Patient Recruitment: US Perspective

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ABSTRACT. There are many ethical, legal, economic, scientific, and practical problems associated with conducting drug trials in children. The single most difficult is subject identification and enrollment (ie, recruitment). This article reviews various aspects of the recruitment process and proposes potential solutions to recruitment problems. ***Pediatrics*** **1999;104:619–622;** ***pediatric, drug trials, subjects, recruitment, enrollment.***

ABBREVIATIONS. FDA, US Food and Drug Administration; IRB, institutional review board.

There are many ethical/moral, legal, economic, scientific, and practical problems with conducting clinical trials.[1–13] However, the hypothesis of this review is that recruitment is the single most difficult problem to overcome to conduct pediatric trials; it is the most common cause of delays, increased costs, and failure to complete drug trials.

The recruitment process can be separated into a number of concrete steps, each with its own unique problems, including 1) identifying eligible patient population(s); 2) explaining the study; 3) obtaining true informed consent; 4) maintaining ethical standards; 5) recruiting adequate, representative sample; 6) retaining subjects until study completion; and g) minimizing the risk/benefit ratio.

Inclusion/exclusion criteria often determine how easy it is to identify an appropriate patient population. Sponsors, the Food and Drug Administration (FDA), institutional review boards (IRBs), and investigators must work together to identify only those inclusion/exclusion criteria that are scientifically meaningful and necessary. Use of overly restrictive criteria can limit the ability to extrapolate results to all appropriate patient populations. Criteria should not exclude large numbers of patients who are likely to eventually receive the therapy. Subjects should not be excluded simply because they are medically more complicated, slightly more likely to experience toxicity, or less likely to respond, as long as simple, scientifically designed rational dosage adjustments are likely to protect such subjects. Careful design of rational inclusion/exclusion criteria can improve subject recruitment.

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Access to patients differs among investigators, collaborators, and treating physicians. Access is not always proportional to the investigators' qualifications to perform clinical research. Quality of science should be the primary concern of well designed studies; conducted quickly is not necessarily conducted well. However, qualified investigators must find ways to improve their access to populations of suitable subjects. Guidelines are needed for appropriate methods to do this, including guidelines for ethical use of advertising and ethically acceptable finder's fees (see below). More use also should be made of databases containing lists of informed, willing subjects and their parents. Whenever possible, parents and patients who would be willing to enroll in experimental trials should be identified before onset of the trial. Institutions and investigators need to develop more efficient (preferably automated) methods to identify, inform, and educate potential subjects. Potential methods that need to be explored include use of Internet news groups, third-party payers, disease interest groups, as well as subjects who have participated in studies in the past and their family members and friends.

Methods are needed to minimize disincentives to enrollment that already exist. Denial of insurance coverage for any treatment associated with research is one major issue that needs to be addressed, perhaps through legislation (eg, HB 230, Maryland F-D-C Reports, Inc, p 8, February 19, 1997). Another disincentive is the negative guinea pig perception of clinical research held by many patients and their parents/guardians. Efforts are needed to educate the population about the need for research and to clarify that the empiric use of medications without data are merely a form of unsupervised research. Finally, study designs must minimize the inconvenience (including time, travel, and discomfort) associated with study participation.[14]

Realistic and practical guidelines are needed to help IRBs decide on the acceptable magnitude; basis (time, discomfort, complexity); type (money, toys, care, attention); and focus (subject vs guardian) of inducements. These guidelines should include ethically acceptable payment for time and inconvenience, as well as finders fees. Examples of acceptable finder's fees include providing compensation for individuals who identify potential subjects without interacting or influencing these potential subjects. Guidelines must cover both concrete and implied inducements. Treating physicians, for example, can have excessive influence—implied or actual—over the patients they treat. Guidelines are needed to

deal with this influence, and data are needed on the effect of both influence and inducements on enrollment and consent.[15] This is especially important for studies that provide or appear to provide preferential treatment or access to new, unproven, but perceived as effective, expensive therapies that are available only to study subjects. Experience with AIDS drugs has demonstrated how difficult this can be.[16,17]

Methods used to explain studies and obtain truly informed consent are problematic. Studies are needed to investigate the adequacy of the consent process in children and their parents. It is important to ensure that sham consent is not obtained. My experience, as well as findings from numerous articles in the lay press, attests to the fact that not all study subjects are even being made aware that they are enrolling in an experiment.[14,18,19] Some subjects are merely told they are agreeing to be part of a protocol. The FDA, IRBs, and institutions all have responsibility to ensure that the investigators who conduct pediatric clinical trials do so with the highest ethical standards. Unfortunately, the traditional academic insulation from financial and other potential conflicts of interest is being eroded. Academic investigators are becoming more susceptible to pressures that have always existed in the private sector. As financial incentives increase and patient recruitment becomes more difficult, pressure on investigators to compromise ethical or scientific standards increases. Potential solutions include providing funding that is independent of these pressures. Expanded governmental funding of drug trial networks such as the National Institute for Child Health and Human Development support of their Pediatric Pharmacology Research Unit Network is urgently needed. Direct financial support of pediatric studies by the FDA budget (deficient when compared with FDA support of adult studies) should be expanded as well.

Expanded review of the current consent and enrollment process is also needed. Details that should be examined include who explained the study and exactly how this was done, who answered questions and how accurate the answers were, and what implied or actual incentives were used. This review will require development of practical guidelines for IRBs to decide on what constitutes acceptable enrollment methods. These guidelines should include whether, and in what situations, consent should be obtained by for-profit corporate employees, treating physicians (with or without compensation), investigators, members of the investigator's staff, independent staff, or an ombudsman. Guidelines should cover the entire enrollment process, including patient identification, inducements, patient and guardian understanding, as well as proof of guardianship and whether all guardians or just one might agree, what cognitive levels are required for what types of studies, and how language barriers must be managed.

Certain details of consent must be decided on a case-by-case basis only by the local IRB. Other aspects of the consent process are universal. Recruitment guidelines, however, must protect subjects but not cripple the entire process. No one will benefit if studies become impractical or impossible to conduct. Studies are needed to assess how well local IRBs are advancing scientific knowledge while protecting subjects. Some method of IRB certification and external performance review is needed. Perhaps IRBs should perform masked evaluations of standardized protocols periodically. The performance of both overly restrictive and overly lenient IRBs should be improved.

All pediatric trials require investigators to maintain the highest ethical standards. Unfortunately, any evaluation of ethics is subjective, not absolute. Local IRBs are clearly charged with attempting to maintain ethical behavior. However, not all IRBs are adequately trained or experienced in the practical or scientific aspects of pediatric clinical trials, and seldom are they given adequate resources to monitor performance. Unfortunately, this results in significant variability in the outcome of the review of the same study by different IRBs. Although some local differences are to be expected, the magnitude of the variability encountered suggests that differences exist in motivation (or reward) and understanding, rather than just local differences in interpretation of the risks and benefits of any given trial.[8] Guidelines by which to review IRB performance are needed. Fee-for-service research must be especially examined to assess the impact of conflicts created by excessive financial inducements to investigators, staff, subjects, and institutions or corporations. Methods must be developed to more consistently, but rapidly, approve scientifically and ethically acceptable protocols, while preventing the conduct of ethically or scientifically flawed studies. This may best be done by ensuring that all pediatric studies are conducted by, or approved by, investigators who are trained adequately and experienced in pediatric drug trial design and conduct, but who also are protected from potential conflicts of interest.[13] IRBs also must work to avoid exposure of subjects/guardians and investigators to undue influence or inducements. This is a special problem with very expensive or sought-after (but unproven) treatments for which access to treatment is limited (such as that seen with certain AIDS treatments). For these treatments, subjects or guardians (or even some treating physicians or investigators) may see enrollment as a right rather than a choice.[17,20] Consideration also must be given to post-study access to effective therapy as well as long-term follow-up and notification of unexpected adverse effects.[20] The scientific design of studies must be examined carefully for ethical conflicts, such as where new treatments are unlikely to be better and, possibly, worse. One example of a method to deal with some conflicts is the use of independent research staff who are used by, and responsible to, institutions rather than to investigators or corporations. IRBs must improve community and lay involvement in the review process.

Study design often concentrates on adequate subject numbers. As important, or more so, is the need to recruit and retain adequate numbers of a representative population. IRBs and investigators must work to ensure that studies investigate the risks and benefits of a potential therapy in as much of the popu-

lation who will eventually be exposed to the treatment as possible. This requires that both the number and the type of subjects proposed for the study are appropriate. Inclusion and exclusion criteria must be examined carefully to be sure that the results will be applicable to the largest possible and feasible group of potential patients (see comments above).

Retention of subjects both during and after a trial must be considered an important part of study design. This is needed both to identify delayed effects and to provide ongoing patient access to effective treatment.

The quality of the data collected during studies is critical. Poorly conducted studies expose subjects to risk without the benefit of improved knowledge. Expediency of study completion must not be allowed to take precedence over quality of data. Unfortunately, good data are sometimes more expensive to obtain, but quality control should not be sacrificed for lower costs.

Selective publication must be avoided.[21,22] Unfortunately, many pediatric trials are either not completed or not published. IRBs should be encouraged to promote (if not require) that results of all studies are presented or published. If not, future subjects may be enrolled in studies that are unnecessary or predicted to fail. It also is important to avoid selective data analysis or presentation. All results, not just those favorable to a sponsor's products or unfavorable to a competitor's product, must be presented or published.

Collaborative groups such as Pediatric Oncology Groups and Children's Cancer Study Groups for cancer, the National Institute for Child Health and Human Development neonatal network for newborns, the Southwest Pediatric Nephrology Study Group for renal diseases, and the Pediatric Pharmacology Research Unit offer greater promise for improvements in the recruitment, retention, conduct, and completion of pediatric trials. Use of patients in actual practice sites offers access to large ambulatory population, as do health maintenance organizations, populations who could be enrolled in clinical trials or outcome studies. Unfortunately, unless carefully monitored, such increased access can result in a less rigorous consent process.

Legislative activities such as the new FDA pediatric labeling initiatives, the pending Maryland law to mandate insurance coverage of research care, new National Institutes of Health regulations requiring inclusion of children, and proposed legislation to provide incentives to adequately study drugs in children (Senator DeWine, R-Ohio, personal communication) all promise to improve pediatric subject recruitment.

Study designs that minimize risk and maximize information and benefit to patients both increase enrollment and decrease ethical problems. A number of promising approaches have been developed or proposed, including recruitment of more representative (real life) populations[23]; use of more scientifically designed learning versus confirmation studies; and use of less invasive techniques such as stable isotopes, functional magnetic resonance imaging, urine, saliva, or surplus clinical samples in pharmacokinetic studies. Population pharmacokinetic/pharmacodynamic studies, minimum sample designs,[24] pharmacogenetic testing, and transdermal sensors all are examples of designs such as concentration rather than dose-controlled trials. In addition, use of triangular test design (Fig 1)[24] to minimize sample size by

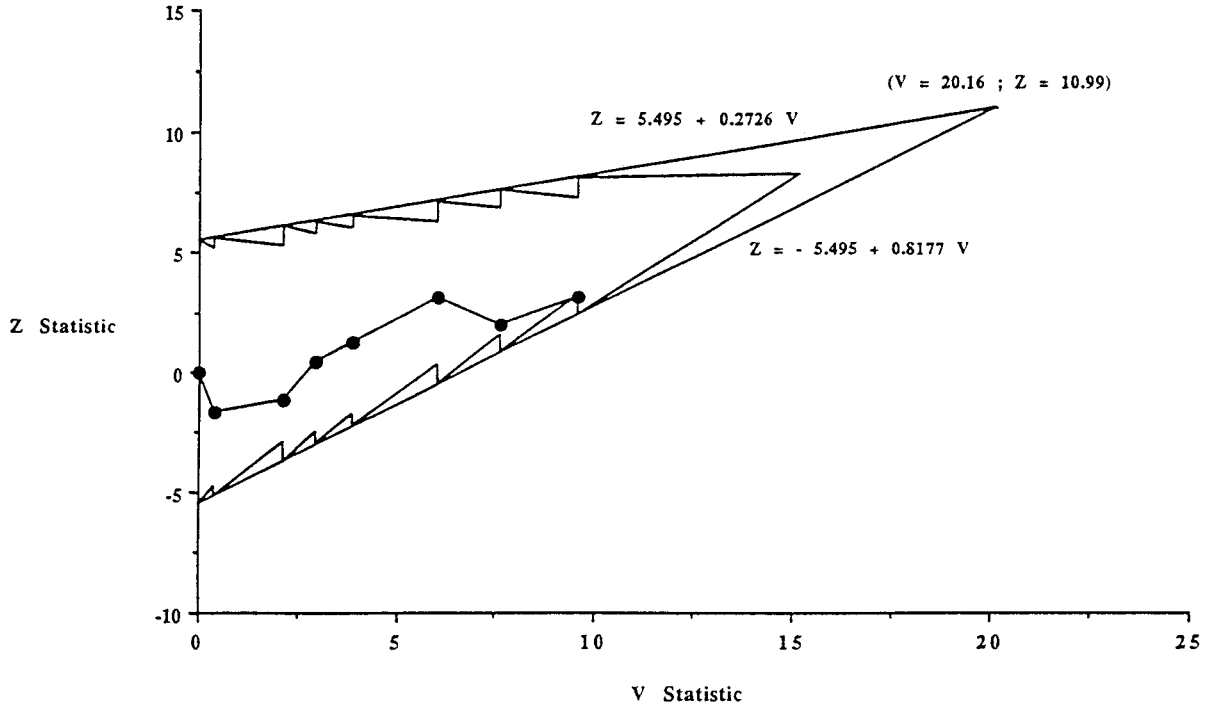

Fig 1. Triangular test and sample path.[24]

allowing early study termination are examples of promising developments.[25]

Finally, published educational is needed to inform and motivate patients and their guardians about both the need for pediatric clinical trials and the components of informed consent and study enrollment.

Clinical trials are possible, but challenging. Subject recruitment and retention are difficult problems, but they must be, and can be, overcome if children are not going to continue to be subjected to the uncontrolled experimentation that occurs when unstudied doses of unproven therapies are given to them, as occurs whenever any of the 80% of medications unapproved for use in pediatric populations are used.

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