

Retention of asthmatic patients in a longitudinal clinical trial

Bruce G. Bender, PhD,^{a,d} David N. Ikié, PhD,^{b,c} Thomas DuHamel, PhD,^e
and David Tinkelman, MD^a Denver, Colo., and Seattle, Wash.

Background: Prevention of study patient attrition and assessment of its impact on outcome data are problems that receive little attention despite their obvious importance in asthma research.

Objective: The medical, demographic, and psychologic characteristics of asthmatic children and adults who dropped out of a yearlong medication trial were assessed to determine whether this group differed from those who completed the study, potentially introducing bias into the data set and interfering with completion of the study's objectives.

Methods: Profiles of 362 adult and pediatric asthmatic patient dropouts from the multicenter trial were contrasted with profiles of those who completed the study. Despite a 1-month prerandomization screening, 24% of patients failed to complete the trial for varied reasons, which largely included noncompliance and treatment dissatisfaction.

Results: Although attrition rates were equal among adults and children, dropout-completer differentiation was not. Adult completers did not differ from dropouts in any variables. However, pediatric dropouts were more likely than completers to be female (67% and 36%, $p = 0.008$) and to have more reactive airways (PD_{20} , 2.29 ± 1.32 and 5.2 ± 1.23 , $p = 0.05$), to have reduced scores on tests of intelligence (Full Scale IQ, 102.2 ± 2.6 and 112.5 ± 1.6 , $p = 0.002$) and problem solving (Wisconsin Card Sorting Test Error Scores, 39.8 ± 4.1 and 29.1 ± 2.0 , $p = 0.01$), and to have increased behavioral problems (Child Behavior Checklist Total Problem Score, 60.7 ± 2.5 and 53.6 ± 1.1 , $p = 0.003$).

Conclusion: These findings demonstrate the potential of patient attrition to bias outcome in clinical trials and underscore the necessity of: (1) preventing its occurrence, (2) correctly assessing its causes, and (3) determining its ultimate impact on study results. Strategies for each of these three tasks should be implemented at the study's initial planning stages. (*J Allergy Clin Immunol* 1997;99:197-203.)

Key words: Patient attrition, asthma trial

More than a matter of inconvenience, patient attrition in clinical trials can significantly compromise study objectives. In particular, attrition can lead to two shortcomings: (1) statistical power can be reduced to the point at which the study's major hypotheses cannot be fairly tested; and (2) bias can corrupt the data set, changing and distorting conclusions from those that might be drawn were the target population adequately represented. Most salient is the case in which dropout rates are higher in a single treatment group, either because of inadequate illness control or unacceptable side effects, with consequent improvement in outcome data in that group. In one such case, a disproportionate dropout rate in asthmatic children treated with placebo (45%) in

contrast to those treated with inhaled corticosteroid (5%) forced the investigators to alter the study's goals and design after 22 months of follow-up.¹

Although many studies of asthma treatment have occurred at a single site with durations of 3 months or less, the capacity of large, longitudinal, multicenter clinical trials to provide a wealth of information about the disease and its treatment is now increasingly recognized. That such studies are especially important to childhood asthma, in which both disease and treatment factors interact with developmental processes, is reflected in the National Heart, Lung, and Blood Institute's initiation of the Childhood Asthma Management Program,² a 5-year study of 1000 children with asthma. The potential for patient attrition expands, however, with the breadth and length of such studies. Although relatively few clinical trials have followed up patients with asthma for 12 months or longer, attrition rates in long-term pediatric studies have been reported at approximately 25%,³⁻⁵ despite prerandomization screenings lasting at least 2 weeks.

The opportunities for early departure of patients increase as the duration of involvement in the patients' lives lengthens. This is so not only because the window is widened within which symptom exacerbation and medication side effects can occur but also because the possi-

From ^athe Department of Pediatrics and ^bthe Division of Biostatistics, National Jewish Center for Immunology and Respiratory Medicine, Denver; ^cthe Department of Preventive Medicine and Biometrics and ^dthe Department of Psychiatry, University of Colorado Health Sciences Center, Denver; ^ethe Department of Psychiatry and Behavioral Science, University of Washington School of Medicine, Seattle.

Received for publication June 14, 1996; revised July 18, 1996; accepted for publication July 22, 1996.

Reprint requests: Bruce G. Bender, PhD, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St., Denver, CO 80206.

Copyright © 1997 by Mosby-Year Book, Inc.
0091-6749/97 \$5.00 + 0 1/1/76688

TABLE I. Psychometric tests

Name	Characteristic measured	Administered to	
		Children	Adults
Wechsler Intelligence Scale*	intelligence	X	X
Rey Verbal Learning Test	attention and memory	X	X
Woodcock-Johnson Psycho-educational Battery	achievement skills	X	
Wisconsin Card Sorting Test	problem solving	X	X
Child Behavior Checklist	behavior problems	X	
Profile of Mood States	mood problems		X

*The Wechsler Intelligence Scale for Children-Revised was administered to children, and the Wechsler Adult Intelligence Scale-Revised was administered to adults.

bility of complications in the lives of patients, which interfere with trial participation, is increased. Major life changes such as divorce, retirement, long-distance moves, or serious illness⁶⁻⁸ and psychologic dysfunction in patients⁸⁻¹⁰ have been associated with early departure from clinical trials.

The effective prevention of patient attrition can occur only after obtaining a more complete understanding of the factors that undermine patient completion of a clinical trial. This understanding remains incomplete in part because most clinical trial reports account only for the immediate circumstances surrounding patient dropout (e.g., failure to attend visits, medication noncompliance) and not those that might provide insight into the underlying causes, such as the characteristics of early dropout patients. Inadequate symptom control, a frequently cited reason for patient attrition, may not in fact adequately account for the complex reasons, many of which are psychologic, that lead study patients to leave the trial.

The medical, demographic, and psychologic characteristics of children and adults with asthma who dropped out of a yearlong medication trial are assessed here to determine whether this group differed from those who completed the study, potentially introducing bias into the data set and interfering with completion of the study's objectives. In addition, the implications of these results are examined with reference to the planning and execution of future, long-term clinical trials for patients with asthma.

METHODS

The study of 771 patients, ages 6 to 65 years, at a total of 31 centers in the United States was sponsored by the American Academy of Allergy and Immunology. Of these, 102 were children (ages, 6 to 17 years) and are referred to either as "children" or "pediatric patients." Results from this double-blind, placebo-controlled, randomized trial revealed that beclomethasone dipropionate and theophylline were equally effective in controlling asthma symptoms in children,⁵ that beclomethasone was somewhat more effective in adults,⁶ and that the two drugs were associated with differing side effects.^{5,6}

Patients who presented themselves for participation in the trial underwent a 1-month prerandomization screening during which they were required to attend several visits for documentation of their asthma symptoms. In an attempt to facilitate

patient compliance and retention, patients who failed to complete these screening visits did not continue past the study baseline. Despite this strategy, 24% of the patients who entered did not complete the study for various reasons, which most commonly included noncompliance or inadequate symptom control.^{5,6} Only 11 of the 31 participating centers had convenient access to a psychologist to conduct the psychologic testing protocol, designed to evaluate patient psychologic characteristics and drug-specific psychologic changes. With results from only those centers participating in the full protocol, data from 362 patients (102 children, 260 adults) are included in the dropout-versus-completers comparison.

Baseline evaluations

Patient evaluations at baseline included documentation of demographic (age, race, sex), physical (height, weight), and asthma-related variables (asthma severity rating, years of asthma, FEV₁, PD₂₀), and psychologic characteristics. The psychologic evaluations included tests of both cognitive abilities and behavior or mood changes. Some measures were common to both the pediatric and adult protocols, whereas others were different for the two groups. This was particularly necessary in the choice of instruments used to profile psychologic characteristics in the two groups; adults completed the Profile of Mood States, whereas children's behavior was evaluated by the parent-completed Child Behavior Checklist. The psychologic measures are listed in Table I.

Data analyses

The statistical analysis was performed on demographic variables and psychometric and behavioral subscales. All analyses were performed separately on the adult and pediatric study groups and on the subset of subjects that was present at baseline. Comparisons between those subjects who completed the study period (completers) and those who did not (dropouts) were performed by using chi square tests or independent sample *t* tests, depending on the level of measurement of the particular variable. Data in the various study groups are summarized by using means and standard errors for continuous variables and percentages for categorical variables. Two-way analysis of variance was used to determine whether the demographic, psychometric, and behavioral characteristics of the completers and dropouts were different between the two on-trial treatment groups, in which the analysis was performed separately for the adult and pediatric groups. In addition, stepwise multiple regression was used to assess the associations between dropout status and multiple predictor variables. All analyses were performed by using two-tailed tests of significance, and test results are reported with individual *p* values.

TABLE II. Reasons for patient dropout as recorded in study records

	Adult		Child		Total	
	No.	%	No.	%	No.	%
Treatment noncompliance	5	8	10	42	15	17
Treatment adverse effect	11	18	4	17	15	17
Treatment lack of benefit	8	13	2	8	10	12
Other medical condition	8	13	1	4	9	11
Moved from area	3	5	0	0	3	4
Administrative termination	14	23	5	21	19	22
Other reason	13	21	2	8	15	17

All results are for the group of 262 pediatric and adult study patients who participated in the psychologic protocol. Dropout rates and reasons for this group were no different than for the remaining group of patients ($n = 409$) at those 20 centers that did not administer the psychologic protocol.

TABLE III. Baseline demographic, physical, and disease-related characteristics of study patients (mean $\pm$ SEM or percent)

	Children			Adult		
	Completers	Dropouts	<i>p</i> Value	Completers	Dropouts	<i>p</i> Value
No.	78	24		198	62	
Age (yr)	11.5 $\pm$ 0.3	11.9 $\pm$ 0.6	0.52	34.7 $\pm$ 0.7	32.4 $\pm$ 1.5	0.15
Race (% white)	87%	75	0.15	90%	92%	0.64
Asthma severity (% moderate)	40%	58%	0.11	41%	37%	0.59
Weight (kg)	43.2 $\pm$ 1.6	48.5 $\pm$ 3.4	0.12	76.5 $\pm$ 1.3	78.5 $\pm$ 2.2	0.43
Height (cm)	148.1 $\pm$ 1.6	150.2 $\pm$ 3.1	0.55	170.7 $\pm$ 0.6	170.0 $\pm$ 1.2	0.51
Sex (% male)	64%	33%	0.0078	44%	44%	0.90
Years of asthma	7.5 $\pm$ 0.4	7.8 $\pm$ 0.8	0.81	17.4 $\pm$ 0.8	16.3 $\pm$ 1.6	0.51
FEV ₁ (prebronchodilator)	2.08 $\pm$ 0.8	2.03 $\pm$ 0.13	0.78	2.80 $\pm$ 0.05	2.95 $\pm$ 0.10	0.18
PD ₂₀ *	5.20 $\pm$ 1.23	2.30 $\pm$ 1.30	0.047	2.63 $\pm$ 1.14	3.50 $\pm$ 1.28	0.28

The demographic and disease-related characteristics of the 362 patients participating in the psychologic protocol and included in this report are slightly different from those of the remaining, nonparticipating group of 409 patients. Baseline measures indicate that, by relatively small margins, the group of nonparticipating pediatric patients are older, have less severe asthma, are less likely to be female, and have higher FEV₁. The nonparticipating adults have slightly lower weight and less reactive airways than the participating adults. Within the group of nonparticipating adults, dropout patient characteristics were somewhat different than in the group of participating adults. In this case dropouts were younger and were more likely to be nonwhite and female. In the group of nonparticipating pediatric patients, dropouts had more severe asthma, as shown by a higher proportion of moderate versus mild disease.

*PD₂₀ data were available for 240 completers and 77 dropouts (children and adults) and are presented as the geometric mean and geometric standard error.

RESULTS

Twenty-four percent of patients, including equal proportions of children and adults, failed to complete the study protocol. The observed reasons for patient dropout recorded in the study files, along with the percentage of total dropouts represented by each category, are indicated in Table II. Each dropout subject is represented in only one category. Noncompliance accounted for 15 of 86 (17%) early terminations. The remaining dropouts were associated with a variety of causes, including dissatisfaction with treatment effectiveness, undesirable side effects, or other illness. The most ambiguous categories, "administrative termination" and "other reason," included the greatest numbers of patients; although these may have included patients with growing reluctance to continue participation, the method for categorizing dropouts was incomplete and cannot fully account for the

reasons that one in four patients entered but failed to complete this study.

Demographic, physical, and disease-related patient characteristics at baseline are included in Table III. Among pediatric patients, dropouts were more often female; 16 of 44 female subjects (36%) dropped out, in contrast to eight of 58 male subjects (14%) ($p = 0.0078$). Pediatric dropouts also had more reactive airways as indicated by their lower PD₂₀ scores ($p = 0.052$). The two groups did not differ in age, race, height, weight, or other asthma variables. Adult dropouts did not differ significantly from completers with respect to any of the baseline variables.

For both groups, adults and children, analysis of variance results indicated that outcome variable differences were unaffected by treatment group; thus, all findings were the same regardless of whether patients were treated with beclomethasone or theophylline.

TABLE IV. Psychologic scores of pediatric subjects (mean $\pm$ SEM)

	Completers	Dropouts	p Value
No.	78	24	
Rey Auditory Verbal Learning Test	24.1 $\pm$ 0.6	22.9 $\pm$ 1.4	0.39
Woodcock-Johnson Psychoeducational Battery			
Math	515.6 $\pm$ 3.5	511.2 $\pm$ 6.8	0.55
Reading	513.0 $\pm$ 2.6	506.4 $\pm$ 7.4	0.29
Writing	519.8 $\pm$ 2.7	512.8 $\pm$ 6.7	0.26
Wisconsin Card Sorting Test			
Errors	29.1 $\pm$ 2.0	39.8 $\pm$ 4.1	0.01
Set failure	1.20 $\pm$ 0.15	1.73 $\pm$ 0.30	0.10
Wechsler Intelligence Scale for Children—Revised			
Full Scale IQ	112.5 $\pm$ 1.6	102.2 $\pm$ 2.6	0.002
Performance IQ	110.4 $\pm$ 1.5	102.5 $\pm$ 3.0	0.01
Verbal IQ	112.1 $\pm$ 1.7	101.7 $\pm$ 2.2	0.003
Children Behavior Checklist			
Withdrawn	58.2 $\pm$ 0.7	60.8 $\pm$ 1.8	0.08
Somatic complaints	58.9 $\pm$ 0.7	61.3 $\pm$ 1.7	0.12
Anxious/Depressed	58.6 $\pm$ 0.8	63.3 $\pm$ 1.8	0.007
Social problems	57.9 $\pm$ 0.5	62.8 $\pm$ 1.8	0.0007
Thought problems	58.0 $\pm$ 0.5	60.0 $\pm$ 1.6	0.12
Attention problems	57.4 $\pm$ 0.5	61.1 $\pm$ 1.6	0.004
Delinquent behavior	56.9 $\pm$ 0.5	61.1 $\pm$ 1.4	0.0006
Aggressive behavior	57.0 $\pm$ 0.6	63.5 $\pm$ 2.2	0.0002
Sex problems	58.5 $\pm$ 0.7	64.3 $\pm$ 2.5	0.003
Total externalizing	50.0 $\pm$ 1.1	57.4 $\pm$ 2.6	0.003
Total internalizing	52.8 $\pm$ 1.2	58.0 $\pm$ 2.5	0.04
Total problems	53.6 $\pm$ 1.1	60.7 $\pm$ 2.5	0.003

Baseline psychologic test scores revealed no differences between pediatric completers and dropouts in measures of academic achievement or memory skills. However, numerous significant differences distinguished the two groups of children. IQ scores (including verbal, performance, and full-scale IQs) were significantly lower in the dropout group (Table IV). In addition, the dropout group demonstrated more errors on the Wisconsin Card Sorting Test, a measure of problem solving and concept formation. The behavioral profiles, as reflected in the parent-completed Child Behavior Checklist, also included numerous differences. Although none of the mean scores was in a range that indicated a clinically serious psychologic disorder, significantly higher scores in the dropout group indicated more psychologic difficulty than in the group of completers. Dropouts demonstrated higher scores on scales assessing attention, depressed or anxious feelings, and inappropriate behavior. All three composite scores—externalizing, internalizing, and total problems—were elevated in the dropout group.

To determine whether those variables in which dropout-completer differences emerged were independent from each other, a stepwise logistic regression was conducted by using dropout-completer status as the dependent variable. The 10 independent variables included the two scales from the Wisconsin Card Sorting Test, three summary scores from the IQ battery, three

TABLE V. Psychologic scores of adult subjects (mean $\pm$ SEM)

	Completers	Dropouts	p Value
No.	198	61	
Profile of mood states			
Anger	48.5 $\pm$ 0.7	49.5 $\pm$ 1.4	0.48
Confusion	42.1 $\pm$ 0.5	42.9 $\pm$ 1.0	0.54
Depression	44.0 $\pm$ 0.5	45.4 $\pm$ 0.9	0.21
Fatigue	47.2 $\pm$ 0.6	46.7 $\pm$ 1.1	0.70
Tension	45.7 $\pm$ 0.6	47.8 $\pm$ 1.3	0.10
Vigor	54.3 $\pm$ 0.6	52.4 $\pm$ 1.2	0.16
Rey Auditory Verbal Learning Test	27.8 $\pm$ 0.4	26.6 $\pm$ 0.6	0.12
Wechsler Adult Intelligence Scale—Revised			
Full Scale IQ	107.7 $\pm$ 1.1	104.9 $\pm$ 1.8	0.20
Performance IQ	107.7 $\pm$ 1.0	104.5 $\pm$ 1.6	0.13
Verbal IQ	106.5 $\pm$ 1.1	104.6 $\pm$ 1.9	0.39
Wisconsin Card Sorting Test			
Errors	21.7 $\pm$ 1.2	23.4 $\pm$ 2.1	0.48
Set failure	0.78 $\pm$ 0.07	0.77 $\pm$ 0.13	0.94

summary scores from the Child Behavior Checklist, and the physiologic measures PD₂₀ and sex. Dropout status was significantly associated with female gender ($p = 0.012$), lower PD₂₀ ($p = 0.021$), and higher complete blood count externalizing score ($p = 0.038$). After accounting for these variables, the IQ and Wisconsin Card Sorting Test variables were not significant in predicting dropout.

Among adults, no significant dropout-completer differences were found in either the baseline cognitive or affective scores (Table V).

DISCUSSION

In this yearlong clinical trial of psychologic and disease-related differences in asthmatic patients treated with theophylline or beclomethasone, 24% of patients dropped out. All dropout-completer differences, whether significant or marginal, identified increased problems in the dropout group. Significant differences were found only for pediatric patients, among whom dropouts tended to be female, to have lower PD₂₀ scores, to demonstrate more emotional or behavioral problems, and to have lower IQ and problem concept formation skills. Girls with emotional or behavioral difficulties and more severe asthma are, as a group, at greatest risk for dropping out. No significant dropout-completer differences were identified in adult patients. Dropout-completer differences were unaffected by treatment condition. These findings have important implications. When attrition includes a disproportionate representation of patients with more severe disease, study results may be biased. Specifically, generalizability of results to patients with more severe asthma must be approached cautiously. Increased psychologic difficulty among pediatric dropouts may not distort disease-related findings but does potentially bias psychologic out-

come variables and indicates the need to monitor psychologic status of children with asthma included in clinical trials.

The causes of dropout identified in many trial reports may not accurately identify the actual causes of attrition. Patients sometimes do not state the real reasons for dropping out, and staff interpretation of dropout causes may vary greatly in accuracy. Patients are frequently embarrassed by their failure to complete a study commitment and consequently may provide a reason for leaving that will justify their decision. As found in other pediatric asthma studies, reports from this investigation indicated that a majority of dropout patients experienced inadequate symptom control or unacceptable side effects. Because patients are frequently queried about these outcomes, and can by implication be led to believe that these are acceptable reasons for study rejection, such reporting can be the self-fulfilling product of the study method rather than an accurate assessment of patient dissatisfaction. Patients may be motivated to hide their actual reasons for leaving. For example, they may not wish staff to know about personal problems that contributed to their departure. Some patients slip away without explanation; staff interpretation of their departure sometimes involves unacceptable guesswork. The finding here of decreased life skills in pediatric patients with asthma who have dropped out of clinical trials suggests that psychologic factors were a more significant factor in study attrition than the recorded reasons for dropout would indicate.

To increase accurate assessment of the causes of patient attrition, the following recommendations are offered. First, attempt a postdeparture interview. This approach was used in a Macular Photocoagulation Study ancillary study, in which dropout patients were randomly selected from the 11 centers and interviewed by telephone with a standardized questionnaire.⁸ Unfortunately, the use of clinic coordinators rather than interviewers from outside the clinic may have precluded full disclosure of the reasons for study departure, particularly if patients felt any reluctance to complain about study experiences. For maximum accuracy, such interviews should be conducted by individuals not employed at the local study site and unknown to the patient. A long-distance phone call from another city can encourage greater disclosure. Second, use baseline psychologic screening data to characterize patients. Such information provides insight without concern about accuracy of the patient's or staff's exit assessment. Third, include a dropout category such as "reason unknown" rather than encourage guesswork. Fourth, never consider a patient completely gone. Even if patients choose to drop out of the blinded treatment protocol, they may be receptive to later contact, perhaps even including one or more follow-up visits to obtain a final set of measurements. These data cannot be included in treatment comparisons but can be useful in determining how these patients fared and how their departure may have altered study outcomes.

Preventing patient attrition

Although patient attrition must be tolerated to a certain degree, and managed statistically after the fact, the best approach is to prevent attrition from occurring, or at least to minimize it. That patient dropout rates vary across clinical trials partially reflects differences in the patient population sampled, in the treatments used, and in the length of the study. However, it also likely reflects between-study differences in efforts directed at patient retention.

The prevention of patient attrition requires considerable planning before initiation of the trial and continual effort throughout the trial. Further, for studies of children with asthma, the task of planning a program of attrition prevention may necessarily be different than for studies of adults with asthma. The association between psychologic difficulty and dropout suggests that in any pediatric asthma trial, investigators may be advised to include a psychologic screening of patients before treatment randomization. On the basis of the finding in this study of large and consistent dropout-completer differences on the Child Behavior Checklist, the use of parent-completed psychologic questionnaires may be sufficient without inclusion of more costly, individualized psychologic testing.

The decision to include psychologic screening of pediatric patients requires a second decision regarding the application of resulting information. Data from the psychologic screening may be used either to exclude patients from the study or to identify those children and families requiring extra contact and support during the trial. If the study objectives are strictly disease-related and do not include evaluation of psychologic outcomes, the exclusion of patients with decreased life-adaptation skills is unlikely to bias outcomes. However, when psychosocial outcomes including quality of life are to be evaluated, loading the study with higher functioning patients potentially biases outcomes and hinders the study's generalizability. In this case it may be more appropriate to attempt to understand which patients are at dropout risk and build into the study structure more effective means of tracking dropout risk indicators, strengthening study-patient relationships, and preventing dropout.

An effective dropout-prevention program must include numerous components. On the basis of results from this and other investigations of patient attrition in asthma trials, dropout-prevention efforts can be organized into four areas.

Prevention. The inclusion/exclusion criteria for study entry frequently include the requirement that patients demonstrate the willingness and ability to follow study protocol. This requirement is significant because it formally asserts that patients must not simply meet disease criteria; they must also be capable of participating in a clinical trial that may include multiple visits within narrowly defined time windows, undergoing procedures that are not always enjoyable, and conscientiously following a prescribed regimen of drug ingestion, pulmo-

nary measurements, and diary card recording. Many well-intentioned patients are not able to adhere adequately to the clinical trial regimen. For this reason, clinical trials frequently include a screening period lasting from several weeks to several months. This "run-in" or "shake-down" process allows staff not only to evaluate their disease but also to determine whether patients can adhere to trial requirements. Patients who fail to attend appointments, submit incomplete or poorly completed diary cards, resist procedures, or appear otherwise uncooperative are usually poor candidates for an extended trial. Probstfield¹⁰ concluded that "sensitive staff" with a "keen sense for those potential participants who demonstrate less than optimal motivation during screening and recruitment" are essential to the trial's success (p. S51).

Maintenance. Screening patients for dropout risk before randomization into the study will help to exclude some poor trial candidates but is not by itself sufficient to prevent attrition. Once enrolled in the study, patients must continue to experience satisfaction with their participation. Most essential is the sense that clinic staff are warm, friendly, and personally interested in the patients and take ample time with them during visits.^{8,11} Other procedures used to enhance satisfaction and prevent dropout include providing financial compensation, assisting with transportation, offering convenient physical access and appointment times, sending newsletters, providing written or telephone contact between visits, remembering patients on special occasions (e.g., Christmas, birthdays), and maintaining contact with the primary care physician.^{12,13} For pediatric patients, giving the child small gifts during visits and offering special activities such as parties or trips to concerts or sports events can increase positive attitudes toward long clinical trials.

Intervention. Participants in a clinical trial who are at risk for dropping out typically demonstrate behavior patterns that serve as "red flags," forecasting their possible departure. A few patients may announce to study staff that they have reached a point at which they no longer want to participate in the trial. However, it is much more likely that patients will demonstrate their intention to drop out through actions rather than words. Patients at risk for early departure from the trial may begin to miss appointments, fail to return phone calls, submit incomplete or poorly filled-out diary cards, complain about particular procedures, claim that they are very busy and do not have time to schedule a routine appointment, or simply demonstrate a general lack of enthusiasm and interest in the study. Such behaviors should alert staff to intensify their efforts to reach out to these patients, increase communication, sympathize with problems, respond to complaints, and demonstrate sincere interest.¹¹ When patient counseling reveals an unwillingness or inability to continue with the full protocol, it may be necessary to negotiate a modified protocol to include those procedures essential to the study and within the patient's motivational reach.¹⁰ This

latter step may involve changing the patient's medication regimen; decreasing the patient's workload by means of, for example, eliminating daily diary cards or decreasing the number of required blood draws; and reducing the frequency of study visits. An effective dropout intervention strategy must include a system for early identification of at-risk behaviors and regularly scheduled staff meetings at which problem cases and potential solutions are discussed.

Recovery. Although "early departure" patients may be considered by many investigators to be permanently lost to follow-up, it is sometimes possible to re-establish contact with dropouts.¹⁴ The reasons for dropout are varied and frequently occur because of major life changes or crises such as divorce, job change, or retirement.⁸ As patients adapt to or resolve such changes, interest in completing the trial may return. Probstfield et al.¹⁵ have proposed a dropout recovery program including regular attempts to re-establish contact with the patient, negotiate return to the study, and offer positive reinforcements. These procedures included a centralized formula for identifying patients who have dropped out or who are close to dropping out, on the basis of visit attendance, level of dietary adherence, and level of medication adherence. Patients identified in this manner were then targeted by a program-wide series of steps that began with a physician-initiated contact with the patient during which concern about the patient's lagging participation in the trial was expressed. Whenever possible, face-to-face meetings were then scheduled, with ongoing counseling addressing patient concerns or complaints and, when necessary, renegotiation of the participant's responsibilities in the trial. It is noted, however, that such efforts must not be coercive or compromise patient confidentiality.¹³

In summary, the problem of patient attrition in clinical trials requires three different task objectives that include preventing its occurrence, correctly assessing its causes, and determining its ultimate impact on outcome data. These tasks must be anticipated before initiation of the trial, with strategies addressing each put into effect from the onset of the investigation.

REFERENCES

1. Waalkens HJ, van Essen-Zandvliet EEM, Gerritsen J, Duiverman EJ, Kerrebijn KF, Knol K, et al. The effect of an inhaled corticosteroid (budesonide) on exercise-induced asthma in children. *Eur Respir J* 1993a;6:652-6.
2. Cherniack RM. Childhood Asthma Management Program (CAMP): Clinical Trial. Presented at the Annual Meeting of the American Thoracic Society, New Orleans, May, 1996.
3. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF, et al. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis* 1992;146:547-54.
4. Waalkens HJ, van Essen-Zandvliet EE, Hughes MD, Gerritsen J, Duiverman EJ, Knol K, et al. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. *Am Rev Respir Dis* 1993b;148:1252-7.
5. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol be-

- clomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64-77.
6. Collins JF, Bingham SF, Williford WO, Weiss DG. Who drops out of clinical trials-The VA Cooperative Study experience [abstract]. *Controlled Clin Trials* 1981;2:78.
 7. Cramer JA, Collins JF, Mattson RH. Can categorization of patient background problems be used to determine early termination in a clinical trial? *Controlled Clin Trials* 1988;9:47-63.
 8. Orr PR, Blackhurst DW, Hawkins BS. Patient and clinic factors predictive of missed visits and inactive status in a multicenter clinical trial. *Controlled Clin Trials* 1992;13:40-9.
 9. Clancy J, Noyes R, Anderson DJ. Anxiety disorder: neurotic behavior in research subjects. *Compr Psychiatry* 1983;24:508-13.
 10. Probstfield JL. Adherence and its management in clinical trials: implications for arthritis treatment trials. *Arthritis Care Res* 1989; 2:S48-S57.
 11. Goldman AI, Holcomb R, Perry HM, Schnaper HW, Fitz AE, Frohlich ED. Can dropout and other noncompliance be minimized in a clinical trial? *Controlled Clin Trials* 1982;3:75-89.
 12. Bell RL, Curb JD, Friedman LM, McIntyre KM, Payton-Ross C, The BHAT Research Group. Enhancement of visit adherence in the national beta-blocker heart attack trial. *Controlled Clin Trials* 1985;6:89-101.
 13. Meinert CL, Tonascia S. Clinical trials. Design, conduct, and analysis. New York: Oxford University Press, 1986.
 14. Robinson A, Bender BG, Linden MG, Salbenblatt JA. Sex chromosome aneuploidy. The Denver Prospective Study. In: Evans JA, Hamerton JL, Robinson A, editors. Children and young adults with sex chromosome aneuploidy: follow-up, clinical, and molecular studies. *Birth Defects* 1990;26:59-115.
 15. Probstfield JL, Russell ML, Henske JC, Reardon RJ, Insull W. Successful program for recovery of dropouts to a clinical trial. *Am J Med* 1986;80:777-84.

Bound volumes available to subscribers

Bound volumes of The Journal of Allergy and Clinical Immunology are available to subscribers (only) for the 1997 issues from the Publisher, at a cost of \$88.50 for domestic, \$116.10 for Canadian, and \$108.50 for international subscribers for Vol. 99 (January-June) and Vol. 100 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby-Year Book, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318; phone 1 (800) 453-4351 or (314) 453-4351.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.