

Clinical trials: Are these your patients?

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Many clinicians base their treatment choices on trial outcomes. To determine if clinical trial results apply to the general patient population, several factors need to be considered. The exclusion and inclusion of patients in a trial may present selection bias. Adherence to therapy in trials often varies widely compared with adherence seen in clinical practice. Endpoints used in trials compared with endpoints used in practice are not always comparable. The performance and publication of clinical trials can be affected by investigator or publication bias. Finally, reporting of data as mean values may not always relate to the outcome in individual patients. By understanding some of these issues, clinicians can begin to better relate trial results with patient treatment options. (J Allergy Clin Immunol 2003;112:S107-11.)

Key words: Clinical trials, clinical endpoints, surrogate markers, selection bias

One of the key differentiating factors between real world practice and clinical trials are the patients. Many clinicians base their treatment choices on trial outcomes, but do these results offer an accurate picture of efficacy in the general patient population? To adequately answer this question, several factors need to be considered. Exclusion and inclusion criteria are designed so influencing factors can be eliminated; however, the very process of exclusion often creates selection bias. Also, numerous physician and patient barriers preclude participation in populations that, by definition, meet the inclusion and exclusion criteria. Adherence to therapy in trials often varies widely compared with adherence seen in clinical practice; this can naturally affect analysis of trial results. Endpoints used in trials compared with endpoints used in practice are not always comparable. The performance and publication of clinical trials can be affected by investigator or publication bias. Finally, reporting of data as mean values may not always relate to the response of individual patients. By understanding some of these issues, clinicians can begin to better relate trial results with patient treatment options. Also, this paper will explore each of these factors in the hopes of introducing issues that can be considered in the design of future clinical trials.

Abbreviations used

AQLQ: Asthma Quality of Life Questionnaire
FEV₁: Forced expiratory volume at one second
PEFR_{AM}: Peak expiratory flow rate in the AM
RCT: Randomized controlled trial

RECRUITMENT OF PATIENTS: IS THERE SELECTION BIAS?

The first step in differentiating between the patients you see in clinical practice and those studied during clinical trials is understanding the selection process of that study. In any clinical trial, numerous barriers to patient enrollment exist. Because of these barriers, a common criticism of randomized trials is that the entry criteria may choose a subgroup of patients who do not represent the population as a whole.

Barriers to participation in controlled trials

A systematic review of three bibliographic databases from 1986 to 1996 identified 78 papers reporting barriers to recruitment of clinicians and patients to randomized controlled trials (RCTs).¹ According to the review, clinicians face many barriers including time constraints from clinical practice and lack of staff and training, especially in small research settings.¹ Many physicians also worry about the impact on the doctor-patient relationship; the ethics of treating a patient conventionally or recruiting the patient for a research trial was of concern to many physicians.¹ Additional physician concerns for patients included fear of unknown drug side effects, reluctance to recruit more severely ill patients, and a feeling of responsibility if the patient receives placebo rather than the study drug.¹ Because of the possibility of adverse events or placebo treatments, some physicians have a difficult time providing informed consent to patients.¹ Some physicians cited more personal barriers, including a loss of professional autonomy or individual decision-making; the loss of the ability to individualize patient care; and the burden of being accountable to a third party, such as a pharmaceutical company.¹ Finally, some physicians were deterred from participating in clinical trials because of the lack of rewards, especially the lack of benefit to the physician or the institution.¹

The review identified many patient barriers to recruitment as well, including additional demands on their time over and above what would normally be required during standard care, such as extra office visits, frequent blood draws, and additional travel. Patient preferences also played a key role; many patients like their current treatment and do not want to change. Other barriers centered on the experimental nature of the study. Some patients

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TABLE I. Reasons why patients were not qualified for admission into asthma and rhinitis studies

Asthma studies	Rhinitis studies
Patient's smoking history	Rhinitis that is too well controlled
Exclusion of asthma medications that patients are unwilling to stop	Patients are happy with current medications and do not want to change
Current asthma therapy is so effective patients do not want to participate in clinical trials	Patients underestimate level and severity of symptoms
Exclusion of medications for other medical conditions	Immunotherapy dose is not stable for three months
Too much or too little rescue medication use	Presence of concomitant medical diseases
Patient's FEV ₁ is either too high or too low	Presence of concomitant allergic diseases such as asthma or sinusitis
Patients do not want to commit the time away from work or school	Exclusion of current medications
Patients will not go on placebo during washout phase because of concerns about increased asthma	Patient's smoking history

had strong concerns about receiving ‘experimental’ therapy. Others did not want to take a risk of receiving placebo rather than the treatment drug. Finally, many were adverse to the entire randomization process.¹ Worry caused by uncertainty was another patient barrier; the unproven effect of the experimental treatment and fear of the unknown were two commonly cited concerns.¹ Finally, as with physicians, many patients refused to enter a study because of issues surrounding informed consent.¹ Some patients simply required more information on the study drug than was available. Some could not understand the consent form because of poor readability. Others were not given enough time to consider the information.¹

The authors of the review concluded that there are many potential barriers to recruitment in clinical trials, both from the clinicians’ perspective and the patients’ perspective. This may lead to the selection of a subgroup of patients in studies. To rectify this bias, trials should be as simple and straightforward as possible. Furthermore, only clinics with dedicated research staff should perform clinical trials. Improvements in the designs of future studies may help overcome these barriers to recruitment.¹

The recruitment process in clinical trials and its effect on trial results

Gross et al² conducted a review of published RCTs to determine how information about their study sample assembly was reported and to describe the proportion of potential study participants who were actually enrolled. Of 172 RCTs published in four high-impact medical journals between April 1999 and April 2000, 90 (52%) reported the number of persons who were evaluated by the investigators for eligibility, and 74 (43%) reported the number of persons who were actually eligible for participation.² Of the studies that reported quantitative recruitment information, the median proportion of screened persons who were eligible for participation was 65% (interquartile range, 41%-82%) and the median proportion of eligible persons who enrolled was 93% (interquartile range, 79%-100%). Some trials reportedly enrolled every person screened for eligibility; others screened as many as 68 people for each person finally enrolled. The authors of the review concluded that many

RCTs published in major medical journals do not always identify how many screened subjects finally are randomized. If only a small percentage are randomized, it is difficult for readers to gauge the extent to which participants may represent a highly selected subgroup.²

Selection of clinical trial patients

Some investigators have a “stable” of patients with specific diseases who enter into many trials, resulting in the selection of a type of patient who “fits” into various clinical studies. For example, patients who fail initial screening may be manipulated to fit the study criteria (eg, “come back early in the morning when the weather is colder so your forced expiratory volume at one second [FEV₁] will be lower”). Also, insufficient payments to the physician may allow for selection bias (eg, “if my patient goes in this trial I am paid X dollars, but I lose 2X dollars from potential clinic income received during the length of this trial”).

An informal survey of experienced clinical research coordinators from my research department at Asthma and Allergy Associates in Colorado Springs, Colorado looked at the percent age of patients who actually qualify for clinical studies. We also looked at the reasons certain patients did not qualify. We found that only 15% of patients from clinical practice qualified for asthma clinical trials, and only 30% qualified for rhinitis trials. Reasons for not qualifying for asthma studies included patient’s smoking history; exclusion of asthma medications that patients are unwilling to stop; current asthma therapy is so effective patients do not want to participate in clinical trials; exclusion of medications for other medical conditions; too much or too little rescue medication use; patient’s FEV₁ is either too high or too low; patients do not want to commit the time away from work or school; and patients will not go on placebo during washout phase because of concerns about increased asthma (Table I). Reasons for not qualifying for rhinitis studies include rhinitis that is too well-controlled; patients are happy with current medications and do not want to change; patients underestimate level and severity of symptoms; immunotherapy dose is not stable for three months; presence of concomitant medical diseases; pres-

ence of concomitant allergic diseases such as asthma or sinusitis; exclusion of current medications; and a patient's smoking history (Table I).

The result of this selection process is that patients who in a normal clinical setting would qualify for treatment are excluded from study. This introduces a selection bias into the trial, leading to the inclusion of a small subgroup of patients that do not represent the general patient population.

ADHERENCE TO THERAPY IN TRIALS VS CLINICAL PRACTICE; HOW DOES THIS AFFECT OUR ANALYSIS OF TRIAL RESULTS?

Data suggest that adherence in trials is much better than in clinical practice. Therefore, treatment results seen in trials may vary widely from efficacy noted in clinical practice. Most double-blind, placebo-controlled trials only follow patients for a short period of time. Although this may provide accurate treatment results for studies of drugs that are normally only administered for a week or two at a time, it may not be sufficient for chronic disease treatment.

Jónassen et al³ studied drug adherence in a double-blind, randomized placebo-controlled trial of 122 children aged 7 to 16 years with mild asthma receiving long-term budesonide treatment. Patients received either 100 µg or 200 µg daily of inhaled budesonide or placebo for 27 months.³ Adherence was assessed by counting the number of remaining doses of medication in the inhaler at three months, and then every six months after that.³ They found that, although adherence to inhaled budesonide was high in the first few months of trials, it dropped after 3 months of treatment. At the 3-month interval, adherence was 75% but it dropped to 53% at 9 months; it stayed around 50% for the rest of the trial.³ The authors suggested that the first three months of treatment reflect typical clinical trial results, and the latter months reflect actual clinical practice.³

A randomized, double-blind, placebo-controlled study of 681 nonsmoking, asthmatic men and women looked at treatment efficacy for an initial 12-week study period.^{4,5} Patients were 15 to 85 years of age, with chronic, persistent daytime symptoms, FEV₁ 50% to 85% of predicted, and β-agonist reversibility of at least 15%. Montelukast was given as one 10-mg tablet daily in the evening, versus matching placebo. Inhaled β-agonist was permitted as needed.^{4,5} After the initial 12-week period, some patients remained in an open-label extension with beclomethasone as the active control for as long as 140 weeks.^{4,5}

During the initial 12-week period, patients receiving montelukast showed significant improvement in lung function, as evidenced by FEV₁, compared with patients receiving placebo.^{4,5} During the open-label extension, the improvement in FEV₁ was maintained in adult patients during continuous once-daily evening administration.^{4,5} The initial improvement in FEV₁ with inhaled beclomethasone in the open-label trial was better than montelukast, but after prolonged therapy, the FEV₁ results for the two groups were the same. Because we

would not expect beclomethasone to lose its efficacy, the most likely explanation is that these patients did not adhere to their inhaled steroid therapy and, therefore, the mean FEV₁ values declined with time. The montelukast FEV₁ values maintained their levels throughout the study, suggesting that there was good compliance with this oral therapy. However, it is important to note that the number of patients in the extension, particularly in the beclomethasone arm, is small. The number of patients in the extension study ranged from 269 at week 19 to 13 at week 140 for montelukast and 77 at week 19 to 3 at week 140 for beclomethasone.^{4,5}

Because short-term randomized, placebo-controlled clinical trials do not always accurately represent a drug's effectiveness over the long term, it may be helpful to have "real-world" studies follow standard clinical trials. This would most likely provide clinicians with a better picture of the efficacy of a drug, and could help control for the adherence differences in clinical studies versus clinical practice.

ENDPOINTS USED IN TRIALS VS ENDPOINTS USED IN PRACTICE; ARE THEY COMPARABLE?

The ideal surrogate endpoint should be reproducible, clinically available, easily quantifiable, and show a dose-response effect.⁶ Accurate surrogate endpoints should clearly indicate what the objective of treatment was in the patients studied.⁶ They should also adequately reflect the treatment goal or goals.⁶ Furthermore, overreliance on a single surrogate endpoint as a measure of therapeutic success may reflect a narrow clinical perspective.⁶ In asthma studies, it is important to determine if currently used endpoints—FEV₁, peak expiratory flow rate in the AM (PEFR_{AM}), Asthma Quality of Life Questionnaire (AQLQ)—do, in fact, meet these criteria. For rhinitis studies, researchers need to evaluate if total nasal symptoms score is truly an effective marker for therapeutic success.⁶

It is difficult to extrapolate clinical study endpoints into clinical practice. Because researchers in clinical trials and clinicians in clinical practice may be evaluating very different endpoints, the perception of treatment efficacy can vary widely. The key difference seems to lie with the fact that clinical trials base results on mean data, whereas clinicians base results on physician judgment (Table II).

Zhang et al⁷ assessed several endpoints of asthma control to select a combination of variables measured at baseline or early in asthma therapy predictive of long-term clinical response. In two clinical trials with mild-to-moderate asthma patients (n = 1576) receiving montelukast, inhaled beclomethasone, or placebo, FEV₁, daily symptom score, β-agonist use, and PEFR_{AM} were recorded during baseline and at the end of 12 weeks of treatment.⁷ They found large within-patient variability, and no more than moderate correlation between changes in: FEV₁ and PEFR_{AM}; daily symptom score and FEV₁;

TABLE II. Extrapolating clinical study endpoints into real-world practice

Clinical studies	Real-world practice
Mean PEF _{AM} averaged over 1 mo	Level of symptoms since the last visit: peaks, valleys, trends
AQLQ	Is daily controller therapy preventing exacerbations?
Mean monthly PEF _R	Level of asthma control: β -agonist use, $\pm$ PEF _R , ability to exercise, nocturnal symptoms
Mean monthly puffs of β -agonist	Individual issues: not taking medications when feeling well, poor inhaler technique, steroid phobia, overuse of rescue inhaler, etc
Results based on mean data	Decisions based on physician judgment

and daily symptom score and β -agonist use.⁷ The overall predictive values for FEV₁ and daily symptom score were 70% to 80%.⁷ Therefore, they concluded that multiple measurements over time are needed to establish a more complete patient response profile to treatment. Because asthma endpoints have a complex relationship among themselves, it is difficult to estimate long-term response to treatment using common, surrogate clinical markers of asthma control.⁷

ARE CLINICAL TRIALS BIASED?

An important factor that can call results into question is study bias. Whether intentional or unintentional, bias introduced into a study can significantly skew results. More than 20 years of clinical studies were reviewed for potential financial conflict of interest.⁸ A total of 1664 articles were reviewed; 37 contained criteria for inclusion in the analysis. The reviewers found that industry-sponsored trials were more likely to report positive results for the treatment being studied (OR = 3.60).⁸ Also, industry sponsorship was associated with restrictions on publication.⁸ They concluded that financial relationships with industry can influence biomedical research and publication.⁸

In addition to financial bias, some evidence exists that clinical trial results also bias publication. Clinical trials that show positive results are three to nine times more likely to be published than trials that do not show positive results.⁹⁻¹¹ Negative trial results take twice as long to publish than positive results; they are also more likely to never be published at all.⁹⁻¹¹

Many trials are also under-reported. Less than one third of clinical trials approved by an ethics committee in Spain had been reported in peer-reviewed journals three years later.¹² Because of these findings, *The Lancet* has suggested that independent review boards should follow the results of trials they review to make sure that even negative results get published.¹²

The results received in trials can also be biased depending on sponsorship. Stelfox et al¹³ reviewed 70 articles on calcium channel blocker therapy. They found that 96% of authors of articles supporting these products had financial relationships with the manufacturers; 60% of the authors of “neutral” articles had financial ties; and 37% of authors of critical articles had financial ties. Only 2 of the 70 articles disclosed the financial relationship.¹³ Another summary of 1140 clinical trials showed that

industry-sponsored studies are 3.6 times more likely to give favorable results.¹⁴ This suggests that when financial relationships are present, authors are more likely to favor the sponsor’s product. In addition, authors admit to suppression of unfavorable results.¹⁴

Occasionally, bias can occur in well-designed studies. Unintentional loss of blinding, or subtle and unconscious cues may affect the results. For example, research staff may observe a treatment effect in some patients and not others. This may result in a more positive attitude towards those study patients compared with the rest of the group. Also, patients may compare notes during clinic visits. One patient may notice a treatment effect or side effect that may influence their perception of their own treatment response, as well as their diary card entries and possibly may influence the perception of other research patients who are in the research facility at the same time. If any of these occur, blinding is lost and the quality of the results should be questioned.

**REPORTING OF DATA AS MEAN VALUES;
HOW DOES THIS MEASUREMENT RELATE
TO INDIVIDUAL PATIENTS?**

Mean FEV₁ data are usually the primary endpoint in asthma studies. Patients have different degrees of response to treatment; mean values may reflect the expected improvement to be seen in all patients. However, it is important to determine if this measure actually relates to individual patients. A wide range of data may indicate that the study actually consisted of several subgroups of patients, some of whom responded well to treatment, some of whom did not.

To evaluate these differential responses, a randomized, placebo-controlled study in adults and adolescents 15 years of age and older with asthma evaluated the response to montelukast, beclomethasone, or placebo. After treatment, patients receiving beclomethasone showed statistically significant mean improvement in FEV₁ compared with montelukast ($P < .001$). The mean improvements in FEV₁ were 5% for placebo, 11% for montelukast ($P < .001$ vs placebo), and 15% for beclomethasone ($P < .001$ vs placebo).

To further explore the differences between inhaled beclomethasone and montelukast, the distribution of response for FEV₁ was examined in a previously conducted study. The frequency plot of percent change of FEV₁ from baseline demonstrates a bell-shaped curve for both

montelukast and beclomethasone.¹⁵ The distribution showed no separation between responding and nonresponding populations.¹⁵ Rather, a range of responses exists for both treatments. It appears that the differences in mean response between montelukast and inhaled beclomethasone were largely driven by a subset of patients in the inhaled beclomethasone group who had a large response for this endpoint.¹⁵ Because this range of response has been shown for an inhaled steroid and a leukotriene receptor antagonist, we might expect to see similar ranges of response for all treatments we use for asthma and allergies. Future studies should include the distribution of response to the primary endpoint, such as FEV₁.

CONCLUSIONS

For the various reasons cited in this review, clinical trial results may not adequately reflect treatment outcomes in the general population. Whether from selection bias, adherence differences, or inappropriate surrogate endpoints, results can often be misleading. This can be misleading for both the physician and patient. Therefore, it is important to understand the issues that differentiate the trial outcomes from real-world results.

Numerous barriers to recruitment in clinical trials can lead to the selection of a subgroup of patients in studies. Therefore, trials should be as simple and straightforward as possible and only be performed at clinics with dedicated research staff. Improvements in the designs of future studies may help overcome these barriers to recruitment. Obtaining information on the number of screened subjects who were finally randomized is also important. If only a small percentage is randomized, participants may represent a highly selected subgroup. In addition, because short-term trials do not always represent a drug's effectiveness over the long term, it may be helpful to have "real-world" studies follow standard clinical trials. This would most likely provide clinicians with a better picture of the efficacy of a drug, and could help control for the adherence differences in clinical studies versus clinical practice. Using surrogate endpoints that are reproducible, clinically available, easily quantifiable, and show a dose-response effect is essential in any trial. Publication bias can present a number of problems. Industry-sponsored trials are more likely to report positive results for the treatment being studied and are often associated with greater restrictions on publication. Also, clinical trials that show positive results are more likely to be published than trials that do not show positive results. In general, when financial relationships are present, authors are more likely to favor the

sponsor's product. Finally, although mean FEV₁ data are usually the primary endpoint in asthma studies, it is important to determine if this measure actually relates to individual patients.

By considering and evaluating these issues, clinicians can better judge the ability of a drug to effectively treat patients seen during day-to-day clinical practice. The ultimate goal of any drug trial is to provide proof that it can improve patient outcomes; therefore, better designed trials that incorporate these concepts will clearly benefit both the clinician and patient.

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