Keys to Success with Clinical Trials

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Since clinical trials provide access to novel therapies years before they become available on the open market, some physicians may be curious about participating in the clinical trial process. Indeed, becoming a clinical trial investigator can positively impact a private practice in several ways. First, investigational therapies can provide treatment alternatives for difficult or burdensome cases, such as patients with irritable bowel syndrome, refractory inflammatory bowel disease (IBD), and intractable constipation. Participation in clinical trials can also enhance the practice's standing as a cutting edge practice and can increase the practice's revenue stream without the hassle of insurance carriers. Finally, involvement in clinical trials can renew physicians' academic interchange with peers by encouraging participation in meetings, publications, and lecture series.

Preparing to Make the Commitment

Before becoming involved as a clinical trial investigator, physicians need to consider whether they are ready to make this commitment. Clinical trials require the investment of the doctor's time, the practice's personnel, and other resources, so physicians should evaluate their capacity to meet these needs.

Time

Explaining a clinical trial to patients is a task best performed by the principal investigator (PI), and physicians should consider each patient as a potential study candidate. If extra time cannot be allocated for this discussion, then physicians should not consider enrolling as a clinical trial investigator. Since the patient's trust is with the doctor, the physician must be an active player when enrolling patients; support staff cannot be expected to do all the introductory work. All the physicians in a practice should agree to this undertaking.

Once a trial has started, the physician will need to meet with clinical research organization (CRO) monitors, review protocols, sign off on laboratory work, and be available to staff and patients to answer questions or address misunderstandings of protocol requirements. Also, the PI should plan to travel as needed. The PI will be asked to attend investigational meetings and follow-up sessions, and these requirements will detract from the physician's office schedule.

Personnel

In addition to the doctor's time commitment, involvement in a clinical trial also places burdens on office personnel. One way to meet this demand is to hire a dedicated research coordinator. Physicians should not

assume that the practice's current staff will willingly accept added responsibilities; indeed, staff often resent the extra work clinical trials entail, and this resentment may lessen recruitment and sustained enrollment. Failure to sustain enrollment is a major concern, since unsuccessful recruitment will damage the practice's reputation for future trials.

Having a dedicated clinical trial coordinator means that the practice will have the personnel needed to review potential protocols and analyze the practice's database to ensure that the appropriate patient population is being considered for the study. Since quick turnaround is expected in the research industry, clinical trial sponsors may be displeased if a practice takes too long to complete the required regulatory paperwork; the clinical trial coordinator can focus on addressing this need for prompt turnarounds. If a practice can negotiate a contract with indemnification language and governing laws, negotiate a budget, and complete the US Food and Drug Administration (FDA) forms and sponsor-specific forms within 5–7 business days, the practice's involvement in future projects will be much more attractive.

When working with clinical trial sponsors, physicians should keep in mind the perspective of the pharmaceutical company, in which the clock starts as soon as the bench work for discovering a new compound is complete. There are a limited number of years during which the company can capitalize on a new drug before the patent expires and generic competitors enter the market, so pharmaceutical companies have time-sensitive goals for site initiation, enrollment of the first patient, completion of enrollment, attainment of primary and secondary endpoints, and data analysis.

Oversight

Finally, practices that participate in clinical trials should be prepared for constant CRO monitor visits, queries, and reviews of accumulated data. By participating in a clinical trial, the practice is opening itself to added scrutiny, as a number of procedures and guidelines must be reviewed; these include good clinical practice (GCP) guidelines, informed consent policies, adverse event reporting guidelines, and instructions for avoiding coercion in certain populations. An experienced clinical research coordinator can ensure that the practice adheres to standards that meet the GCP definition accepted by the FDA and device and pharmaceutical companies.

Because fulfilling all these tasks in-house will involve a great deal of work, physicians may want to consider partnering with a site management organization or a clinical trial management organization. These organizations can assume many burdensome administrative tasks, although they usually do so in exchange for a hefty share of the budget. These organizations are quite knowledgeable and may negotiate better contracts and budgets, as well as lessen the investment needed in terms of site space and staff involvement, and guide the novice physician or practice through the clinical trial.

Principal Investigator: Education and Responsibilities

As the PI, the physician is responsible for numerous aspects of a clinical trial. The PI's first responsibilities are to ensure that the protocol's inclusion and exclusion criteria are met and to consider whether the benefits of participation in the trial outweigh the potential medical risks. In addition, the PI must monitor participants' compliance with study requirements; this can be done via Interactive Voice Response Systems, medical records, drug accountability, and/or follow-up visits. Failure to monitor patients adequately can sabotage the entire study and damage the site's reputation. The choice of appropriate patients for study enrollment is critical to this process (Table 1). The PI and his or her team must also ensure adherence to the protocol, fulfillment of regulatory responsibilities, and maintenance of data quality. Finally, the PI must update trial enrollees of any new risks or benefits that evolve as the trial progresses.

The PI's main concern during the study is safety and not simply meeting target enrollment. The PI is responsible for transmitting the risks and benefits of the study treatment to patients, even if data are unclear or unknown. For example, the PI may need to translate data from animal studies to human subjects; this situation most often occurs in phase I studies. The PI must also remain up-to-date on risk and benefit information that may be reported in a variety of sources. In addition to data in the investigation's brochure, the PI should remain abreast of studies in the peer-reviewed literature, CRO

Table 1. Questions the Primary Investigator Should Ask Before Enrolling Patients

- Is the honorarium coercive?
- Has the enrollee been in many different research studies that may influence the results of this trial?
- Is the patient's medical history so complex that safety and efficacy may be jeopardized?
- Is the patient taking medications that may interfere with the test product?
- If there is a placebo arm in the trial, have potential participants been educated about the standard of care and the placebo?

Table 2. Phases of Clinical Trials

Phase I	Trials test the safety of an investigational product in a small number of healthy volunteers.
Phase II	Trials test the safety and efficacy of an investigational product in volunteers who have the condition the product is intended to treat.
Phase III	Trials test the safety, efficacy, and dosage of an investigational product in volunteers who have the condition the product is intended to treat. A product's benefits have to outweigh its risks in order for it to be approved by the US FDA.
Phase IV	Trials take place after the investigational product has been approved by the US FDA.

FDA=Food and Drug Administration.

and sponsor updates, and information that is related to the public via the Internet and other media.

Because of potential pitfalls with phase I studies, doctors should be cautious when enrolling patients in these trials, especially as a new investigator. Safety is paramount in phase I studies; these trials are usually based on pilot studies in animals regarding potential pharmacologic and toxicologic barriers, but these barriers have yet to be studied in humans, so there is a need for a 24-hour surveillance unit. Also, since phase I trials are not intended to evaluate efficacy, there are ethical as well as medical risks. There is no prior experience with the investigational agent that can be used to educate patients about its risks and benefits in a truly informed manner (Table 2). Additionally, there is a risk of sensitizing the patient to a biologic therapy that may not be available upon conclusion of the trial, which may lead to a delayed hypersensitivity reaction upon retrial of the agent at some future time. Phase I trials may pay better and usually involve healthy human volunteers, but the risk of unforeseen adverse events may exceed the comfort level of the novice PI.

Finances

When utilized successfully, clinical trials offer additional revenue for a practice without the hassle of dealing with insurance or third-party companies, but this additional revenue comes with work. Although it may seem that the practice's staff performs much of the work, the PI's role is not marginal. The PI's attention to obtaining appropriate trials for the practice, recruiting and retaining subjects, and ensuring compliance with drug safety, adverse event reporting, and data collection will determine the success of the clinical trial program and its impact on the bottom line.

Negotiating an acceptably profitable budget depends on careful line-by-line itemization of the practice's costs and overhead expenses. Once agreed upon, the payment schedule is usually quarterly and is directly dependant on patient enrollment. Often, the sponsor will agree to pay start-up costs and storage fees (since study records often must be archived for 15–17 years).

Once payments are made, profits should be divided according to a predetermined policy. After overhead and salaries are met, the distribution may be based on productivity (ie, enrollment), or it may be a generalized equal distribution. The latter division is based on a group mentality that assumes that patients originate from the entire practice and that everyone helps to meet overhead. In this case, divisible proceeds should be treated similarly.

A final financial consideration is the possible need for additional malpractice coverage. Most practices' malpractice insurance does not cover clinical trials, so doctors may need to speak with their carrier regarding this coverage gap. Although we insist on an indemnification letter in all of our trials, we still carry insurance for all employees involved in clinical trials.

Recruitment and Retention

Recruitment

The key to successful recruitment in clinical trials is the development of trust among the physician, the study coordinator, and the patient. This relationship is particularly crucial with IBD trials, since these patients tend to be extraordinarily well informed. They know the literature and are both cautious and fearful of doctors who do not understand their specific needs or who are not informed about the various therapies that are available.

Study investigators also need to maintain open lines of communication with referring doctors. To achieve this goal, the PI needs to emphasize that he or she is not taking patients away from the referring doctor and that the clinical trial offers new therapies that are not yet on the market. Mailings and other communications with referring doctors are often unsuccessful unless they appear on the doctor's personal stationery. Lecture and discussion groups have some value, but they will be of lesser value if they do not have a significant question-and-answer period that allows for 1-on-1 interaction. Radio advertisements work best if they run during the workday so that patients who respond have immediate access to the study coordinators. Mailings on the doctor's personal stationery with a note to the patient regard-

ing the trial have been reasonably effective but must maintain the patient's privacy by adhering to appropriate Health Insurance Portability and Accountability Act precautions.

Finally, a candid discussion is always necessary regarding the role of a placebo in the study and the side effects of the drug. The physician should emphasize that the trial is not an "experiment" and the patient is not a "guinea pig," but rather an active participant in the development of data on a new therapy. A follow-up call on the same day after the first inquiry is essential, and most studies will require that there be a plan for treating patients beyond the end of the trial, such as an open-label or compassionate arm of the trial or the option to move on to another trial. Maintaining patient satisfaction after the end of the study is often difficult if the patient achieves extraordinary success with their first investigational treatment.

Retention

Patients need time in order to fully understand the schedule commitment that laboratory testing and procedures demand. Once patients complete the study, however, they can be "poster children" among their friends and contacts for further study development. A nurturing and friendly environment is essential for retention. The patient must feel welcome and feel that they are being treated as an individual, not just a number. The study participant should have easy telephone or e-mail access to the study coordinator or the physician, and the doctor should see the patient at each visit if possible. In addition, transportation or a modest honorarium (or even lunch) may be required for patients who are traveling a long distance. If a cash honorarium is provided, it should not be a reason for enrollment. All appointments should be confirmed 24 hours in advance, and patients should be given reminder cards when they leave the office. Each scheduled visit should then be reconfirmed by the coordinator or the physician, if needed, and patients should be told what will be required at the next visit (ie, history, physical, blood specimen, or procedure). Patients should understand that they play a significant role in advancing experience with the investigational treatment, and they should be reminded that their existing, FDA-approved medications were developed based on just such studies.

Recruitment and Retention Methods

There are many ways of recruiting patients for clinical trials. Some methods prove more effective than others, particularly in certain populations (Table 3). For example, most clinical trials have an age limit, so physicians may need to employ specific, age-related strategies such as population-specific advertising for some studies. This method works best when there is personal contact between the researcher and the subject, often brokered by a trusted intermediary such as a primary care physician, minister, or prior study participant. A simplified informed consent process is highly desirable.[1]

Physicians should consider whether patients are more likely to respond to messages delivered via telephone, mail, advertisements, or other methods. In a Welsh population of smokers, for example, telephone calls to recruit patients into a smoking cessation trial were found to successfully enroll 68% of smokers who were not initially intending to quit.[2] Similarly, a Boston University study for colorectal cancer screening that involved 3 different recruitment tactics found that investigator-initiated direct contact was significantly more cost-effective than Internet or referral letter methods. Accrual rates were higher with the investigator-initiated direct contact method (35.4%) versus the Internet (16.7%; P=.02) or letters (2.1%; P<.001).[3]

In contrast, in a pediatric obesity study, targeted mailings and referrals from primary care physicians were most effective; positive recruitment methods—such as general advertising in media, health flyers, and word of mouth—yielded fewer total subjects but better retention for enrollment to the randomization phase of the study. The overall yield was 164 patients randomized out of 940 family contacts.[4] In a University of California, Los Angeles dietary assessment trial, Internet-based recruitment was also found to be effective. After overcoming a 6-month development period during which website programmers' time and active team involvement were required, the speed and efficacy of recruitment and data collection eventually outweighed the initial costs.[5] Some studies, such as a study of acupuncture for chronic back pain, showed that the efficacy of treatment did not differ among recruitment strategies (mailed letters vs open advertisements in a health plan magazine).[6]

For some clinical trials, physicians may need to consider patients' race or ethnicity when selecting a recruitment strategy. Minority group recruitment strategies can focus on sites where patients congregate, such as barber shops, community health and senior citizen centers, and houses of worship; such recruitment is always by word of mouth, however, not just via signs and posters.[7] Recruitment of minorities in the United Kingdom required intensive staff training to overcome language barriers; this training proved particularly useful when there was open contact with local gatekeepers who could serve as intermediaries when culturally appropriate. Reciprocal benefits between gatekeepers and solicited patients prevented recruitment fatigue, which was a factor in overcoming barriers in more diverse populations.[8] Finally, testimonials delivered via video and audio produced higher response rates and greater information credibility than pictures with text. Curiously, the response among black patients

Table 3. Recruitment Strategies and Outcomes

Reference	Study population or investigational treatment	Techniques	Results/Comments
Raynor HA, et al[4]	Pediatric obesity	• Targeted mailings, PCP referral Versus • Word of mouth, media, health fairs	• Better numbers Versus • Fewer numbers but better retention (164 randomized out of 940 family contacts)
Sherman KJ, et al[6]	Acupuncture for chronic back pain among integrated health plan members	Mailings versus open advertising	• No difference
Walker HJ, et al[9]	General public	• Testimonials with video and audio on website • Minority representation in testimonials	• Greater credibility than pictures and text alone
Tzelepis F, et al[2]	Adult Welsh smokers (N=1,562)	• Telephone smoking QUITLINE support (recruited by phone only)	• 52% enrolled • Cost: $59 per patient; 68% had no initial interest in quitting • Most effective with older, highly educated, married, or divorced patients
Sheikh A, et al[8]	Asthmatic South Asians (Indian, Pakistani, and Bangladeshi)	Interviews with research personnel and community leaders	• Too diverse population • Language barriers Versus • Researchers' attitudes • Open contact with gatekeeper intermediary (reciprocal benefits)
Schroy PC III, et al[3]	Colorectal cancer screening	• Direct patient contact • Internet • Referral mailing	• 35.4% • 16.7% • 2.1%
Arab L, et al[5]	Dietary assessment	• Internet-based only	• Required 6-month development period • Eventual speed and efficacy outweighed initial costs

PCP=primary care physician.

was favorable, whereas a sampling of white patients were negative, particularly if a greater number of minorities were shown in the video; however, post-hoc analyses showed such testimonials to attenuate racial biases.[9]

Conclusion

Clinical trials offer patients access to medications and services that are not yet available in the open market. This is particularly important for difficult-to-treat patients. Secondary benefits of clinical trials include enhancing a practice's revenue stream without the hassle of dealing with third-party insurance carriers and having the opportunity to participate in collegial meetings.

Successful trials are primarily dependent on the physician's devotion to the concept of a potential benefit to the patient and his or her willingness to commit time. These factors, in conjunction with a support staff of experienced coordinators and regulatory personnel, are essential for a seamless effort. The "nuts and bolts" of daily queries, CRO monitoring visits, and vigilance over accumulated data still require physician oversight. Nonetheless, the benefits outweigh the time required. Recruitment and retention strategies vary with the target patient population, but they always represent an exciting challenge.

Those physicians willing to accept this challenge and responsibility will find a new source of satisfaction in the practice of medicine.

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