

RECRUITMENT AND RETENTION OF PATIENTS AND SITE MANAGEMENT

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Abstract: *Recruitment and retention of patients for clinical trials have become increasingly challenging. This article provides an overview of those challenges and outlines reasons for failure. The keys to success in recruitment and retention—planning, organization, staff, and resources—are discussed. Examples and practical approaches are provided.*

Introuction

This is a time of considerable change in clinical research. It is getting more difficult to recruit patients for many reasons: scandals, institutional review board (IRB) constraints, the Health Insurance Portability and Accountability Act, and rising costs. The scandals, within and outside of the profession, have been played out in the national media. Both the public and politicians are worried about clinical research. The result has been increasing regulation and reticence by IRBs to approve protocols.

The exact impact of the Health Insurance Portability and Accountability Act is unknown, but the Act will make it more difficult to find and recruit people through traditional medical records approaches. All of these factors are increasing the cost of clinical research.

There are many examples of what the public faces. A physician in a failing clinic in Southern California, who developed a lucrative clinical trials practice, was found to have committed many types of fraud and misconduct. He pressured patients to enroll in studies, ignored inclusion/exclusion criteria, and enrolled people in multiple simultaneous

studies. For a hormone replacement study, when patients failed the urine test, he substituted urine with the right hormones that he kept in the refrigerator. He blamed the staff.

At Johns Hopkins a healthy 24-year old woman died in a study after being given a drug under an IRB-approved protocol that was not approved for that particular use. The first person on whom the drug was tried got sick, but researchers went ahead with the trial. Johns Hopkins was faced with many issues, including the reporting of adverse events, the lack of care and review by the principal investigator or the IRB, and the lack of oversight. The federal government shut down all research at Johns Hopkins until the institution could explain what happened. When average citizens read about things like this, they carry away an attitude that participating in clinical trials is potentially dangerous.

Recruitment Failure

Common reasons for failure to recruit patients for clinical trials are delayed start-up, inadequate planning, insufficient effort and staff, and over-optimistic expectations. Clinical trials never start on time. Planning for recruitment is rarely adequate. Sufficient effort and staff are rarely

committed to recruitment. Everybody thinks things will work out fine because in the clinic, they have been stumbling over patients who have these diseases or characteristics needed for the study.

The National Institutes of Health (NIH), and the Food and Drug Administration for many of the trials it reviews, now require adequate numbers of women, minorities, and unless you can defend why children should not be involved, children in trials. This raises the ante for clinical research in many ways. My environment is largely NIH-funded. Every quarter, NIH sends a request for a report on how many and what type of people we have recruited. If we fail that, they begin cutting our budget.

A recent issue of the *Annals of Internal Medicine* had a discussion about concerns that clinical trials were not adequately generalizable because they were taking a tiny sub-segment of the population or the disease, and that more attention needed to be paid to a more representative sample of people in the real world. This, obviously, depends on the type of disease you are studying. Often, finding a generalizable population

will be quite difficult because many people in the general population will fall away, either by becoming ineligible or refusing to participate. To get an eligible and willing sample of 100 participants, you may need to screen 800 to 20,000 people.

For example, some years ago, I was involved with the NIH-funded multiple risk factor trial that randomized 11,000 middle-aged men aged 35 to 54. They were in the top 15% of cardiovascular risk by Framingham criteria. We had 20 centers nationwide with a lot of experience. We thought this study would be easy to do, but wound up screening 360,000 men to get 10,000 subjects, a yield of less than 3%. It was an enormous task and we were unprepared for it.

Effective Recruitment and Retention

Recruitment and retention are the result of planning, organization, staff, and resources. In order to recruit adequately, you must plan (Table 1). In addition to establishing realistic estimates of the number of patients and the amount of effort needed, you must always identify back-up populations because the first population rarely provides adequate numbers. Generally, a pilot or feasibility study will provide an estimate of how many people you must screen at the front end in order to get enough eligible participants. You must always carefully record what you are doing.

Recruitment starts with adequate staff who are well trained. Sometimes you can pre-screen patients through chart review or other methods to increase the recruitment yield. You need an organized clinic, with regular staff meetings and weekly targets/reports to analyze recruitment.

Budgeting staffing is complex. I have been through studies where staffing for recruitment was based on the assumption that clinic staff, particularly early in the study, had nothing else to do so that they could handle recruitment. In some instances, if you are lucky, this works out. But this becomes increasingly difficult as the study gets underway and staff time is needed to attend to study subjects. Think about the wide variety of things these staff need to do, including attending training, identifying the study population, eliminating ineligible patients, contacting potential participants through a variety of methods, reminding them by telephone, and re-contacting them when they do not show up. Take vacations, sickness, and resignations, and the need for re-training, into account.

We estimate that it took 60 minutes to contact one person, with a yield of 10%. It took one full-time staff member 24 weeks to recruit 100 people. The cost was about \$240 per recruit, without the costs of supervision, telephone, supplies, indirect costs, and so forth.

Practical Recruitment Approaches

Recruitment methods can be for a population sample or patients. Population recruitment includes telephone, letter, household, advertising, and the Web. Patient recruitment methods include clinics, hospitals, advertisements, referrals, and the Web. Gilliss et al., in a mammogram study, found broadcast media to be the most effective recruitment method and Web recruitment to be a non-starter.

When recruitment is going badly, sites loosen criteria to increase their yield, convince the sponsor that it does not need as many subjects (often a very hard sell), extend the recruitment period, change the study design, recycle potential subjects who had borderline values in the initial screening, and re-contact potential subjects who were ambivalent about enrolling. There are many reasons why people do and do not participate in clinical trials. The top stated reasons that people participate in trials are to provide benefits to others from the results because they trusted the doctor treating them, and because the trial offered the best treatment available. The top reasons why people do not participate in trials are that they trusted the doctor treating them or randomization worried them.

We recruited subjects for a study of East African victims of torture. In the Twin Cities of Minneapolis-St. Paul, we have a large number of refugees from the horn of Africa (Somalia, Ethiopia), many of whom were tortured by militias, armies and the police. We were studying how they adjusted to what was an extraordinarily difficult experience.

We were trying to find 800 people. We took two years to plan and organize the recruitment of this population. We assigned four full-time staff members to recruitment. It cost us about \$500 per person for each of the 800 subjects. We met with community leaders and organizations; sent out printed material, although

TABLE 1 Recruitment Planning and Conduct	
Planning:	<ul style="list-style-type: none"> • Establish realistic estimates of the number of subjects and amount of effort needed • Identify back-up populations • Conduct a pilot or feasibility study • Record experiences
Conduct:	<ul style="list-style-type: none"> • Adequate staff • Staff training • Pre-screening to increase yield • Organized clinic • Regular staff meetings • Weekly targets/reports

many of these folks, especially the women, were not literate; placed announcements on East African radio stations; hired research assistants from East Africa (many of whom were physicians); and put together a census.

We were faced with two crises: the release of the movie Black Hawk Down and the shutting down of an organization that sends money back to Somalia and Ethiopia due to suspected terrorist links. Black Hawk Down, the story of the Rangers and the helicopter that crashed, did not present the Somalis in a favorable light. The subjects stopped coming the day after the movie was released.

About six months ago, the attorney general judged that one of the organizations that sends money back to folks in Somalia and Ethiopia was related to al Qaeda and shut it down. The owners were arrested. This ultimately turned out to be false, but the community immediately ceased contact with us after that. Much work was needed to re-establish contacts and participation.

Issues in Retention

Most studies depend on participants remaining with the study until the end. The reasons that people are non-adherent to study protocols are side effects in drug studies (by far the most common reason), unwillingness to change behaviors (e.g., diet, exercise, smoking cessation), lack of understanding of study instructions, lack of family support, or they changed their mind. People who are not retained well are those who: were ambivalent when they were enrolled in the study, did not understand their commitment, and had unrealistic expectations about the study. Patient discontinuations in clinical trials decrease power and validity, and undermine any treatment effect.

We tend to forget what we are asking study subjects to do, including: attend study appointments, undergo tests and procedures, fill out questionnaires and diaries, be interviewed, participate in

study treatment(s) or control(s), and follow other study protocols. We must have a clear contract with subjects so that they understand the expectations. There are many reasons why people do not stick with the study, including: prior beliefs, response to treatment or control, side effects, time commitment, family/work conflicts, unwillingness or inability to change behavior, misunderstandings, socio-demographic factors, and they changed their minds.

Table 2 outlines key issues in study retention. In study design, we commonly conduct multiple baseline visits, using a placebo or the drug in a run-in period, to see who will fall by the wayside early in the trial. That way, people who are ultimately randomized know what they are in for and have demonstrated that they are committed to the study.

TABLE 2
Key Issues in Study Retention

- Study design
- Personnel
- Facility
- Scheduling
- Technical issues

The Keep it Simple Stupid (KISS) principle must prevail with most study designs. We find that feasibility/pilot studies tell you a lot about whether the protocol will work with real people. Design protocols for compliance; this encompasses a wide range of things from staff to newsletters to Christmas cards and so forth. We have, with trepidation, involved some real potential participants in study design. There are also monetary and other incentives for patients.

Study staff and clinicians must have certain characteristics: friendly, motivated, flexible, responsible, and willing and able to follow protocols.

They must be included in the study budget in adequate numbers. Compliant staff leads to compliant patients.

Facilities issues include convenient parking; a general awareness of the study within the facility; a comfortable, non-threatening environment; and on-site child care. In urban areas, you can never underestimate convenient parking. People do not want to have to find parking or find their way to your study. When people appear at the information desk at the hospital, the volunteer behind the desk should know about the study and where to send the subjects.

Scheduling is important. Issues include a contact person, continuity of care, flexible appointment times, and appointment reminders. We encourage a single contact person so that there is some sense of bonding between the subject and the person calling to remind him/her and set up appointments. If we can, we try to assign the same nurse and staff to each participant for the same reason. We are very flexible on appointment times, and we are as likely to run an evening clinic as a Saturday clinic. To get people in, you must adapt to their schedule, not to the staff schedule. We use a wide variety of appointment reminders, such as phone calls, letters, study calendars, and stickers.

Compliance costs money, just like recruitment does. Ensuring patient compliance requires resources. You must plan and have a staff member who is assigned to compliance.

Summary

Recruitment and retention are difficult and are getting more difficult. But they are not impossible. You need a plan, a clear organization with responsibilities for recruitment and retention, well-trained staff who are assigned to the study, and a willingness to invest the necessary resources. If you do all this, you will get good participants and have a good study.