stop taking all of his/her regular asthma medications. We will prescribe albuterol for your child to use to control asthma symptoms. Albuterol is a short-acting inhaled bronchodilator and is commonly prescribed for mild to moderate asthma in children. We will monitor your child's asthma symptoms during this period, and additional medication will be prescribed if needed. This screening period will help us decide if your child should enroll in CAMP.

2. Treatment

If qualified for the study, your child will be assigned to be in one of three groups for asthma treatment. The assignment is made using a chance procedure similar to rolling dice.

Children assigned to Group 1 will receive two study medicines: budesonide (also known as Pulmicort®), and albuterol (also known as Ventolin® or Proventil®). The budesonide is given by inhalation twice a day. The albuterol is a back-up medicine to be used only as needed to control your child's asthma symptoms. Budesonide is an inhaled steroid.

Children assigned to Group 2 will receive two study medicines: nedocromil (also known as Tilade®), and albuterol. The nedocromil is given by inhalation twice a day. The albuterol is a back-up medicine to be used only as needed to control your child's asthma symptoms. Nedocromil is a nonsteroidal anti-inflammatory agent (like cromolyn).

Children assigned to Group 3 will receive a dummy inhaler that does not contain any medicine, and albuterol. The dummy inhaler will be used twice a day. The albuterol is a back-up medicine to be used only as needed to control your child's asthma symptoms.

Budesonide is an experimental medicine for moderate asthma not yet licensed in the US. Nedocromil has been approved by the FDA for treating mild to moderate asthma in patients age 12 and older. Many children of all ages have received these medicines in Europe and Canada. Long-term studies are needed, however, to see whether either of these medicines or albuterol is better for treating asthma. The study will also find out about side effects of these medicines.

Neither you nor the study doctors and nurses will know whether your child is receiving an active medication or the dummy inhaler. This is necessary to find out about the effect of the medicines without bias in favor or against any of them.

3. Education

During the first few visits, you and your child will learn how to use the study medicines, how to use a peak flow meter, and how to complete the study diary cards. You and your child will also learn about asthma. You will learn what triggers it, how to tell when it is getting worse, what to do should an attack occur, and how to clean and organize your home environment. You will keep a daily diary of asthma medicines taken, asthma symptoms, and peak flow meter readings.

4. Followup in the First Year

- After your child begins a medication, there will be followup visits to the clinic at 2 months and every 4 months from baseline.

- About 3 to 6 months after joining the study, a technician will visit your home to collect a house dust specimen.

- At 2, 4, and 8 months, we will review your child's progress, provide new medicines as needed, and repeat height and weight measurements and breathing tests. The

methacholine inhalation test will be done at the eight month visit. These visits could take up to 90 minutes.

- At the end of the first year, we will do a complete exam. It will include height and weight measurements, sexual maturation, breathing tests, and bone density measurements. We will repeat the interviews with your child that measure some of your child's behavior and feelings. We will repeat the interviews with you about your child's behavior, family relationships, and how your child's asthma affects your family life. These evaluations could take up to two hours.

- If your child has been doing well for 8 months in a row, we may decrease the daily asthma medication. This will depend upon your child's albuterol usage, asthma symptoms, and spirometry results. The reduction can occur anytime during the study after the first 8 months.

- At any time during the study, if your child's asthma is inadequately controlled, your child's asthma will be treated by your regular doctor according to his/her discretion. We will still ask your child to come in for his/her regularly scheduled visits. Treatment will be changed if asthma symptoms change.

5. Visits in the Following Years

The study will continue for 5 years or possibly longer. Until the end of the study, visits will be similar to the first year except that there will be only 3 visits each year. Your child will repeat the intelligence, attention, memory and academic achievement tests during the third and fifth years. After 3 years and after moving to a new home, we will collect another house dust specimen from your home. After 5 years, we will repeat the allergy skin tests, and collect and analyze a blood sample.

Risks/Discomforts

- We will monitor all children in the study for adverse effects on behavior, changes in growth patterns and bone density (thickness), and other side-effects which occasionally occur in patients receiving one or more of these medicines.

- The study requirements include taking blood samples of about one tablespoon (15 cc) for testing at the beginning of the study and after 5 years. This is upsetting for some children. Other than the pain of the needle stick and occasional bruising, it is not harmful.

- The amount of calcium (density) in your child's spine will be measured once a year using a bone densitometer. The child will lay still on a table for 5 to 10 minutes for the measurement. There is no discomfort. Each year the measurement will expose the child to about ¼ the amount of radiation of a standard chest x-ray.

- Budesonide may cause cough, throat irritation, and hoarseness. It is a steroid and may affect growth. It may also have a bad taste, and may cause headache, nausea, and

dryness of the throat. Nedocromil may have an unpleasant taste. It may also cause headache and nausea. Albuterol may cause tremor, palpitations, and irritability.

- Allergy skin tests involve placing a small drop of solution on the skin and then pricking the skin through the drop. Some children may have an additional set of skin tests where a small drop of solution is placed underneath the skin with a needle. These skin tests may lead to a local hive or itching. Allergy reactions such as wheezing or generalized hives very rarely may result from skin testing.

- The sexual maturation exam (Tanner staging) will include the examination of pubic hair growth, development of genitalia in boys and girls, and breast development in girls. This examination may be embarrassing for your child; we will try to minimize any embarrassment.

- The safety of these drugs during pregnancy is unknown. Girls who have reached puberty will receive counseling about pregnancy and may be asked to take a pregnancy test. Girls who become pregnant will stop the study medication and will be treated according to the best medical judgment of their doctor. The girl will continue to return to the CAMP clinic for examinations and interviews.

- Methacholine may cause your child to experience mild asthma symptoms. The methacholine test consists of breathing in increasing doses of methacholine. Each time the dose is increased, a breathing test is performed. If asthma symptoms develop, the test ends. The asthma is reversed and symptoms are relieved by inhalation of albuterol (a bronchodilator) or, if needed, by other asthma treatments.

- It is possible that lung function tests may cause cough, wheeze, or shortness of breath. Inhalation of albuterol will be used to relieve the symptoms.

Benefits

Benefits for participation in this study include:

- Complete respiratory and allergy evaluations
- Assessment of home environment with instructions for reducing allergic symptoms along with provision of mattress and pillow covers for dust mite allergy
- Complete asthma education self-management program
- Medicines for asthma provided free of charge
- Twice daily administration of asthma medication
- Study doctors and nurses will be available to manage asthma if it flares
- Children and parents will be invited to outings and group activities especially designed for study participants and their families
- Children will be given small personal rewards (such as: sugar-free gum, small toys, tee shirts, baseball tickets, coupons for food) from time to time.

In addition, there will be reimbursement for travel, cost of a meal, and parking.

Alternatives to Participation

If you do not wish to have your child participate in this study, you may continue to receive asthma care from your regular doctor. We will also refer you to other sources for asthma care, allergy evaluation, asthma education programs, and developmental and educational testing. If you do choose to participate, you and your child may withdraw from the study at any time without penalty.

Rights and Responsibilities

- Your child's entry into the study is voluntary.
- Your child may withdraw from the study at any time and still get care at this institution. However, we would like to know the status of all patients at the end of the study. We may telephone you periodically, even after you withdraw from the study, to ask you about your child's asthma. Even if you do not respond to phone calls, you may still receive the same quality of medical care available at this institution.
- Clinic staff are available to answer any questions or discuss concerns you or your child may have now or in the future.
- The success of this trial depends on regular and complete data collection. If you know now that your child will be unable to come to the clinic for regularly scheduled visits for 5 years, please do not enroll.
- You are responsible for informing clinic staff of changes in your child's address and phone number.
- We ask that you discuss with us any plans for your child's participation in another drug study before you enroll in that study.

Confidentiality

The investigators working on this study know that confidentiality is an important concern to many people. Every effort will be made to keep your records confidential. Our procedures are:

- We will ask you to provide your child's home address and phone number. This information is kept in a locking file cabinet in a secure place, and separate from other study data. Only direct-care clinic staff are allowed to see or use that information.
- Study data are identified by study ID codes only. These data are kept in a secure place. Only people working on the study (or your child's doctor if you request it) will have access to study data.
- The identity of all study participants is confidential. When the results of this study are published, no data will be listed by name or ID number.

- Data important to your child's medical care may be placed in your child's medical record at this clinic. Clinical data with name will be released only to you. Clinical data with ID number will be released to the study coordinating center. Clinical data without name or ID number may be released to the US Food and Drug Administration (FDA) and the pharmaceutical sponsors of the study without your child's or your consent. Release of information about your child to any other person(s) or organization(s) will require your written consent.

- As a way to establish and maintain a trusting relationship with your child, it is necessary that we keep confidential any discussions that we have with him/her about certain sensitive subjects (eg, alcohol or drug use, sexual activities) unless your child permits otherwise, or unless there is a strong compelling medical reason for doing differently.

Your child's participation in this research project is completely voluntary. You have the right to withdraw your child from the research study at any time. Even if you do not want your child to join the study, or if you withdraw your child from the study, your child will still receive the same quality of medical care available to your child at _____. Your decision also will not jeopardize your employment at _____. You and your child should ask the principal investigator listed below any questions you may have about this research study. You may ask him/her questions in the future if you do not understand something that is being done. The investigators (or doctors) will share with you any new findings that may develop while your child is participating in this study.

If you want to talk to anyone about this research study because you or your child think you have not been treated fairly or think your child has been hurt by joining the study, or you have any other questions about the study, you should call the principal investigator, _____ at _____ or call the Office for Research Subjects at [telephone #]. Either the principal investigator or the people in the IRB office will answer your questions and/or help you find medical care if you feel your child has suffered an injury. The [name of institution], and the Federal Government do not have any program to provide compensation to you if your child experiences injury or other bad effects which are not the fault of the investigators.

The information obtained from this study will be included in the Privacy Act System of Records 09-25-0126, Clinical Research: National Heart, Lung, and Blood Institute Epidemiological and Biometric Studies, HHS/NIH/NHLBI, Federal Register, Vol 56 FR pp. 1295-1296. January 11, 1991.

This project has been explained to my child in my presence, in language that is understandable. My child has been encouraged to ask questions, both now and in the future, about the research study. I have had the opportunity to have my questions answered. If I have other questions later, I understand that I can contact a study center staff member [name and telephone #].

If you agree to your child's participation in this study please sign your name below.

_____

CAMP Protocol

Appendix: Patient Consent and Assent Statements

Subject's signature
(including children, when applicable)

_____
Signature of Parent or Guardian (when applicable)

_____
Witness to Consent Procedures*

_____
Signature of Investigator

_____
Date

*Optional unless patient is illiterate, or unable to sign

Note: Signed copies of this consent form must be a) retained on file by the Principal Investigator, b) given to the participant, and c) put in the patient's medical record (when applicable).

Childhood Asthma Management Program (CAMP)

*Child's Assent to Participate in the Study**

The CAMP study is trying to find out the best way to treat asthma in children as they grow up. Three types of treatment will be tested.

I agree to be in the CAMP Study. For the next 5-6½ years I will be asked to take my study medicines two times a day, and come to the clinic in two months and every 4 months for check-ups. I will be asked to use my peak flow meter and fill in my diary card every day.

At most check-ups, I will have my height and weight taken and will do a breathing test. In the next few weeks and once a year, a doctor will look at me and check to see how I have grown and will take an x-ray. In six weeks and at my 3 and 5 year check-ups, I will be asked to take some tests like in school. In six weeks and once a year, I will be asked some questions about my life and my feelings. In the next few weeks and at my 5 year check-up, I will have skin and blood tests done. For the blood test, a nurse will take a small amount of blood from my arm.

It is OK to have the nurse, doctor, or other persons ask me questions about my asthma and my life. I also know that I will be asked to come to asthma classes with my parents.

I may decide not to be in the CAMP study at any time. If I choose not to be in the study, I can still receive my usual medical care. No one will be angry with me if I decide not to be in the study.

At any time, I may ask questions about the study. If I have questions, I may ask _____.

_____ _____

(Date) (Signature of Child)

FOR CAMP STAFF ONLY:

I have reviewed the contents of the Informed Consent Statement with _____ at his or her level of understanding. I feel he or she understands the study requirements.

_____ _____

(Date) (Signature of CAMP Staff Member)

**Readers need a 5th grade level of education*

CAMP Protocol

Childhood Asthma Management Program (CAMP)

*Child's Assent to Participate in the Study**

The CAMP study will try to find out the best way to treat asthma. Three types of treatments will be used. The study will last 5 to 6½ years.

I agree to be in the CAMP study. I agree to do some things. I will be asked to take my study medicines. I will be asked to come back in two months and every four months. I will be asked to use my peak flow meter. I will be asked to fill in my diary card.

At most visits I will do three things. I will have my height and weight checked. Then I will do a breathing test. At some visits two other things will happen. A doctor will look at me and check how I have grown. I will have an x-ray. I will do this a few weeks from now. Then I will have these visits every year.

I will be asked to take some tests in six weeks. I will take some of these tests every year. I will take some of these tests again in 3 years and 5 years.

I will have a small amount of blood taken at the start of the study. I will have it taken again when I finish the study.

The CAMP staff may ask me questions. I will learn about asthma. I will get books and games. These will help me learn.

I may say at any time that I do not want to be in the CAMP study. If I choose not to be in the study, I can still receive my usual medical care. No one will be angry with me if I do not want to be in the study.

I may ask questions any time. If I have questions, I can ask _____. I may say at any time that I do not want to be in the study.

_____ _____

(Date) (Signature of Child)

FOR CAMP STAFF ONLY:

I have reviewed the contents of the Informed Consent Statement with _____ at his or her level of understanding. I feel he or she understands the study requirements.

_____ _____

(Date) (Signature of CAMP Staff Member)

CAMP Protocol

Appendix: Patient Consent and Assent Statements

**Readers need a lst grade level of education*

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