
Minimizing attrition in a long-term clinical trial of pediatric asthma

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Background: Despite increased attention focused on the need to prevent patient attrition in long-term clinical trials, high dropout rates have threatened the success of numerous studies.

Objective: To evaluate the disease, demographic, and psychological factors associated with missed visits and study dropout to help improve patient management in long-term clinical trials.

Methods: Predictors of attrition were examined within the Childhood Asthma Management Program (CAMP), a large, multicenter clinical trial that followed up 1,041 children with asthma for 4 to 6 years.

Results: Eighty-two percent of patients attended all study visits. The tendency to miss visits was increased among older children with milder asthma, lower intellectual and social competence, and more symptoms of behavioral problems and emotional distress. Forty-two patients who missed 3 or more visits in a row and did not attend the final visit were considered study dropouts; these patients at baseline had milder asthma; lower cognitive, academic, and social competence skills; and more family conflict and distress than found among participants who remained in the study. The 49 children who had erratic attendance but did not drop out also had lower intellectual and academic skills and less family social support.

Conclusions: The 4% dropout rate in CAMP was lower than reported in any previous long-term asthma trial. The findings of milder disease, decreased psychological resources, and increased distress in problem-attendance patients can assist in identifying patients who are at risk for missed visits or dropout during the trial either to block their entry into the trial or to focus efforts at maintaining their attendance once enrolled in the trial.

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INTRODUCTION

Maintenance of patient participation is a significant challenge to the completion of a successful clinical trial. Once recruited,

patients may not remain faithful to the trial. Longer clinical trials frequently require a greater number of visits and more work between visits, including daily diary card completion and use of study medications. Patient motivation to continue their commitment to a longitudinal study may decline over time.¹ Dropout rates in longitudinal studies are often large and can threaten the validity of results. Patient attrition rates, generally reflecting the proportion of patients who left and did not return to the study, have been reported at 60% in a study of infant cardiopulmonary risk,² 46% in a rheumatoid arthritis study,¹ 32% in a diabetes clinical trial,³ and 37% in a study of respiratory distress syndrome.⁴ Studies of pediatric asthma have fared somewhat better, but dropout rates of approximately 25% in longer asthma studies^{5–8} have undermined their success. Few studies of pediatric asthma have continued longer than 1 year, and none have evaluated the rates of attrition or factors associated with them. This report from the Childhood Asthma Management Program (CAMP) examines the demographic, psychological, and disease-related factors associated with study attrition. Information from this study can assist in the development of strategies to increase patient participation in future pediatric asthma clinical trials.

METHODS

CAMP was a multicenter, randomized, double-masked clinical trial initiated and funded by the National Heart, Lung, and Blood Institute (NHLBI) with the purpose of determining

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the effects of 3 inhaled treatments on mild-to-moderate childhood asthma throughout 4 to 6 years.^{9,10} Extensive screening measurements were taken, including documentation of disease characteristics and administration of a battery of psychological tests, before patients were randomized into the trial. Patients who missed screening visits or were unwilling to participate in specific examination procedures during the screening period were not randomized into the study.

Patients

Between December 1993 and September 1995, a total of 1041 children^{9,10} 5 to 12 years of age were enrolled in the 8 clinical centers (Albuquerque, NM, Baltimore, MD, Boston, MA, Denver, CO, St. Louis, MO, San Diego, CA, Seattle, WA, and Toronto, Ontario, Canada). All participants met exclusion criteria, which included allowing no more than 1 hospitalization or 5 oral steroid bursts in the preceding year, and inclusion criteria, which included history of asthma symptoms or treatment for at least 6 months; evidence of mild-to-moderate asthma documented during a 28-day screening period that required diary card documentation of asthma symptoms, medication use, and peak expiratory flow rate levels; sensitivity to methacholine; and completion of prebronchodilator and postbronchodilator spirometry with good technique and prebronchodilator percentage of predicted forced expiratory volume in 1 second (FEV₁) of at least 65%.^{9,10} Only patients who were able to adhere to the numerous protocol demands during the 28-day screening period were randomized into the trial.

Study Attendance

Once enrolled, no patients were excluded from participation for the duration of CAMP. Patients were randomized into 1 of 3 groups, receiving budesonide, nedocromil, or placebo. All patients received albuterol as needed for symptoms or to prevent exercise-induced bronchospasm. A significant commitment was required of participants. Each was seen at 2 and 4 months following randomization and every 4 months thereafter.⁹ In addition, numerous patient tasks were completed during the trial, including use of study medication, diary card completion, and twice-daily peak expiratory flow rates. Recognizing that patient attrition could threaten the ability of CAMP to achieve its objectives, numerous procedures were built into the study to educate and motivate patients to complete their participation in CAMP. Despite these procedures, some study visits were not attended and some patients dropped out of CAMP. This investigation was initiated to document the frequency of missed visits and patient dropout and to identify the associated disease, demographic, and psychological characteristics of patients, which may serve to improve identification and management of attrition risk factors in future longitudinal trials. Dropouts were defined as those patients who missed 3 or more consecutive visits and the final visit before the washout period. All others who missed 3 or more visits were categorized in the erratic attendance group, characterized by their start-and-stop pattern of

visit attendance. Patients in the good attendance group were those who missed 2 or fewer visits.

Strategies used to maximize retention. Procedures used to improve patient participation included formation of a patient education center, training of study coordinators, and facilitation of strategies implemented at individual sites to track and intervene where participation waned.

The CAMP patient education center. A patient education center was developed at one CAMP site (Denver) and charged with the responsibility of producing study-specific educational materials to educate participating children and their parents at all 8 sites about their disease and the asthma-management strategies incorporated into the study. Materials were developed for use at the study initiation and later to address ongoing patient education needs as they were identified. Three major areas of self-management were highlighted in the CAMP patient education program: anticipate problems before they arise, determine the appropriate responses, and rehearse and practice behaviors that are effective solutions.⁹ The program was structured to be comprehensive to address the various challenges encountered by the participants and their caretakers and included sections on environmental controls, inhaler skills, the asthma action plan, and asthma medications. Strategically, asthma education was viewed as an ongoing process. In addition to written materials, videos were developed to reinforce key messages and to demonstrate how children with asthma and their parents made decisions about managing their asthma. Patients and parents received a CAMP newsletter 3 times each year; the newsletter was produced at 2 reading levels with different contents for older and younger children. As the participants became older during the trial, a new newsletter was produced with appearance and content more appealing to adolescents.

Study coordinator training. The patient education center program was implemented at all 8 centers following central meetings at which study coordinators, including physician assistants, nurses, or clinical research assistants, were trained in use of the educational materials. This training was accompanied by an educator's manual that contained content and strategies for educating and motivating patients. Emphasis was placed on positive, personal interactions with patients. Two additional planning retreats were conducted during the study to provide CAMP coordinators with workshops on managing study patients and promoting protocol adherence and to allow in-depth discussion among coordinators to help develop more effective means of maintaining patient interest and motivation. Guest speakers with experience in other clinical trials provided additional information on managing the challenge of motivating and retaining patients in the CAMP trial.

Development of additional patient motivation strategies. Numerous additional procedures were implemented by staff to reinforce full participation in the study protocol. Financial compensation was provided. Participants were offered incentives, such as free cab fare to study visits, CAMP parties, group trips to sporting events, movie coupons, toys, T-shirts,

and other small items. Each individual study site designed its own incentive program according to available resources and perceived participant interests. At some sites, frequent participant parties were planned; others relied more heavily on providing material incentives. All participants received certificates of appreciation, and parents received letters of thanks from the NHLBI project officer.

Each CAMP site was also encouraged to develop a systematic program for identifying patients at risk of dropping out of the study. Staff frequently held case conferences to discuss patients who were having difficulty with study adherence and to generate plans to encourage further participation.¹¹ Strategies successfully used to maintain participation in other clinical trials, which were divided into stages such as prevention, maintenance, intervention, and recovery,³ were implemented by all centers. Central to these attrition-prevention strategies was adoption of the philosophy that all CAMP staff shared the responsibility of establishing a positive relationship with patients and their families to ensure satisfaction and continued participation. Coordinators were encouraged to take ample time to discuss problems and encourage patients and to make adaptations in the interest of patient satisfaction. Changing appointments to more convenient times, explaining all procedures, giving feedback about test results, communicating with the child's primary care physician, addressing family requests, and responding promptly to emergencies was central to this philosophy of care. Patients who missed appointments, failed to complete diary cards, resisted specific study procedures, or were generally demanding or uncooperative were viewed not as troublesome participants whose exit from the trial would ease staff burden, but as individuals needing and deserving more staff attention and effort. This patient-centered philosophy was adopted centrally and consistently encouraged by the project officer, the data coordinating center, the steering committee, and all principal investigators.

Baseline Measures

Three categories of baseline measures were examined for their potential to predict study dropout. These included demographic, disease-related, and psychological measures, all occurring before randomization. Demographic variables included age, sex, and parent education level. This last variable is closely associated with socioeconomic status and consisted of the highest level of formal education achieved by any parent or caregiver living in the child's home.

Disease-related measures reflected disease severity and control at baseline. Pulmonary function (percentage of predicted FEV₁ and forced vital capacity [FVC] before and after administration of bronchodilator) was evaluated. Airway sensitivity was measured by PC₂₀ (methacholine dose, administered incrementally for 2 minutes by inhalation, at which a 20% decrease in FEV₁ occurs) and functional control by days of oral steroid use in the past 6 months or days of school missed because of asthma in the past year.

Psychological variables included measures of cognitive ability, emotions and behavior, and family functioning at

baseline. Cognitive ability measures included estimated IQ,¹² academic,¹³ and attention¹⁴ skills. Measures of emotions included self-reported symptoms of depression¹⁵ and anxiety.¹⁶ Parent responses to a standardized behavioral questionnaire¹⁷ produced a social competence score and externalizing (including inappropriate and sometimes aggressive behavior), internalizing (including withdrawn and depressive behavior), and total problem scores (a composite of the externalizing and internalizing behavior problems). Parents also responded to a questionnaire about family life,¹⁸ which produced 3 composite scores: cohesion (closeness among family members), expressiveness (tendency to communicate warmth and support), and conflict (disagreement and fighting among family members). The social support score reflects the degree to which the family has friends and outside family members from whom they draw help and support.¹⁹

Data Management and Analysis

A centralized database was maintained for CAMP by the Johns Hopkins Center for Clinical Trials. The distributed database management system received data input from all centers under a quality assurance structure that included training and certification of data entry technicians at each site, double entry of data, monthly performance feedback, ongoing review of data entry, and periodic batch editing.

Poisson regression²⁰ of the following form was used to evaluate the relationship between the number of missed visits and baseline demographic, disease-related, and psychological variables: $E(Y) = \exp(\alpha + \beta X)$, where E denotes the expected value (or mean) of a Poisson variate Y , Y is the number of missed visits, α and β are the intercept and slope, respectively, when the model is in the log linear form, and X is a covariate. A natural logarithm of the number of required visits is used as an offset. In this exponential model, a 1-unit increase in covariate has a multiplicative impact of $\exp(\beta)$ on the expected value of the number of missed visits. If β is more than 0, then the covariate has a positive effect on the number of missed visits. In addition to this modeling, differences among the 3 groups (dropouts, erratic attendance, and good attendance) on demographic, disease-related, and psychological variables were compared using a 1-way analysis of variance. A 2-tailed $P < 0.05$ was considered statistically significant for these comparisons.

RESULTS

Frequency of Missed Visits and Dropout

Most participants were strongly adherent to the study-visit protocol. One or more study visits were missed by 184 participants. Eighty-two percent of CAMP patients missed no visits, and 91% missed 2 or fewer visits (Table 1). Ninety-one patients, or 9% of the total group, missed a total of 3 or more visits. Of these, 42 met criteria for dropout and 49 for erratic attendance.

Table 1. Missed Visit Frequency during the CAMP Trial*

No of missed visits	Frequency	Percent
0	856	82.3
1	71	6.8
2	22	2.1
3	21	2.0
4	15	1.4
5	4	0.4
6	11	1.1
7	6	0.6
8	6	0.6
9	5	0.5
10	4	0.4
11	9	0.9
12	3	0.3
13	2	0.2
14	5	0.5

* The length of individual patient participation in the Childhood Asthma Management Program (CAMP) varied from 4 to 6 years, depending on time of enrollment. A minimum of 12 study visits were required, but for patients enrolled early during the recruitment phase as many as 17 visits were completed. Those who enrolled late in the recruitment period were seen for no less than 4 years. All participation in the CAMP trial ended between March and June 1999, at which time patients entered an observational phase during which use of study medication was stopped. At the last visit during this washout phase, patients were given the option of enrolling in the CAMP Continuation Study, a 5-year observational study.

Missed Visit Predictors

As seen in Table 2, the number of missed visits was higher with increased child age and lower parent education level. Greater missed visit frequency was associated with milder disease at baseline, including higher pulmonary function measures (prebronchodilator percentage of predicted FEV₁, prebronchodilator percentage of predicted FVC, postbronchodilator percentage of predicted FEV₁, postbronchodilator percentage of predicted FVC), lower airway sensitivity to methacholine, and fewer days of oral steroid use as measured at baseline. The number of days of asthma-related school absence in the year before enrollment was greater for those with a greater number of missed study visits. Psychological variables predictive of missed visits included increased behavior problems and decreased social competency scores from the Child Behavior Checklist, increased impulsivity, increased self-reported depressive symptoms, and decreased intellectual and academic skills. Results from the measures indicated that increased conflict and decreased cohesion and social support were associated with more missed visits (Table 2).

Dropout, Erratic Attendance, and Good Attendance Groups

Differences at baseline among the 3 groups are reflected in Table 3. No differences emerged among the 3 groups in patient age, sex, or parent education level. Patients in the dropout group had milder disease at baseline than the good attendance group. Dropouts exceeded the good attendance

group on all baseline prebronchodilatory and postbronchodilator measures. The erratic attendance group did not differ from the good attendance group on any disease-related variable. Intellectual and academic skills were lower in the dropout group and the erratic attendance groups than in the good attendance group, but no difference in impulsivity/attention scores separated the groups. Children who were dropouts had higher average depression symptom scores. The dropout and erratic attendance groups both had lower social competence scores and increased externalizing problem scores, indicating tendencies toward acting-out behavior problems. The erratic attendance group alone had an increase in internalizing problems, reflecting a tendency toward withdrawal and depression. The dropout group had a higher mean family conflict score, whereas the erratic attendance group had a lower mean social support score than the good attendance group.

DISCUSSION

Attrition in CAMP was lower than in any previous long-term asthma study. Remarkably, more than 80% of patients missed no study visits, and only 4% of patients who met the criteria for study dropout in CAMP (3 or more consecutive missed visits and failure to return for the final visit) dropped out of the trial. In the group of 184 patients who did not attend all visits, the tendency to miss visits was greater in older children with milder asthma, less intellectual and social competence, and more symptoms of behavioral problems and emotional distress at study onset.

During the 5-year study, many personal situations changed. Children became adolescents with busy lives and increasing need for independence from family; families experienced divorces, job changes, and household moves; and in some cases the perceived benefit of study participation changed. As in any large group of families, stories emerged of dramatic problems, including alcoholism, parental psychopathology, legal difficulties, automobile crashes, serious childhood illness, and death of a family member. Observations made and reported anecdotally during the trial by study staff concurred with the findings that psychologically distressed families had more difficulty maintaining a commitment to study participation. The relationship between distress and study attrition has been previously documented in reports of an increased tendency for patients who leave a trial to have depression,² lower socioeconomic status,²¹ lower education level,¹ lower social support,^{22,23} and higher life stress scores.²⁴

Study dropout and erratic attendance were infrequent in CAMP and were associated with several disease-related and psychosocial variables but not with age and sex. Thus, although older children were more likely to miss some study visits, they were not at increased risk of dropping out. Both problem-attendance groups had psychological difficulty at baseline, including increased problem behavior scores and lower IQ, academic skills, and social competence. At the same time, the psychological characteristics of the 2 groups were slightly different. The dropout group demonstrated increased psychological distress in the form of higher self-

Table 2. Poisson Regression Model: Relationship between Missed Visits and Baseline Demographic, Disease, Psychological, and Family Variables

Variable	Exp(β) (95% confidence interval)	P value
Demographic		
Age	1.04 (1.00–1.07)	0.04
Sex (female = 1, male = 2)	0.95 (0.82–1.10)	0.47
Parent education (HSNC = 1, HSCM = 2)	1.53 (0.76–3.07)	0.23
Disease related		
Prebronchodilator FEV ₁ , % predicted	1.02 (1.01–1.02)	<0.001
Prebronchodilator FVC, % predicted	1.02 (1.01–1.03)	<0.001
Postbronchodilator FEV ₁ , % predicted	1.02 (1.02–1.03)	<0.001
Postbronchodilator FVC, % predicted	1.02 (1.02–1.03)	<0.001
Natural log of PC ₂₀	1.22 (1.15–1.30)	<0.001
Days of oral steroid use in last 6 mo	0.97 (0.95–0.99)	<0.001
Days of school missed for asthma	1.02 (1.01–1.03)	<0.001
Cognitive		
IQ	0.98 (0.98–0.99)	<0.001
Achievement skills	0.98 (0.98–0.99)	<0.001
Impulsivity	1.01 (1.00–1.01)	0.002
Attention–vigilance errors	1.00 (0.99–1.00)	0.21
Attention–distractibility errors	1.00 (0.99–1.00)	0.07
Emotions and behavior		
Anxiety symptoms	1.01 (1.00–1.01)	0.08
Depression symptoms	1.03 (1.02–1.04)	<0.001
Social competence	0.97 (0.96–0.97)	<0.001
Externalizing problems	1.04 (1.03–1.04)	<0.001
Internalizing problems	1.02 (1.01–1.03)	<0.001
Total behavior problems	1.03 (1.02–1.04)	<0.001
Family		
Cohesion	0.92 (0.88–0.96)	<0.001
Expressiveness	1.01 (0.97–1.06)	0.53
Conflict	1.10 (1.06–1.14)	<0.001
Social support	0.99 (0.98–0.99)	<0.001

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HSNC, high school not completed; HSCM, high school completed or more; PC₂₀, methacholine dose at which a 20% decrease in FEV₁ occurs.

reported depressive symptoms and family conflict. The erratic attendance group had more tendency toward reticence and withdrawal and reported that their families had less social support from friends and family. During study recruitment, family reports of social isolation and the presence of psychological difficulty may flag the need for increased scrutiny before randomization into the study.

Although the dropout and erratic attendance groups both had behavioral difficulty and diminished adaptive skills that may have interfered with study participation over time, differences between the 2 groups in disease severity may help explain why patients in the erratic attendance group did not drop out of the study. Dropout patients at baseline had milder asthma, reflected in higher pulmonary functions, than in the good attendance group. Diminished perception of benefit to this group may have contributed to declining participation motivation. In a 10-year study of rheumatoid arthritis, patients with increased joint flares were more likely to remain in the study than those with fewer flares, suggesting that study support through these episodes was an incentive for continued participation.¹ Patients with more problematic asthma

may likewise experience more benefit of study continuation. Patients who presented with mild illness and increased psychological difficulty at baseline may be identified as dropout risks during clinical trial recruitment.

Long-term clinical trials are essential to establishing the natural course of asthma and the longitudinal impact of treatments. Negative aspects of a trial, such as the demands of frequent visits and concerns about receiving placebo medication, discourage participation. Unfortunately, the challenges to recruitment and participation maintenance are increasing. Greater numbers of clinical trials, negative publicity about clinical trials in the popular media, emergence of alternative asthma treatments while patients are in a long-term trial, and increasing economic and time pressures on families may work against the successful completion of new trials. Other changes in health care practices, including decreased availability of medical insurance or increased out-of-pocket expense even with insurance, may further erode interest in clinical trial participation. Such phenomena increase the importance of adopting effective strategies to encourage participation.

Table 3. Baseline Demographic, Disease-Related, Cognitive, Emotion and Behavior, and Family Differences Among Attendance Groups*

Variable	Dropouts (n = 42)	Erratic attendance (n = 49)	Good attendance (n = 949)†
Demographic			
Age, y	9.18 ± 2.25	8.98 ± 1.96	8.93 ± 2.12
Sex, % male	62	59	60
Parent education, % high school graduates or more	98	100	98
Disease related			
Prebronchodilator FEV ₁ , % predicted	99.2 ± 16.1‡	94.1 ± 15.3	93.5 ± 14.1
Prebronchodilator FVC, % predicted	108.7 ± 14.8‡	104.3 ± 14.4	103.8 ± 12.9
Postbronchodilator FEV ₁ , % predicted	108.1 ± 13.2§	105.5 ± 11.8	102.6 ± 12.6
Postbronchodilator FVC, % predicted	111.2 ± 1.97‡	109.1 ± 13.2	106.1 ± 12.5
PC ₂₀ , geometric mean, mg/mL	1.54 ± 3.08	1.16 ± 4.55	1.09 ± 3.16
Days of oral steroid use in last 6 mo	1.90 ± 5.63	2.00 ± 3.76	2.90 ± 5.15
Days of school missed for asthma in last 6 mo	6.83 ± 9.55	7.04 ± 10.3	5.14 ± 6.69
Cognitive			
IQ¶	100.3 ± 14.3§	100.4 ± 13.5§	106.6 ± 15.3
Academic skills¶	99.5 ± 16.0‡	100.6 ± 14.4‡	105.0 ± 13.6
Impulsivity¶	99.1 ± 14.6	98.0 ± 14.7	97.1 ± 14.6
Attention–vigilance errors¶**	88.2 ± 18.0	93.8 ± 16.1	90.7 ± 16.1
Attention–distractibility errors¶**	88.8 ± 20.8	88.4 ± 18.0	88.8 ± 17.8
Emotions and behavior			
Anxiety symptoms¶	49.2 ± 11.1	47.6 ± 10.8	47.1 ± 11.4
Depression symptoms¶	8.73 ± 9.76‡	7.20 ± 7.10	6.61 ± 5.93
Social competence¶	47.4 ± 9.91‡	46.1 ± 9.06§	50.6 ± 8.75
Externalizing problems¶	53.2 ± 11.5‡	54.6 ± 10.3§	49.9 ± 9.35
Internalizing problems¶	54.3 ± 11.3	57.2 ± 8.44§	52.7 ± 10.2
Total behavior problems¶	54.4 ± 11.7	56.4 ± 9.03§	51.2 ± 10.1
Family			
Cohesion¶	7.44 ± 2.18	7.31 ± 1.82	7.71 ± 1.51
Expressiveness¶	6.51 ± 1.87	5.98 ± 1.69	6.44 ± 1.75
Conflict¶	3.66 ± 1.98‡	3.35 ± 1.90	3.03 ± 2.01
Social support¶	74.3 ± 17.1	73.0 ± 17.4‡	77.9 ± 14.5

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PC₂₀, methacholine dose at which a 20% decrease in FEV₁ occurs.

* Data are presented as mean ± SD unless otherwise indicated.

† Due to the death of 1 child during CAMP, all analyses are based on a total sample size of 1,040 children.

‡ $P < 0.05$.

§ $P < 0.01$ (compared with the good attendance group).

¶ Higher scores indicate more positive functioning.

|| Higher scores indicate increasing problems.

** Procedures and normative values for these tests were applicable only for children 6 years and older.

In summary, results from this study indicate that patients who have milder asthma, increased psychological distress, and lower adaptive skills may be at risk for study dropout despite early study commitment and that dropout risk is increased when their illness is mild and the perceived benefit of the study diminished. Tracking problem attendance, increasing telephone calls and mailings to patients, providing emotional support, offering convenient appointments, negotiating and contracting with patients for increased participation, and maintaining contact with the primary caregiver were reported to be effective intervention strategies for preventing attrition in long-term clinical trials^{1,3,25–27} and were used in this study. The inclusion of a patient education center, study

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