CAMP Continuation Study (CAMPCS) Protocol

Abstract

This protocol is for the CAMP Continuation Study (CAMPCS), a 4.5 year observational followup study of the children enrolled in the Childhood Asthma Management Program (CAMP).

CAMP is a multicenter randomized clinical trial designed to determine the effects of three inhaled treatments for mild to moderate childhood asthma (inhaled albuterol alone, albuterol with inhaled budesonide, and albuterol with inhaled nedocromil) on pulmonary function observed over a 3.5 to 5.5 year period. Data collected on the 1,041 children who enrolled in CAMP between the ages of 5 and 12 will provide valuable and first time ever insights into the impact of long term therapy on the natural history of asthma and the safety of long term use of inhaled steroids early in childhood (i.e., between ages 5 and 12). The CAMP cohort has been studied more thoroughly than any other group of children with asthma, with careful collection of data describing lung function growth, clinical course, allergic and psychological characteristics, and allergen and irritant exposures, allowing evaluation of the interrelationships of these factors with asthma outcomes. However, since 95% of the boys and 74% of the girls enrolled in CAMP did not achieve maximal linear growth nor maximal lung function by the close of CAMP, CAMP will not provide a complete assessment of the impact of early treatment with inhaled steroids on growing children.

During the transition phase from CAMP to CAMPCS, study medication was withdrawn, and children were monitored for lung function, bronchial hyperresponsiveness, growth, and asthma control. At the end of the 4 month medication washout, care for asthma was transferred to the physician who cared for the child prior to enrollment in CAMP. CAMP provided the family and the treating physician with a summary of the child's clinical course and treatment during CAMP, as well as recommendations for continued asthma care.

In CAMPCS, we will extend followup of the CAMP patients under the observational model used in the transition phase of CAMP for an additional 4.5 years. At the end of this extended followup, 90% of the girls and 60% of the boys should have achieved maximal height and level of pulmonary function. The data collected in CAMPCS will thus allow us to complete the assessment of the effects of long term treatment early in childhood on asthma outcomes and physical growth and development.

Data collection procedures for transition and for CAMPCS will be similar to those used in CAMP. Counting the two visits done in the transition from CAMP to CAMPCS and including the first CAMPCS visit, patients will return for visits a total of 3 times in the year following the withdrawal of medication in order to define the time course of effects due to medication withdrawal.

CAMP patients were recruited to CAMPCS at the last CAMP visit (ie, last transition phase visit) and will be seen at 6 month intervals, with telephone contacts between the 6-months visits. Height and weight will be measured at each visit. Spirometry will be performed pre- and post- bronchodilator at the annual visit; at the semi-annual visit, airway reactivity to methacholine will be assessed. Physical maturation (Tanner staging) will be assessed annually. Bone density will be measured 84 and 108 months after CAMP randomization. Data collection for mediating factors will include information on asthma symptoms and tobacco smoke exposure since the last visit or telephone contact (this information will be collected at each contact time). Data on asthma medications used in the past seven days will also be collected at each contact. Limited information on the psychological characteristics of the family and child and the child's quality of life will be collected annually. Information on environmental exposures (self report by interview) will be collected annually. Allergy skin testing will be performed 96 months after CAMP randomization, and serum IgE and blood eosinophil levels will be measured 84 and 108 months after CAMP randomization. Bone age and lens photography will be performed at the last CAMPCS visit.

1. Objective and specific aims

1.1 Objective

Followup of the Childhood Asthma Management Program (CAMP) population will continue for an additional 4.5 years in an observational followup study, CAMP Continuation Study (CAMPCS).

The objective of the CAMPCS followup to the CAMP randomized trial is to determine the effects of 3.5 to 5.5 years of anti-inflammatory therapy administered early in childhood (the double masked protocol during CAMP) on the time course of the progression of asthma through puberty as indicated by lung development, physical growth, and bone density; by the pattern of bronchial reactivity; by the occurrence, relapse, and remission of asthma symptoms; by the use of asthma medications; by the need for health care services; and by self-reported quality of life.

By following the CAMP population for an additional 4.5 years in CAMPCS, 90% of the girls and 60% of the boys will have passed through puberty and reached an age at which maximal linear growth and maximal lung function have been achieved, and CAMPCS will provide a more complete picture of the effects of long term, early use of anti-inflammatory medications.

1.2 Specific aims

Primary Aim:
Controlling for age, gender, and ethnicity, determine whether 3.5 to 5.5 years of anti-inflammatory therapy started early in childhood (ages 5-12 years) affects:

1. The rate of increase or maximal level of lung function (FEV_1, FVC, FEV_1/FVC; additionally controlling for height).
2. The rate of increase or maximal level of attained height.
3. The rate of increase or maximal level of attained bone density.
4. Airway responsiveness to methacholine later in childhood (additionally controlling for height).
5. Occurrence, relapse, or remission of respiratory symptoms.
6. The use of asthma medications later in childhood.
7. The use of health care services (emergency department visits, hospitalizations, and physician visits) later in childhood.
8. Self-reported quality of life later in childhood.
9. Development of lens opacities.

Secondary Aim 1:
Information on important modifiers of the long-term outcome of childhood asthma will be collected over the course of the CAMPCS followup and considered as mediating variables in determination of the effects of early anti-inflammatory therapy specified in the primary aim above. Modifier variables to be measured longitudinally and examined for potential mediating effects are:

1. Additional treatments for asthma received during the 4.5 years of followup during CAMPCS
2. Exposure to tobacco smoke (passive and active)
3. Degree of atopic disease (serum IgE level, blood eosinophil count, skin test positivity)
4. Manifestations of atopic disease (presence of eczema and upper airway disease)
5. Duration of asthma
6. Psychological problems in the child or family (as determined from a brief battery consisting of the Child Behavior Checklist, the Youth Self Report, Young Adult Self Report and the Brief Symptom Inventory)

Secondary Aim 2:

Use CAMPCS data to refine the determination of asthma phenotypes for the genetic ancillary study component of CAMP through the use of additional followup data on responsiveness to O-agonist administration, reactivity to methacholine, response to treatment with anti-inflammatory medications, maximal level of lung function achieved at the end of childhood, and persistence of respiratory symptoms. The DNA analyses will have been completed as part of the CAMP ancillary study. Refinement of the phenotypes can be accomplished from the planned CAMPCS data collection.

2. Background

2.1 Introduction

In 2.2, we provide the rationale for continued followup of the CAMP population, including a general discussion about the available data on the questions CAMP/CAMPCS will address. In the remaining subsections, we review the currently available literature relating to these questions in more detail: studies on asthma outcome (2.3); symptom remission and relapse (2.4); how lung growth modifies symptom occurrence (2.5); the importance of maximal lung growth for adult obstructive lung disease (2.6); how anti-inflammatory treatment could influence positively and negatively maximal lung growth, height, and bone density (2.7); factors other than symptoms and lung function that could influence asthma natural history (2.8); psychological factors and their influence on asthma (2.9); and polymorphisms of the O2-AR (2.10).

2.2 Rationale for continued study of the CAMP cohort

The research aims of CAMP include study of the potential role of treatment early in the course of asthma (mild disease treated in young children) in altering the natural history of the disease. CAMP will evaluate the effects of 3.5-5.5 years of anti-inflammatory treatment on lung growth and development. The CAMP initiative was foresightful in raising questions about the potential long term benefits and risks in anti-inflammatory therapy. Recently published studies underscore the controversy over the clinical question "when should anti-inflammatory therapy be initiated?" Emerging data suggest that the model of asthma as a disease of reversible airway obstruction is changing and that asthma has a component of airway injury and repair which leads to irreversible obstruction. Preliminary, uncontrolled community studies show that inhaled corticosteroid treatment early in the course of mild disease may prevent airway injury and repair and thus alter the natural history of asthma. It has been hypothesized that early treatment may result in greater lung function at the time young adults reach their "lung plateau", which may in turn reduce the risk of chronic obstructive pulmonary disease.

Questions also remain about the long term safety of inhaled corticosteroids. When the CAMP protocol was designed, there was evidence that untreated asthma itself impaired growth. There was some indication that high dose steroids had systemic effects, but CAMP hypothesized that low-medium dose corticosteroids would not. However, 3 recently published studies reveal that children receiving modest doses of inhaled steroids experience a decrement in linear growth as compared to children with asthma not receiving steroids. Because the studies were only one year in length, it is unclear whether this decrement represents a delay in growth or growth suppression. Furthermore, studies in adults suggest diminished bone density and increased risk of cataracts among those who use inhaled corticosteroids for prolonged periods. It is not yet known if children have similar risks. CAMP measured height 3 times per year, and bone density annually; CAMP measured bone age and screened children for cataracts during its final phase.

Thus CAMP will provide the first long term, longitudinal data on these issues. However, the central research question raised in CAMP -- the impact of early treatment on lung growth and development -- is most completely answered by evaluating the impact on maximal lung growth and on asthma outcomes as a young adult, which requires following the children through puberty. When CAMP concluded in 1999, only 5% of the boys were age 18 or older and only 26% of the girls enrolled in CAMP were age 16 or older and thus completed puberty and attained their adult linear height and maximal lung development. By the end of the 4.5 year continuation of followup in 2004, 60% of the boys and 90% of the girls will have reached ages 18 or older and 16 or older, respectively. This duration of followup will thus allow a more complete assessment of the impact of early treatment with inhaled steroids on growing children. The roles of early, long term treatment with anti-inflammatory medications, exposure to allergens and irritants, and variability in the course of the disease in the attainment of maximal lung function, and in the

remission or relapse of symptoms have not been studied previously.

The CAMP cohort has been studied more extensively than any other cohort of children with asthma. There has been careful collection of data describing the clinical course and its treatment including data on use of albuterol for symptoms and use of prednisone for well defined exacerbations, and detailed descriptions of atopic characteristics of the children, allergens and irritants in the environment, and frequent and systematically collected spirometry and measures of methacholine reactivity. These data will begin to answer important questions. More complete answers are possible when data collection is extended to the point when a majority of CAMP children will have completed puberty.

Given the uncertainties regarding the effect of long term treatment on outcome of the disease and on growth and bone density, practicing physicians need information that can come from a longer term follow-up of the CAMP cohort. The NAEPP Guidelines have provided a basis of treatment, but also acknowledge the current questions and controversies regarding treatment in children due to the lack of long term, prospective studies. The data obtained in CAMPCS will provide answers for these questions.

2.3 Studies of the outcome of childhood asthma

Long term studies of outcome of childhood asthma have been published from as early as 1945 (1-28; details of these studies are summarized in Table 5.1). While these studies have widely different methodologies, it is possible to make some estimates of percentages of children who improve and those who remain with symptoms as they grow into adulthood. By early adulthood, 37% (range, 14-65%) of school-age children with doctor-diagnosed asthma were in remission (generally defined as no asthma symptoms in 3 years) and another 32% were improved (generally defined as symptoms within 1-3 years but not within 12 months, or significantly less severe symptoms from the last survey). Significant disease persisted in approximately 36% of patients. Most studies employed questionnaires sent to patients, with estimates of asthma obtained by report of symptoms in the past 12 months. Some of the studies involved examination of patients at the time of follow-up, however, even these studies used self report of symptoms in the past 12 months or 3 years to obtain information about the status of asthma.

Most of these studies have been conducted on hospitalized or hospital clinic patients, leading to possible bias in selection of more severely ill patients. There is only one long term follow-up study of a cohort of children with recurrent wheeze recruited in a community setting, the one established in Australia by Williams and McNicol in the early 1960s (29). Of interest, outcomes of asthma in the Williams and McNicol cohort at age 21 years were similar to outcome in the studies of hospital and clinic patients (18, 30). Relapse of wheeze/asthma symptoms after a period of wellness has been studied less frequently. In the 10 studies with information on this outcome, 20% of the populations studied had relapsed in early adulthood (4, 7, 9, 16, 18-20, 22, 24, 28). Martin et al documented a 20% relapse rate by age 21 years in the Williams and McNicol cohort (18).

Studies on the Williams and McNicol cohort have been extremely valuable in our understanding of the long term outcome of asthma. Two hundred eighty five children with wheezing at age 7 and 106 children in the same setting with no history of wheeze have been studied at ages 10, 14, 21, 28, and, most recently, 35 years of age. The description of the children included detailed questionnaires about symptoms, allergy skin testing, serum IgE levels (first done at age 21 years), spirometry, measures of airway reactivity (first done at age 21 years), and psychological testing. This set of observations has led to a substantial increase in understanding of childhood asthma and its outcome. However, this study did not have longitudinal contact with the children, and information on outcome was limited to interview data

obtained at times of follow-up. These and other studies have noted that patients in early adulthood cannot remember with any accuracy the presence of asthma reported 7-10 years previously by parent report. Therefore, use of recall only to determine the presence of symptoms in the past 3 years or even 12 months is likely to under report the true occurrence of symptoms. Furthermore, the studies of the Williams and McNicol cohort did not include information of exposures that may have influenced results and there was almost no information on treatment of the children. The only attempt to understand the effect of treatment on the course of asthma was to categorize treatment at age 14 years as appropriate or inappropriate based on level of symptoms at that time. Based on this single analysis, the investigators concluded that treatment had no impact on outcome. Treatments currently available for asthma (inhaled steroids and non-steroidal anti-inflammatory medications more potent than cromolyn) were not available until late in the course of this study; these medications have not yet been assessed for their impact on long term outcome through puberty.

While most follow-up studies have focused on symptoms, there is some information on the effects of asthma on lung function. School age children who have continuous respiratory symptoms are most likely to have lower levels of lung function and a worse prognosis, as measured by lower levels of pulmonary function (19, 30, 31). Martin and coworkers (30) assessed pulmonary function in a subgroup of the Williams and McNicol cohort at 21 years of age. Statistically significant differences were found between subjects when grouped by initial disease severity. For the most severely ill group, the mean FEV_1 was 80% predicted compared to 99% predicted for the most mild group and 100% predicted for the controls. Kelly et al (31) studied this cohort again at age 28 years with similar results for FEV_1. The degree of airway obstruction as assessed by FEV_1/FVC ratio was even more striking, with mean values of 67% in the severe group, 80% in the group with more mild but intermittent symptoms, and 85% (considered to be normal) in those no longer with any asthma for at least 3 years and the controls (31). These findings could have important implications for decline in adult life, as maximal attained level of function may be an important predictor of rate of decline of lung function (32, 33). Weiss et al (34) analyzed the effect of asthma on lung growth in a cohort of 5- to 9-year-old children from a population sample in East Boston over a 13 year-year period. Boys with asthma had larger vital capacity (about 8% larger than boys without asthma) and girls had a lower FEV_1 and FEF_{25-75}%. Lebowitz et al (35) found that children with persistence of physician diagnosed asthma followed from before the age of 14 years had an FEV_1 10% below normal in their early 20s. There was no effect of gender in the Lebowitz study. Available data suggest that doctor-diagnosed asthma in adults is associated with development of irreversible airway obstruction, or chronic airway obstruction (6). Other investigators have noted that patients with more severe asthma have an accelerated decline in lung function over long times of follow-up (33, 36).

2.4 Concern about relapse of asthma symptoms after periods of apparent remission

This concern was initially identified by Ryssing in 1959 in a follow-up of a clinic based cohort originally identified and followed by Flensborg in 1945 (9). Flensborg reported that approximately 40% of children followed up for 15-20 years were completely free of wheezing for a 1-2 year period prior to follow-up (28). In the Ryssing follow-up, some of the original 40% had remained free of overt asthma during the 15 years of additional follow-up, but many others reportedly free of wheezing in the original study had recurrence of wheeze. Martin et al also identified subpopulations of the Williams and McNicol cohort who became asymptomatic in adolescence only to have asthma symptoms return in their early 20s (18). Bronnimann and Burrows evaluated relapse rates over 9 years in the Tucson epidemiologic project (7). Of 99 subjects classified as having had asthma in the past, 38% relapsed (children 10 to 19 years of age upon entering into the study had a relapse rate of 25% in the 9 year follow-up). Factors associated with relapse were history of any wheeze, chronic productive cough, and smoking. Other studies suggest

that persistent airway hyperreactivity and atopy may also be factors associated with relapse, but there is no documentation of the relationships. The roles of variability in the clinical course, exposure to allergen and irritants, and treatment of asthma with anti-inflammatory medications to relapse as an outcome have not been studied. Specifically, no study has considered the importance of adjusting for changes in lung function with age in considering symptoms remission and relapse.

2.5 The relationship of lung growth to asthma symptoms

The occurrence of respiratory symptoms is correlated with level of lung function, although that correlation is not a close one. Lung function increases from early childhood to attain its maximal level in early adult life. FEV_1 peaks for girls at age 15 and stays at a stable level until about age 35 or 40 years when it gradually starts to decline. In males, the peak is reached approximately 5 years later at age 20 with a similar onset for the decline phase. The importance of this growth-plateau-decline curve and the correlation of respiratory symptoms with pulmonary function level means that symptoms are maximal at the extremes of life, i.e., before age 5 and after age 70 and that with growth of lung function there is a tendency for respiratory symptom occurrence to decrease as a function of lung growth. This is extremely important in understanding the natural history of asthma, in that as lung function increases, respiratory symptoms can be expected to decrease. Hence, the tendency for asthmatics to "outgrow their asthma" is really a function of the growth of lung function and not a function of a change in the intermediate phenotypes of allergy and airway responsiveness (Weiss, personal communication). It also means that the relationship between inflammatory processes in the lung and symptoms is potentially confounded by lung function growth. This is a strong argument for longitudinal data on the impact of treatment on this growth-plateau-decline curve.

2.6 Importance of plateau phase of pulmonary function in young adults with asthma

Lung function, expressed as FEV_1, reaches maximal level in late adolescence or early adulthood and remains stable for several years before declining throughout the rest of life. The stable maximal level of FEV_1 is termed the plateau phase. Recent investigations have highlighted the importance of the plateau phase, in that low levels of FEV_1 in early adulthood are associated with development of chronic airway obstruction in later adult life (Weiss, personal communication). Because of the relationship between the plateau phase and subsequent development of chronic airway obstruction, there has been increasing interest in factors that influence pulmonary function in children as they approach and reach adulthood, particularly in high risk populations. Determinants of the plateau phase are multifactorial and complex and include asthma and airway hyperresponsiveness. Indeed, asthma is the most common disease in childhood that decreases the FEV_1 in the early adult years. Precise definition of these determinants calls for prospective investigations of high risk children starting early in childhood or adolescence and continuing through puberty.

2.7 Long term impact of treatment with inhaled steroids

2.7.1 Length of therapy and duration of effects

There have been several trials of inhaled steroids over months in adults and children. In each trial, symptoms and pulmonary function improved during treatment, but the benefits of treatment were maintained for only short periods when inhaled steroids were withdrawn (37-43). In CAMP, there was be a 4 month interval of observation after withdrawal of therapy. Given the longer time of therapy in CAMP (3.5-5.5 years), it may be that 4 months will not be long enough to see a waning of therapy. Following the cohort in CAMPCS allows a greater time of observation to assess the long term impact of long term therapy than has been done in other studies.

2.7.2 Height as an outcome of childhood asthma and its treatment

The title of a recent editorial in the Am J Respir Crit Care Med, "Choosing a long term controller medication in childhood asthma. The proverbial two-edged sword" (44), indicates the dilemma facing clinicians in regard to height as an outcome. For decades, reduced growth was known to occur from asthma that was poorly controlled. Treatments available in the 1960s did not affect height, with the exception of oral steroids, which had a clear negative impact. Inhaled steroids were designed to maximize effects locally in the lungs while minimizing effects on height. Most articles published from the early 1980s did not find any effect of inhaled steroids on growth (45-50). Allen reviewed 21 studies representing 810 patients with asthma with meta-analysis (51). There was no statistical evidence for an association between beclomethasone dipropionate therapy and growth impairment, even with higher doses and longer therapy durations, or among patients with more severe disease. Wolthers reviewed the literature on effects of inhaled steroids and concluded that an effect of inhaled steroids identified by some investigators during short term follow-up was a physiologic deceleration only, with no effect on long term growth (52). A study of children treated with budesonide for 3-7 years supported the conclusion of other studies that low dose inhaled steroids (up to 400 μg per day) had no effect on growth (53).

In contrast, Hollman reported a case in which low dose inhaled steroids produced overt glucocorticoid excess (54). Four recent double masked placebo controlled trials with inhaled beclomethasone have demonstrated significant decreased linear growth over periods ranging from 6 to 12 months (55-58), generating further concern about inhaled steroid therapy. In one study, growth did not catch up during a washout period of 5 months (57), but did in longer term followup. Yuninger et al found that adults with asthma had normal attained height regardless of the severity of the asthma or its earlier treatment and concluded that effects of asthma and its treatment on height were most likely to be delays rather than limitations.

However, there has been no long term prospective follow-up study of the effects of asthma symptoms and treatment carefully documented on attained height. CAMPCS will help to complete this gap in information.

2.7.3 Bone density as an outcome of childhood asthma and its treatment

Adinoff and Hollister first documented the effects of steroids used for asthma treatment on bone density, and concluded that even every other day steroids had a significant adverse impact (59). As with height as an outcome, clinicians first assumed that inhaled steroids would not have an adverse impact on

bone density. Most studies have used short term biochemical markers of bone turnover (60), which provide no direct evidence of presence or absence of osteoporosis. Toogood et al first demonstrated that intermediate and larger doses of inhaled steroids increased bone turnover (61). Packe et al (62), Hanania et al (63), and Ip et al (64) demonstrated that higher doses of beclomethasone decreased bone density in adults. At present, our knowledge about bone mineral density in children receiving continuous long term treatment with inhaled steroids is limited. Kinsberg et al did not find a difference in bone density between normal and asthmatic children (65). Recently Agertoft and Pedersen reported a case control study in 157 asthmatic children treated with inhaled budesonide (mean daily dose of 504 µg) and 111 age-matched children with asthma but no treatment with steroids, with follow-up for 3-6 years (66). Inhaled beclomethasone had no effect on total body bone mineral density, total body bone mineral capacity, and total bone calcium (67). There is no study of asthma and its treatment on maximal levels of bone density achieved in late adolescence and young adulthood.

2.8 Factors related to persistence of asthma

A review of the literature suggests that a number of factors may influence outcome of asthma: atopy (presence of positive skin tests, eczema early in life and its persistence, allergic rhinitis, level of IgE, presence of peripheral blood eosinophilia, and family history of asthma or an allergic disease; 68-77), smoking both passive and active (35, 77, 78), bronchial hyperreactivity (71, 79, 80), and degree of severity of asthma in childhood (5). No long term study of childhood asthma has included a comprehensive evaluation of these risk factors on outcome (31, 35, 68-70, 76, 78, 79, 81-83) (ie, on risk of persistence of symptoms, abnormalities in pulmonary function in the absence of symptoms, and relapse of symptoms after periods of remission). No study has included an evaluation of the role of environmental exposure on outcome, either in absolute terms or relative to specific sensitivities.

2.9 Role of psychological factors in childhood asthma

The relationship between asthma and psychological function is bi-directional. Asthma, particularly severe asthma, can be a chronic stressor that taxes individual and family psychological resources and induces or exacerbates pre-existing psychological problems. Individual and family dysfunction frequently undermines good care (84). Families with notable disorganization and conflict, in particular, often have great difficulty performing the behaviors necessary to good asthma management, while a sick child in such a family may be more easily drawn to denial of symptoms or to medication nonadherence as expression of their anger (85). The psychological and disease risk factors, therefore, are interactive and must be studied with a methodology that takes this bi-directional relationship into account.

No study published to date has included an analysis of the impact of psychological functioning of the patients and families on long term outcome. CAMP data collection does include psychological assessment and hence will provide new information in this area.

2.10 Role of polymorphisms of the O2-AR

O2-ARs are expressed on a number of cells in the lung, including smooth muscle, epithelial cells, vascular smooth muscle cells, various immune cells including mast cells, eosinophils, neutrophils, and macrophages, and cholinergic nerve terminals. When activated, O2-ARs on bronchial smooth muscle

cause pronounced relaxation resulting in bronchodilation. Although inflammation clearly plays a pivotal role in the pathogenesis of asthma, β-agonist drugs aimed at the reversal of bronchospasm remain a cornerstone in treatment of the disease. Chronic use of β-agonists for asthma is currently a controversial issue because several studies that have found associations between increased β-agonist use and fatal or near fatal outcomes. In addition to playing a role in the response to therapy, such genetic variation may also affect other aspects of asthma, such as the degree of airway hyperresponsiveness and disease severity.

Recently, it was found that the gene encoding the β2-AR is polymorphic within the human population (86). Although an aberrant β2-AR is clearly not the major cause of asthma, many studies of human asthma and various animal models have suggested that defective β2-ARs may accompany asthma (86, 87). The results of some of these studies are confounded by potential effects of concurrent medication use on β2-AR expression or function, and indeed some studies fail to find altered β2-AR in asthma. The bulk of the data, nevertheless, suggests that β2-AR dysfunction may play a role in defining the phenotype in some asthmatics.

Nine polymorphisms have been identified, four of which result in changes in the encoded amino acid. Early studies have suggested a clustering of one β2-AR genotype among severe steroid-dependent asthmatics and among asthmatics requiring immunotherapy, supporting the evolving concept that polymorphisms of the β2-AR are disease modifiers. The two predominant hypotheses under study at the present time are: 1) Arg16 to Gly polymorphism in asthmatics is associated with phenotype traits of more severe disease with increased airway responsiveness, depressed responsiveness to β-agonists, more frequent β-agonist use, greater steroid use, and greater degree of allergic inflammation (as assessed by eosinophil counts and serum IgE levels), and 2) Gln27 to Glu polymorphism in asthmatics is associated with phenotypic traits of less severe disease with less airway responsiveness, enhanced responsiveness to β-agonists, less frequent β-agonist and steroid use, and less allergic inflammation.

Currently the CAMP population and their parents are participating in a CAMP ancillary study of the inheritance of the β2-AR polymorphisms within families of children with asthma. This study is also intended to examine the phenotype-genotype association, but only using the data generated before randomization into CAMP (such as use of β-agonists during the screening period and baseline airway responsiveness). A goal of CAMPCS is to examine longitudinal severity and treatment related phenotypes for their β2-AR genotype relationships.

3. Preliminary data

3.1 Introduction

In 3.2 we detail the experience of the CAMP research team. In 3.3 we describe CAMP publications in general. Key CAMP performance data are presented in 3.4.

3.2 Experience of CAMP research team

The CAMP research team is an internationally-recognized multidisciplinary group of experts on childhood asthma. Reuben Cherniack, the Study Chair, is senior clinical investigator in asthma/COPD. Expertise is available in the areas of allergy (Adkinson, Zeiger, Shapiro, Strunk, Nelson), pediatric pulmonology (McWilliams, Reisman, Wise), asthma treatment (Szefler, Kelly), asthma risk factors and natural history (Weiss), psychological aspects of asthma (Annett, Bender, DuHamel, Rand), education (Taggart), and biostatistics (Tonascia, Meinert). CAMP nurse coordinators have demonstrated expertise in enrolling and retaining patients; a major strength of the research team is the close bond between the CAMP participants and the nurse coordinators. The CAMP research team has worked together since 1991. Team members were chosen for their expertise and ability to follow patients in a longitudinal, clinical trial. We first demonstrated our ability to work together by writing the CAMP protocol as a group effort. Additional evidence of our ability to work well together can be seen from the productivity related to presentations at national meetings, publications (see 3.2), and the continuation of CAMP through periods of protocol decision making subsequent to the initial creative effort. The group has knowledge and experience in virtually all aspects of pediatric asthma care. Members of the CAMP team have served on the NAEPP Expert Panel on Asthma and in leadership positions in the American Academy of Allergy, Asthma and Immunology, the American Thoracic Society, and the Pulmonary and Allergy Advisory Committee of the FDA and have over 185 person-years of professional experience in the care of asthma patients and asthma research.

3.3 CAMP publications

At the present time, a total of 26 papers have been initiated by CAMP investigators (5 have been published). Several of these are design papers (eg, overall design and methods for the trial and design of the patient education program); most of the remaining papers explore cross sectional relationships in the baseline data.

It is worthwhile highlighting some of the CAMP baseline data which are consistent with the specific aims of this proposal. CAMP enrolled 1,041 children, initially aged 5-12 years, from 8 clinics across the United States and Canada. Sixty percent are male, and 32% are from minority populations. Median age at asthma onset was 2.5 years. Eighty-seven percent of participants had symptoms at least 2 times per week for 6 or more months prior to enrollment. Forty-one percent had at least one parent with a doctor's diagnosis of asthma, and 82% were atopic with at least one positive skin test. Environmental exposures were common, with 30% of children living in homes with a smoking parent and 70% having pets. These data document the representativeness of the CAMP sample and the relatively frequent environmental exposures and prevalence of atopy.

In MS #8.3, we examined the duration of asthma in the CAMP cohort and its relationship to level of lung function and markers of atopy. Duration from diagnosis of asthma ranged from 0.3 to 12.1 years (mean = 5.0 ± 2.7 years). Asthma duration was found to be associated with more severe methacholine responsiveness (ln PC_{20} FEV_1, mg/ml) ($r = -0.11$, $p = 0.004$); lower pre- and post-bronchodilator % of predicted FEV_1 ($r = -0.176$, $r = -0.129$, respectively, $p < 0.001$); higher asthma symptom scores ($r = 0.095$,

p = 0.002) and greater albuterol use for symptoms (r = 0.072, p = 0.022) during the 28-day screening period; more severe markers of atopy, including higher log serum IgE level (iu/ml) (r = 0.105, p = 0.0008), number of positive skin prick tests (r = 0.131, p < 0.0001), and higher peripheral blood eosinophil cells/mm^3 (r = 0.075, p= 0.017); staff evaluation of asthma; and levels of Der p 1 in the house (r = 0.082, p = 0.011). In multivariate models, duration of asthma remained significant for ln PC_{20}, pre-bronchodilator % predicted FEV_1 and mean daily symptom score and albuterol use for symptoms. These data demonstrate that the duration of asthma, even in relatively young children, is associated with lower levels of lung function, greater methacholine airway responsiveness, more asthma symptoms, and higher level of atopic markers. Longitudinal data are needed to confirm these cross-sectional findings and, specifically, to address whether anti-inflammatory therapy can modify these trends which suggest increased atopy and worsening FEV_1 with greater duration of disease.

In MS #8.4, the relationship between increased airways responsiveness and asthma severity is assessed. Decreased methacholine PC_{20} was found to be associated with lower levels of pre-bronchodilator % of predicted FEV_1 (r = 0.29, p = 0.001), more frequent reports of chronic asthma symptoms, persistent wheezing (OR = 1.66, p < 0.001), higher peripheral blood eosinophil counts (r = -0.36, p < 0.0001), and longer duration of asthma (r = -0.11, p < 0.002). These data suggest that, even in children with mild to moderate asthma, there is a consistent relationship between the more severe airway responsiveness and all clinical indicators of disease severity. Again, the suggestion is that these data are consistent with the concept that airways responsiveness may worsen in the absence of aggressive asthma treatment.

The analyses of CAMP baseline data are cross-sectional analyses. Its longitudinal data provides an initial assessment of the effects of inhaled anti-inflammatory therapy on airways responsiveness, level and rate of growth of lung function and occurrence of respiratory symptoms. However, extension of follow-up of CAMP patients will permit more complete assessment of these relationships. Whether long term, early treatment with anti-inflammatory therapy results in maintenance or preservation of maximal growth and lung function with a minimum risk in terms of height growth, decreased bone density, and delayed maturation are questions of major concern to all clinicians taking care of asthma patients with broad implications, not just for childhood and early adulthood asthma, but also for the development of fixed airflow obstruction later in life.

3.4 CAMP performance

As of 30 Jun 99, follow-up of the 1,041 patients enrolled in CAMP is exceptional. After an average of more than 4 years of follow-up, only 5% of patients have missed more than 2 visits in a row and have not been seen since the last missed visit. Of 1,716,798 expected diary days, 1,575,277 (92%) have been returned and, of those returned, 1,364,329 (87%) have data. The overall rate of discrepancies between the keyed record and the paper form, for the latest period of evaluation, is 0.18 per form (0.29 overall since start of CAMP). Incomplete ascertainment of data during visits is not a problem for CAMP. The proportion of specific followup visits missing FEV_1 or peak flow is on the order of 0-2%; FEV_1 PC_{20} is more likely to be missing than any other data item, but the percentage missing is only 5.4% (F8), 5.7% (F20), 7.9% (F32) and 7.4% (F44). Quality grades for spirometry and methacholine challenges are consistently high (3.7 for both measures, on a scale of 0-4). These data confirm that the CAMP data collection effort has minimal loss-to-follow-up and that the quality of the data is high.

3.5 Summary

We have shown that we have a multidisciplinary team of experts that has effectively worked together to create and sustain CAMP with an excellent level of performance (3.2) and productivity (3.3). The manuscripts under preparation (based on the cross-sectional baseline data) emphasize the importance of continuing the longitudinal follow-up of the CAMP cohort through puberty and the impact of asthma duration on airway responsiveness and level of lung function. In 3.4 we described the very high degree of completeness of data obtained in CAMP. We are committed to this research, have the productivity and scientific know-how to conduct it, and have a cohort that is unique and clearly useful for addressing our specific aims. We expect the same level of quality and productivity in CAMPCS as we have achieved in CAMP.

4. Methods of procedure

4.1 Introduction

Our methods are to use the data collection system implemented in CAMP for CAMPCS wherever possible. In this section we present an overview of CAMPCS (4.2), details of the CAMPCS consent and recruitment procedures and how these mesh with CAMP (4.3), and an outline of the patient contact schedule and the contents of each contact (4.4). Details of the measurement approach to independent and mediating variables (treatment, environmental exposures, atopic status, psychological status, and genotype) is provided in 4.5, while 4.6 outlines our measurement approach to our outcome variables. 4.7 considers patient retention. Data management (4.8), quality assurance (4.9), data monitoring (4.10), data analysis (4.11), and study organization (4.12) complete this section.

4.2 General design of CAMPCS

CAMPCS is designed as an extension of the transition phase of CAMP. During the transition phase of CAMP, study medication was withdrawn, and children were monitored for lung function, bronchial hyperresponsiveness, growth, and asthma control. At the end of the 4 month medication washout, care for asthma was transferred to the physician who cared for the child prior to enrollment in CAMP or another asthma caregiver. The CAMP study physician provided recommendations for asthma care to the family and the physician at that time. CAMPCS will continue followup and monitoring for 4.5 years after the transfer of care. While care will be administered by the child's physician, the CAMPCS physician provides recommendations and is a resource for advice about asthma care. At the end of this extended followup, 90% of the girls and 60% of the boys should have achieved maximal height and level of pulmonary function.

The centers participating in CAMP are continuing in CAMPCS with the exception of the Patient Education Center. Hence, the participating centers will be the chairman's office, 8 clinics, the Data Coordinating Center (DCC), and the NHLBI project office. Subcontracts between the DCC and the McKesson BioServices (called the Supply Distribution Center in CAMPCS), the University of Iowa School of Pharmacy (manufacturer of the methacholine solutions), and the DACI Laboratory and Serum Repository have been renewed.

The design summary of CAMPCS is given in Table 5.2. Table 5.3 displays the data collection schedule for CAMPCS. The manuals and forms developed for CAMP are the basis for development of manuals and forms for CAMPCS. What follows is a brief summary of CAMPCS; specific details are discussed in subsequent sections.

In contrast to CAMP, wherein treatment was provided, CAMPCS is an observational study with treatment for asthma managed by the child's physician. Recommendations for treatment in accordance with National Asthma Education and Prevention Program Expert Panel Report (NAEPP Guidelines) will be provided to the family and the child's physician by the CAMPCS physician initially and at each CAMPCS clinic visit. While the provision of medications was a benefit to patients during CAMP, we do not believe that the lack of provision of medications during CAMPCS will be a major deterrent to participation. The bond between CAMP staff and patients is very strong, and many of the CAMP physicians are the patients' asthma physicians to whom care will be "transferred" following the close of CAMP. Further, there is some restiveness among patients and families regarding the demands of the CAMP protocol and the need to have treatment decisions conform to a uniform protocol, indicating that treatment on the usual basis will be attractive to families. The CAMPCS visits and phone calls allow patients and families to sustain the contact with the CAMP staff and provides the reassurance of a second opinion on the asthma care received, while reducing the obligations of participation. The CAMP clinic at

Toronto has been operating since the start of CAMP in an environment where free medication is available outside of CAMP; the success of this clinic indicates that CAMP has offered other benefits to patients and families that are attractive enough to ensure participation.

Children currently involved in CAMP were recruited by reconsent at the last CAMP transition phase visit. There will be 4 contacts with each participant each year, 2 during annual and semi-annual visits, and 2 telephone calls at intervals between these visits. Information will be obtained at all 4 contacts on symptoms and medication use in the interval since the last CAMPCS contact. At the annual visit the primary outcome variable, pre- and post-bronchodilator FEV_1, and associated spirometric measures will be collected. Tanner staging will also be done at the annual visit until full maturity is reached. Psychological tests will be administered to patients and parents annually. Information on quality of life will be collected annually. At semi-annual visits, methacholine challenge data will be collected. Separate visits are required to collect pre and post-bronchodilator FEV_1 and methacholine challenges since both measures cannot be done at the same time. Height and weight will be measured at both the annual and semi-annual visits. Bone density will be measured 84 and 108 months after randomization. Bone age will be assessed at the last CAMPCS visit. Blood will also be obtained 84 and 108 months after randomization; serum will be sent to a central laboratory for determination of total IgE, while a complete blood count with differential and total eosinophil count will be obtained at the individual centers. Skin testing will be done 96 months after randomization. Lens photography (screening for cataracts) will be performed at the last CAMPCS visit.

4.3 Consent and recruitment

Since the age at enrollment in CAMPCS may be as young as 9-10 years, CAMPCS utilizes both assent and consent statements. Parents or guardians of children less than 18 years of age are required to sign the consent statement for the child to participate in CAMPCS. Children of an age or capability of understanding the consent statement are also asked to sign the consent statement. Children who turn 18 after enrolling in CAMPCS will be required to sign the CAMPCS consent statement when they turn 18 in order to continue in CAMPCS.

The consent statement specifies the purpose of CAMPCS, the general design, the expected duration of the study, the data collection procedures and schedule, the risks and benefits associated with participation, the protections against risks, the alternatives to participation, the incentives to be provided, and the protections for confidentiality of the data provided by the patient and family. The assent statement provides similar information in an age appropriate fashion. IRB approval of the CAMPCS protocol and consent and assent statements is required at a clinic before patient activities may begin at the clinic. Individual clinical centers are allowed to add information but not to delete information thought to be essential. The DCC will collect copies of all approved consent and assent statements and will review them for completeness of information. The DCC will monitor for initial IRB approval at each center and annual renewal of approval, as was done in CAMP.

The major threat to the validity of CAMPCS is loss to followup. CAMP is unique in that 5% or fewer of all CAMP participants can be considered lost to followup. This compares particularly favorably with other longitudinal cohort studies in asthma which have lost significantly more patients in a shorter period of time. We believe that we have innovative strategies to recruit most of the CAMP participants to CAMPCS and to ensure an extremely high followup rate for those who enroll in CAMPCS.

Completion of diary cards is on a voluntary basis in CAMPCS because their completion is strongly

felt by some patients and families to be an onerous obligation. On the other hand, since some patients and families have come to rely and value their use as a "checkup by mail", diary cards are offered to patients and families. Making diary card completion voluntary makes CAMPCS more attractive to some patients.

It is recognized that some of the CAMP patients do not have health insurance, and others do not have a medication benefit on their insurance plan. Some clinics plan to care for patients who do not have medical insurance free of charge and work with drug company representatives in obtaining asthma medications for these children.

Discussions about the CAMP transition phase began in November, 1998 and these discussions led very naturally into discussions about CAMPCS. The 2 visits during the CAMP transition phase provided opportunities for patients and families to be given information about CAMPCS, to ask questions about CAMPCS, and to address concerns about participation. The intent was to formally enroll (i.e., obtain signature of the CAMPCS consent and schedule the first CAMPCS visit) at the final CAMP transition visit. Parents and children were mailed the consent and assent statements for CAMPCS two weeks before the last CAMP transition phase visit. At the last CAMP transition phase visit, the consent statement was presented again to the child and parent, and consent was sought.

We anticipate that 80-90% of the patients currently active in CAMP will enroll in CAMPCS. This will yield about 825-950 patients for CAMPCS followup. The only exclusion criterion for participation in CAMPCS is refusal; adherence to CAMP medications is not an inclusion criteria for participation in CAMPCS. It is recognized that many children will be in college at some time during CAMPCS. We anticipate that we can complete in person visits with college students during spring break, winter/Christmas break, and during the summer. In informal discussions, CAMP patients and families have indicated an extremely high willingness to participate in this followup study.

4.4 Visits and telephone contacts

4.4.1 Timing of visits and telephone contacts

Each visit has a 6-month window in which it may be done with a minimal separation between in person visits of 3 months. Each telephone call has a window with a minimum separation from the intervening visit. Patients without a telephone will be contacted by registered mail or e-mail.

4.4.2 Content of visits

One week prior to each semiannual or annual visit, the study coordinator will contact the patient to remind the patient to bring all medications used in the past seven days to the visit, and arrange for holding short-acting bronchodilator for 4 hours and long-acting bronchodilator for 24 hours before the visit.

At each visit, the study coordinator will review medicines used for asthma in the past seven days. Use of medications for other problems will also be recorded. Questions about asthma symptoms, chest symptoms, nose/eye/sinus symptoms and smoke exposure will be asked. The study coordinator will review asthma education principles for early warning signs, content and use of action plan, peak flow meter technique, technique for use of prescribed asthma medication, and routines for remembering to take

medication. Height and weight will be measured.

Procedures specific to the annual visit are pre- and post-bronchodilator spirometry, pre- and post-bronchodilator peak flow, physical exam by physician or physician's assistant (including Tanner staging until full maturity is reached), environmental survey of the patient's primary residence, psychological questionnaires, quality of life questionnaires, bone densitometry (84 and 108 months after randomization), bone age (last CAMPCS visit), blood draw for total serum IgE level, CBC and differential, and total eosinophil count (84 and 108 months after randomization), prick skin testing (96 months after randomization), and lens photography (at last CAMPCS visit). The procedure specific to the semi-annual visit is the methacholine challenge test.

4.4.3 Content of telephone contacts

At the 2 telephone contacts, study coordinators will ask the same questions about medications used for asthma in the past seven days, chest symptoms, nose/eye/sinus symptoms, smoke exposure, etc that are asked at the annual and semi-annual visits.

4.5 Measurement of independent and mediating variables

4.5.1 Treatment

In CAMP, treatment related to the treatment received in CAMP, treatment recommendations subsequent to withdrawal of CAMP study medication, and actual treatment used subsequent to withdrawal of the CAMP study medication. CAMP data collection relating to treatment includes protocol treatment assignment and data on any deviation from that assigned treatment, including use of other daily asthma medications, use of prednisone for exacerbations, and use of albuterol as a rescue medication. In CAMPCS, form items capture the patient's self-report of asthma medication used in the past seven days. Use of oral steroids since the last contact will be queried. Information on nasal steroid use will be recorded. We recognize that CAMPCS will rely on patient self-report and staff assessment of compliance with therapy. These are the same mechanisms used in CAMP.

Recommendations regarding treatment are provided as follows:

- **At the end of CAMP/beginning of CAMPCS**: Care was returned to the patient's physician with a recommendation about asthma treatment based on symptoms in the last year of CAMP, clinical course during CAMP, and the NAEPP Guidelines. A summary of the patient's CAMP history was provided.

- **Subsequent CAMPCS visits**: At the annual and semi-annual visits, reported symptoms and medication use will be used to recommend treatment in accordance with the NAEPP Guidelines. The recommendation will be transmitted to the asthma care physician after each clinic visit. The letter will also transmit results of the pulmonary function tests and any information about the interval clinical course.

Patients will be given diary cards if patients/parents care to use them. Since many patients and parents have become used to communicating with CAMP staff through the diary cards, we anticipate that some patients and parents will want to continue this pattern in CAMPCS. Use of diary cards will be encouraged in CAMPCS.

4.5.2 Environmental exposures

The Home Environment Questionnaire (Form ES) used in CAMP will also be used in CAMPCS to assess environmental exposures. This questionnaire will be administered at each annual visit. The questionnaire concerns the primary residence of the child. The primary residence refers to the location where the participant resides for the majority of the year (e.g., dormitory if attending college). Form ES covers general home characteristics, characteristics of the patient's bedroom, and presence of pets in the home.

During the calls between visits, questions about environmental exposures will cover use of cigarettes, pipe or cigars by the patient, and exposure to second hand smoke.

4.5.3 Atopic status

Degree of atopy will be assessed by:

- Serum IgE level and blood eosinophil level -- Since blood was drawn in CAMP at the 4 year visit, blood draw in CAMPCS is scheduled for 84 and 108 months after randomization. Serum will be sent to a central laboratory for determination of the IgE; a complete blood count with differential will be obtained at the clinic.
- Degree of skin test positivity -- Since skin testing was done at the 4 year visit in CAMP, skin testing in CAMPCS will be done 96 months after randomization

Manifestations of atopy will be assessed by:

- Presence of eczema -- assessed by questions at each visit and by yearly physical exam
- Presence of upper airway disease -- questions will be asked at each visit and at the telephone contacts to assess the frequency and severity of nasal symptoms.

4.5.4 Psychological status for the patient and family

A well documented relationship exists between pediatric asthma and psychological dysfunction. Investigators have long understood that severe asthma can present chronic stress that burdens a child's psychological development and brings increased risk of psychological disturbance. This is particularly true in adolescence, a time of emotional turmoil and a period of development for most CAMP participants during CAMPCS.

Clinicians recognize the significant impact of psychological dysfunction and consequent nonadherence on treatment outcome in both clinical situations and treatment studies. CAMP is no exception. Staff in all eight centers have reported many families in which psychological difficulties have compromised study participation and contributed to poor asthma control. A possible synthesis of these issues is that family dysfunction interferes with day-to-day adherence with study procedures and can result in problems with retention in the trial itself. Family dysfunction often results in child problems that are evident in the Child Behavior Checklist (CBCL; 95). Regular evaluation of the family and child by both interview by CAMPCS staff at the visits and yearly paper and pencil tests is helpful in planning strategies for improving adherence and retention.

Because of the ongoing role of psychological problems in asthma management, inclusion of psychological measures in CAMPCS will help to explain some of the variance in treatment outcome. Evaluation of psychological problems will also be helpful in developing strategies to retain the patients during CAMPCS followup.

The psychological measures included are the CBCL (completed by the parent if participant < 18 years of age), the Youth Self Report (completed by the child; 96) (or Young Adult Self Report for patients over 18 years or older; 97) and the Brief Symptom Inventory (completed by the child; 98). These will be completed annually. The psychologist at each site will also help staff understand the role of currently recognized and newly developing psychological problems in retention of patients during CAMPCS followup; as is currently being done at each CAMP site, the psychologist will meet with the staff at regular intervals to review retention issues and develop plans to approach patients and successfully complete visits.

4.5.5 Skin testing

Skin testing will be performed 96 months after randomization according to the CAMP allergy skin test protocol (99). Each participant will be tested with a core battery of allergens: Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat, dog, American cockroach, German cockroach, penicillium mix, aspergillus mix, Timothy grass, and short ragweed. In addition, each site adds a battery of locally important antigens such as trees, additional weeds, Bermuda grass, and the molds Alternaria and Cladosporium.

4.5.6 Polymorphisms of the O2-AR

The genotyping of O2-AR polymorphisms at position 16 Arg to Gly at position 16 and position 27 Gln27▾Glu has already been performed as part of an ancillary study for CAMP. The technique used is the amplification refractory mutation system (ARMS reaction). This technique allows rapid determination of an individual's genotype at a polymerase chain reaction using primary-specific phyloci of interest. Specifically, a single "downstream" primer and two "upstream" primers are prepared, each of which is an extract match, its most three prime nucleotide of either the wild type or mutant base on the gene of interest. Dr. Drazen, in collaboration with Dr. Weiss, has utilized these ARMS primers to screen for the presence of the O2-AR polymorphisms at loci 16 and 27. Dr. Drazen has developed an allele specific PCR technique. The basis of the technique is the fact that three prime matches between template and primer in the PCR provide for optimal amplification efficiency, while mismatches result in little, if any, product. Thus, primers are used that match each known polymorphism.

Genotyping has been performed as part of cross-sectional evaluation of O2-AR polymorphisms and their relationship to baseline data. We will extend the look at these polymorphisms in relationship to the baseline data to the longitudinal phenotypes and drug treatment phenotypes in CAMPCS.

4.6 Outcome measures

4.6.1 Symptoms and quality of life

CAMP followup visits every 4 months have determined frequency of asthma symptoms and their associated morbidity. We ask the same questions during CAMPCS at each in person visit and during the intervening telephone contacts to determine the following parameters:

- Morbidity assessed by contact with a physician: numbers of times that a physician or a physician's office was telephoned because of asthma symptoms, that the patient was seen at a physician's office because of asthma symptoms, that the patient was seen at an emergency department or urgent care facility because of asthma symptoms, and that the patient was hospitalized overnight because of asthma symptoms (these are answered with the number of relevant events in the interval since the last visit)
- Morbidity assessed by absence from school or work: number of days the patient was absent from school (or work) because of asthma symptoms (these are answered with the number of relevant events in the interval since the last visit)
- Morbidity assessed by asthma symptoms: how many times the patient awakened during the night because of asthma, used albuterol because of asthma symptoms or low peak flow, used prednisone because of asthma, and had asthma symptoms that interfered with daily activity (except for prednisone which is recorded as number of days, these are answered by category ranging from almost every day to never)
- Morbidity assessed by symptoms precipitated by upper respiratory infections and exercise: questions about frequency and association with colds or cough, chest congestion and/or phlegm, wheezing, and respiratory symptoms (cough, wheeze, shortness of breath, and chest tightness) after playing hard
- Patients will also be asked to complete the Pediatric Asthma Quality of Life Questionnaire; caregivers will be asked to completed the caregiver's version of this questionnaire (PAQLQ; 100)

4.6.2 Spirometry

Spirometry will be assessed by methods used in CAMP (101). Spirometry is carried out by CAMPCS-certified pulmonary function technicians with a volume displacement spirometer interfaced to a computer. The equipment specifications and testing protocol meet or exceed American Thoracic Society (ATS) standards. Spirometry is performed at least 4 hours after the last use of a short-acting bronchodilator and 24 hours after the last use of a long-acting bronchodilator. Three acceptable maneuvers that meet ATS criteria (FVC and FEV_1 reproducible with 5%) are required when performing spirometry. Spirometry pre- and post-bronchodilator (2 puffs albuterol by MDI) measurements will be

taken at each annual visit. After administering the bronchodilator, the minimum elapsed time before performing the post-bronchodilator tests is 15 minutes.

4.6.3 Airway responsiveness

Airway responsiveness will be assessed by methods used in CAMP (102). Airway responsiveness is determined by the decrease in FEV_1 after administration of increasing concentrations of methacholine using the Wright nebulizer-tidal breathing technique. Testing is performed by a certified pulmonary function technician according to protocol. To minimize the effects of various factors and the course of asthma on methacholine reactivity, determinations of bronchial reactivity will not be made:

- Within 4 weeks of an upper respiratory tract infection or other viral illness
- Within 4 weeks of use of oral steroids for an asthma exacerbation
- Within 4 hours after the last use of a short-acting bronchodilator and 24 hours after the last use of a long-acting bronchodilator
- If the FEV_1 at baseline is less than 70% of predicted.

If the patient has consumed caffeine within 4 hours of the methacholine challenge, the test is done and the consumption of caffeine is noted on the form. Effort will be made to do methacholine challenge testing on any one patient at the same time of day; the time the test ended will be noted on the form. Two 90 µg puffs of albuterol will be administered after methacholine challenge testing. The patient will not be allowed to leave until the FEV_1 is at least 90% of baseline.

The methacholine dilutions will be prepared quarterly by the University of Iowa School of Pharmacy according to protocol (as in CAMP) and will be shipped to the Supply Distribution Center for shipment to the clinics.

4.6.4 Physical growth and development

A protocol for measurements of somatic growth and development was established in CAMP to help standardize these assessments (103). Standing height and weight will be measured biannually. Standing height is measured with the Harpenden stadiometer (Holtain model #602 or #603); the stadiometer is calibrated prior to each measurement session. Weight is measured with the Detecto scale (model #337) with the patient wearing light clothing and socks or barefoot. The scale is reset to 0 prior to each measurement.

Sexual maturation (Tanner staging) will be assessed annually (once a patient has reached Tanner 5 on all parameters for 2 consecutive visits, this part of the physical exam is omitted). Aside from the measurement of testicular volume, Tanner staging assessments are based on visual inspection of the patient. The Holtain model #711 orchidometer is used to assess testicular volume. Effort is made to have patients and assessors be of the same gender.

Bone density will be measured 84 and 108 months after randomization. During CAMP, the same phantom bone has been circulated each year to each clinic for scanning. The data from these scans are analyzed for evidence of variability between clinics and within clinic over time. This quality assurance procedure will be continued in CAMPCS.

Bone age will be assessed in at the last CAMPCS visit by means of a PA film of the entire left hand and wrist. This same procedure has been done during the CAMP transition period. X-rays will be read centrally for skeletal maturation using the standards of Greulich and Pyle.

4.6.5 Lens opacities

Presence of lens opacities will be assessed by lens photography at the last CAMPCS visit. This procedure was done during the CAMP transition period. Photographs will be read centrally for presence of posterior subcapsular cataracts.

4.7 Patient retention

In informal discussions, CAMP patients have indicated that the bond with the CAMP coordinators and physicians is the most important reason for staying with CAMP. Patients also note that compensation for expenses is appreciated.

Parents and the older children have responded enthusiastically to education and updating on new information on asthma, particularly its treatment but also its pathophysiology. While parties were useful early on in CAMP when children were younger, the education and update sessions have become more popular as the trial has progressed. Hence education and information sessions will also be used to promote retention in CAMPCS.

4.8 Data management

A distributed database management system patterned after that used in CAMP will be used in CAMPCS. The CAMP and CAMPCS databases will be maintained in separate but easily combinable files. The data system for CAMPCS has 2 components: the clinic data system and the clinic spirometry system.

The clinic data system for CAMPCS utilizes the hardware and most of the software used in CAMP. Some software applications will have to be updated to reflect the CAMPCS data forms and tasks, but other changes should be minimal. The CAMP data system is written as an interactive windows application using SAS/AF and SCL. The major functions of the CAMPCS data system will be:

- Patient enrollment
- Data entry of forms
- Inventory of forms and visits keyed for each patient
- Database backup
- Generation of clinic management aids (labels, visit time windows guide, reminders of upcoming and overdue visits)
- Printing sets of blank forms

The system includes a Tutorial component for training staff in the operation and functions of the data system.

The features of the distributed data entry process include:

- Double entry of all data items
- Checks on patient identifiers
- Range checking on all items on entry
- Within-form consistency and logic checks on entry
- Data entry screens customized to the forms

The centralized analysis database will be created from periodic copies of the clinic databases. Snapshots of the clinic databases will be transmitted to the DCC each month for inclusion in the central database. The transfer application will be designed to be triggered by date (i.e., automatically at the first of the month) or by initiation by clinic staff (in case of need for non routine transfer of data).

The clinic spirometry system used in CAMPCS will be an updated version of the present CAMP system. The CAMP system uses a Survey III Dry-Seal spirometer (WE Collins, Braintree, MA) with a Stead Wells bell. The spirometer is connected to a Dell model 450 M model computer equipped with two 150 MB Bernoulli drives and a LaserJet 3P Printer with a Proprinter Emulation cartridge. The software for this spirometry system was developed for CAMP by S & M Instrument Company (Doylestown, PA). The spirometry system software includes an application to prepare backup files and a snapshot of the spirometry data for mailing to the DCC. The data captured electronically are used to calculate FEV_1, FVC, FEV_1/FVC ratio, FEV_3, FEV_3/FVC ratio, FEF_{25-75}, PEFR, FEF_{25}, FEF_{50}, FEF_{75}, and predicted FEV_1 and FVC. A written report of the spirometry or methacholine challenge session is printed at the close of the testing session. The reference equations used in CAMP will be used in CAMPCS.

4.9 Quality assurance

The quality assurance procedures used in CAMP are replicated in CAMPCS. These are:

- Certification of data collectors (e.g., clinic coordinator, pulmonary function technician, skin tester, study physician, psychologist psychometrician, data entry technician, visual acuity examiner, lens photographer); requirements for certification include practice with the procedure including completion of practice data collection forms, test of general knowledge of CAMPCS protocol, reading of study manuals, and signature of a statement agreeing to abide by CAMPCS protocol and acknowledging the need for accuracy and integrity in completion of study tasks and for preserving the confidentiality of the study and patient data.
- Certification of clinics prior to initiation of data collection
- Ongoing feedback on performance in the form of monthly reports and review of performance at study meetings
- Initial and followup training in study procedures via special workshops or discussions at meetings
- Ongoing review of data collection forms by DCC staff and comparison of paper forms to keyed data with feedback regarding and correction of discrepancies
- Double entry of data collection forms
- Range checking during data entry and periodic batch editing to cover more complex checks of consistency and completeness of the keyed data
- Review of each spirometry session by the DCC pulmonologist with written feedback to the pulmonary function technician

- Voluntary disclosure of potential conflicts of interest as represented by stock holdings in companies having a proprietary interest in products under evaluation or other financial arrangements with the trial
- Periodic discussions throughout the course of the trial at meetings of the research group as to the importance of integrity in this or any other research effort
- System specific and appropriate quality control procedures (e.g., for spirometry system, daily check for air leak, a volume calibration using a three-liter syringe, and a timed calibration check and daily cleaning of hoses and connections and weekly cleaning of the spirometer bell)

The data forms and related data system are designed to exclude transmission of name and other personal identifiers to the DCC. Records are identified by the CAMPCS ID number and name code (no change in identifiers will be permitted). Only these identifiers are used in edit messages and correspondence with clinics concerning individual patients. Any forms received at the DCC (e.g., for quality control purposes) are stored in a secure monitored area, with access limited to DCC personnel.

Backup copies of the central master data file and program libraries are generated at regular intervals. These backup files are stored in a secure location, remote from the DCC, to permit regeneration of the master file, should it be destroyed by a computer malfunction, programmer error, fire, or vandalism.

4.10 Data monitoring

Since CAMPCS does not involve comparison of treatment regimens, data monitoring is largely confined to performance monitoring and monitoring for protection of patient safety. CAMPCS will have a DSMB which will meet annually to review the performance of CAMPCS.

Performance monitoring will be directed primarily to the efforts of clinics regarding patient recruitment, followup and data collection. However, all other aspects of activities represented in the study will be monitored as well, including those performed by central laboratories, the drug distribution center, and the DCC itself.

Reports summarizing performance will be prepared at regular intervals by the DCC for distribution to and review by clinic staff, the SC, and the DSMB. Both committees will have responsibility for reviewing performance reports and for recommending corrective actions deemed appropriate based on accumulated performance data. It is anticipated that the primary responsibility for formulating effective actions and for implementation of them will reside with the SC, especially in relation to data collection and protocol issues.

The reports prepared will include a variety of tabulations, such as those produced by CAMP. Analyses will be performed comparing the clinics with regard to such items as rate of patient recruitment, completion of visits and telephone contacts, and number of data collection deficiencies. Assessment of changes in performance will be based on comparisons within clinic involving, for example a comparison of the rate of data collection deficiencies in the most recent time period contrasted with rates observed in earlier time periods. While an overemphasis on competition can lead to problems, it is important for investigators to know the standing of their centers, relative to others, with respect to the quantity and quality of the data supplied. These reports also help maintain the sense of being part of a team with a common goal.

4.11 Statistical power, data analysis and preparation of publications

CAMPCS will have sufficient statistical power for detecting meaningful difference in post bronchodilator FEV_1. Assuming a two-sided type I error of 0.01, a power of 0.90, and 11% within group SD for change from randomization in FEV_1 percent predicted, enrollment of n = 850 children of whom 90% will complete followup, the following compares detectable differences in post bronchodilator FEV_1 for CAMPCS with the original CAMP design:

	Detectable difference in Post BD FEV_1	
Comparison	CAMPCS	CAMP
Bud vs Ned	4.0%	3.8%
Bud or Ned vs Placebo	3.7%	3.5%

If comparisons are limited to patients who have completed growth by the end of CAMPCS, the available sample will be reduced from an estimated n = 850 to n = 650, which raises the detectable differences from 4.0% to 4.5% and from 3.7% to 4.3%. To follow all CAMPCS patients to the termination of growth would require approximately 5 additional years of followup and to follow CAMPCS patients until 90% of the males had terminated growth would require approximately 3 additional years of followup.

Data analysis in CAMPCS will follow the models established in CAMP. Since the data collection forms and procedures used in CAMPCS will be identical to or modeled after those used in CAMP, data from CAMP and CAMPCS may be pooled, and the analyses initiated in CAMP can be continued in CAMPCS. As in CAMP, data collected within the time window of a visit will be included in analyses using that followup time point.

Strategies for preparation of publications in CAMPCS will be based on the strategies used in CAMP -- appointment of a Publications Committee with two subcommittees, one charged with stimulating and organizing the initiation of papers and one charged with carrying out internal review of study papers prior to journal submission. A list of ideas for papers resulting from CAMPCS will be created and a status report on all initiated papers will be maintained for review by the CAMPCS Executive and Steering Committees during every meeting.

4.12 Study organization and meetings

The organizational structure of CAMP will be replicated in CAMPCS. The CAMPCS Steering Committee will be comprised of the study chair, principal investigators from each of the participating centers, the NHLBI project officer and representatives from the psychologists and clinic coordinators. The Steering Committee will be responsible for the design and conduct of CAMPCS. The Publications Committee, a subcommittee of the Steering Committee, will be responsible for organization and oversight of development of manuscripts. The CAMPCS Executive Committee will act as a decision and policy recommending body in the interim between Steering Committee meetings. The Steering Committee/Research group will meet annually.

4.13 Summary

We believe that the methods we have outlined in section 4 accomplish our primary goals of retaining the cohort and utilizing data collection methodologies identical and fully compatible with the original CAMP trial to allow us to have seamless data collection with standardized exposure and outcome measurements over an average of 8.5 years of followup.

5. Tables

5.1 Summary of long term studies of asthma

Author	Year	Number subjects	Years of observation	% Remission	% Improved	% Persistent	% Relapse	% Current wheeze
Flensborg	1945	298	6-15	40	35	21	5	60
Rackemann & Edwards	1952	449	20	31	43	26		
Ryssing	1959	281	13	30	34	15	21	55
Ogilvie	1962	1000	3-33	48		52		
Aas	1963	174		30	30	40		40
Kraepelien	1963	528	8-10	30	47	23		70
McNicol & Williams	1963	295	7	18	30	52		52
Ryssing & Flensborg	1963	442	10-15	37	9	54		54
Barr & Logan	1964	336	17-22					48
Buffum & Settipane	1966	518	10	41	52	6		58
Johnstone	1968	63	11	22	37	31		
Blair	1979	244	20	28	21	51	27	72
Martin	1980	342	14	33	20	47	20	47
Martin	1981	342	14	41	20	39		
Anderson	1986	731	16	65	18	11	6	
Bronnimman & Burrows	1986	15					23	
Burrows	1987	37	9	50		50		
Jonsson	1987	119	25	55		22	23	45
Kelly	1987	323	21	32	23	47	27*	47
Cserhati	1989	441	2-22	57	57	30	13	43
Gerritsen	1989	101	8	57		28		
Lebowitz	1990	88	8	45		17	38	55
Godden	1994	99	25	40				60
Jenkins	1994	741	22					25.6
Ulrik	1995	70	10	14		86		86
Strachan	1996	1060	33					48
Panhuysen	1997	181	24	40				60

*relapse or worse grade

5.2 Design summary

Name
- Childhood Asthma Management Program Continuation Study (CAMPCS)

Objective
- Extend follow-up study of the cohort established by the Childhood Asthma Management Program (CAMP) for an additional 4.5 years to determine the effects of 3.5-5.5 years of anti-inflammatory treatment administered early in childhood on the time course of the progression of asthma through puberty as indicated by lung development, physical growth, and bone density; by the pattern of bronchial reactivity; by the occurrence, relapse, and remission of asthma symptoms; by the use of asthma medications; by the need for health care services; and by self-reported quality of life.

Type of study
- Multicenter, long-term follow-up, cohort study

Population
- 850-950 current participants in CAMP, aged 9-18 years, of whom 1/3 are minority (anticipated)

Treatment
- Prescribed by the patients's physician
- Consultation of treatment provided by CAMPCS physicians at the time of biannual visits; advice provided will consider history of asthma symptoms, quality of life (activity, school and work missed), medication use, and pulmonary function, and will be based on the NAEPP Guidelines

Inclusion criteria
- Current participant in CAMP
- Consent of the guardian and child

Exclusion criteria
- Refusal

Recruitment
- At the last CAMP visit or anytime after that

Duration of follow-up
- 4.5 years

Outcomes
- Rate of increase and maximal level of lung function (FVC, FEV_1, FEV_1/FVC)
- Rate of increase in or maximal attained level of height
- Rate of increase in or maximal attained level of bone density
- Airway responsiveness to methacholine
- Occurrence, relapse, or remission of respiratory symptoms
- Use of asthma medications
- Use of health care services

- Self reported quality of life
- Development of lens opacities

Measures of independent and mediating variables

- Treatment used by the patient will be determined by contacts every 3 months, twice during biannual visits to the clinic and twice during phone calls
- Environmental exposures obtained by questionnaire at annual visits. Exposure to tobacco smoke will be assessed every 3 months
- Atopic status, both the degree and manifestations
- Duration of asthma
- Psychological status will be assessed by questionnaires yearly
- Polymorphisms of the O2AR

Data collection schedule

- Twice yearly visits to the CAMPCS center
- Telephone contacts twice yearly in between the visits

5.3 Data collection schedule

	Visits		Telephone calls
	Annual	Semiannual	every 6 months
Pulmonary function			
- Spirometry	X		
- Methacholine challenge		X	
Physical growth and development			
- Physical exam	X		
- Standing height	X	X	
- Weight	X	X	
- Tanner staging (until maturity)	X		
- Bone density (c84, c08)	X		
- Bone age (last CAMPCS visit)	X		
Respiratory symptoms	X	X	X
Medical history	X	X	X
Treatments used	X	X	X
Environmental exposures			
- Overall	X		
- Tobacco smoke	X	X	X
Atopic disease -- degree			
- IgE (c84, c08)	X		
- Eosinophil (c84, c08)	X		
- Skin testing (c96)	X		
Atopic disease -- manifestations			
- Eczema	X		
- Upper airway symptoms	X	X	X
Vision check and lens photos (last CAMPCS visit)	X		
Psychological characteristics			
- CBCL (parent if participant < 18 years)	X		
- Brief Symptom Inventory (participant)	X		
- YSR (participant <18 years)	X		
- YASR (participant ▾ 18)	X		
Quality of life			
- PAQLQ	X		

5.3. Data collection schedule

	Visits		Telephone calls
	Annual	Semiannual	every 6 months
- PACQLQ	X		

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