

The Clinician as Investigator Participating in Clinical Trials in the Practice Setting

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*This paper has been reviewed and approved by the National Heart, Lung, and Blood Institute.
Endorsed by the American College of Cardiology Foundation.*

Abstract—The rapid development of new drugs, therapies, and devices has created a dramatic increase in the number of trials needed to properly evaluate them. The majority of patients treated today, many of whom could be eligible for participation in these studies, are seen in community hospitals and medical practices that are not affiliated with an academic medical center. Thus, there is a demonstrable need for physicians in private practice to enlist as investigators in these trials. This article is intended to encourage those physicians by describing the need and providing the rationale for their participation. It covers basic requirements for participating in clinical trials and outlines ethical, regulatory, financial, and other logistical issues of importance for the potential investigator and provides an algorithm for selecting a study for participation. Finally, the appendices review basic elements of study design and statistical principles, which may be of interest to a potential investigator. (*Circulation*. 2004;109:2672-2679.)

Key Words: AHA Scientific Statements ■ trials ■ evidence-based medicine

The practice of medicine today is driven by evidence: data derived from published, peer-reviewed reports, many of which come, in turn, from randomized, controlled clinical trials. As the number of new drugs, devices, and treatment strategies has proliferated, so have the trials evaluating them. Many areas of medicine have seen a dramatic increase in clinical trials (Table 1). Published research usually alters practice in a small, incremental fashion, but a few landmark trials¹⁻⁹ have resulted in major changes in medical practice (Table 2). The increasing number of trials overall has generated a need for interested and qualified investigators, as well as for the patients they can recruit. It has been argued that professionalism requires a commitment to the advancement of scientifically sound medical knowledge.¹⁰ One way to fulfill this obligation is through participation in clinical trials. It is our intent to provide information in this article that will encourage interested clinicians and help them take the first steps toward participating in studies that will help develop the structure of ideas known as evidence-based medicine.

Who Should Become an Investigator?

Although physicians based at teaching hospitals often juggle patient care, research, and teaching, there is a sense that those in private practice focus exclusively on patient care, with limited time for research or teaching. The majority of patient care in the United States is delivered in nonteaching hospitals; for example, almost 80% of acute myocardial infarctions in the United States are treated at nonteaching hospitals.¹¹ The vast majority of practicing physicians today are office based: 473 431 versus 157 032 who are hospital based and 166 340 “other.”¹² The numbers are similar for cardiologists: Of those registering at the 2003 American College of Cardiology Scientific Sessions, 4816 listed direct patient care as their primary activity, whereas 1282 indicated medical research as their primary activity; 8040 were in solo or cardiovascular group practice, whereas only 2567 were medical school or university faculty.¹³ It is the clinician in private practice who sees a huge volume of clinical cases, and in a nontertiary center, these cases are generally unselected, which means they are not affected by referral bias. Research questions

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on March 12, 2004. A single reprint is available by calling 800-242-8721 (US only) or by writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0284. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4121, fax 410-528-4264, or e-mail kgray@lww.com. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

Appendix 1 and Appendix 2 are available online only at <http://www.circulationaha.org> (*Circulation*. 2004;109:e302–e304; e305–e307).

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DOI: 10.1161/01.CIR.0000128702.16441.75

TABLE 1. Published Reports of Randomized, Controlled Trials

	1980–1989	1990–2000	Percent Increase
Pulmonary medicine	2997	8248	275%
Gastrointestinal medicine	3293	8779	267%
Cardiovascular medicine	5410	14 845	274%

Numerical results of Medline search by MeSH subject headings, in the English language, of randomized, controlled trials in humans, by decade.

directed at these patients can therefore address many practical issues with the expectation that conclusions derived from them could be immediately applicable to the general population. With the growing need for dedicated investigators and these unselected patients, it is becoming increasingly important for the private practitioner to step into the role of researcher and participate in trials evaluating new therapies and strategies of care.

In this article, we address the practical matters of primary importance to a potential investigator: what background and experience are required, what support staff will be necessary, what the relevant ethical and regulatory issues are, and how a study can be financed. Members of the writing group believe that although a practitioner planning to become an investigator does not necessarily need a strong statistical background, a working knowledge of statistical principles and a basic understanding of study design would be useful. We therefore include appendices (available online at <http://www.circulationaha.org> [Circulation. 2004;109:e302–e304; e305–e307]) that discuss these topics.

Why Participate in Clinical Trials?

As a clinician, there is a tendency to base practice decisions on one's own experience, recalling outcomes from recent cases, which can skew one's subsequent practice. These observations and impressions may be at odds with actual evidence-based treatment and therapies. Until fairly recently, published medical literature was also observational in nature, without evaluation of controlled and usually randomized

interventions. Clinical trials provide a way to pool controlled observations in an objective and scientific way, allowing clinicians to decide with the best available data what therapy will work best for each patient. Shifting from an experience-based to an evidence-based paradigm has characterized medical practice over the past 3 decades, and the clinical trial is the linchpin of this trend. Registries and other studies, however, can also generate important data and should not be overlooked by potential investigators (Appendix 1).

Participation in a trial allows the clinician to remain at the cutting edge of a specific area in medicine, and there are often opportunities for investigators and their staff to meet other investigators from across the country or from around the world to exchange ideas and plan future collaboration. Investigator meetings will frequently include scientific sessions.

Many trials generate a number of published reports besides the main article. Investigators who have contributed to the trial are often invited to be members of writing groups and may become coauthors of articles submitted for publication. An investigator may submit a proposal for additional analyses of trial data that may warrant its own writing group; thus, being a clinical investigator could provide an opportunity to coauthor an article in a scientific journal.

Participation in a clinical trial may add prestige to your practice or institution. Patients who participate in clinical trials tend to receive particularly high-quality care; it has been suggested that even patients in placebo arms of trials tend to do well,¹⁴ although this "trial effect" has recently been called into question.¹⁵ Finally, perhaps the greatest reward for an investigator is the knowledge that the results of a trial will add in some way to the science of medicine and may have an impact on how the profession cares for patients.

Basic Requirements for Becoming an Investigator

The most important qualification for a potential investigator is enthusiasm and a desire to evaluate the question at hand. It is the

TABLE 2. Some Pivotal Trials in Medical Science

	Year Published	No. of Patients	Main Finding
LRC ¹	1984	3806	Reduction in definite cardiac deaths or nonfatal MI in patients with effective cholesterol lowering
GISSI-1, ² ISIS-2 ³	1986, 1988	28 899	Reduction in mortality from AMI in patients treated with streptokinase and aspirin
CAST ⁴	1989	1727	Treatment of asymptomatic or mildly symptomatic ventricular arrhythmias after MI with flecainide or encainide increases mortality
SOLVD ⁵	1991	2568	Reduction in mortality in patients with congestive heart failure and left ventricular dysfunction treated with enalapril
Treatment of <i>Helicobacter pylori</i> infection ⁶	1992	109	Treatment of patients with duodenal or gastric ulcers with antibiotics to eradicate <i>H pylori</i> infection markedly reduces relapses of ulcer disease
NINDS ⁷	1995	624	Improved clinical outcome in patients receiving tissue plasminogen activator for stroke
MADIT-II ⁸	2002	1232	Patients with ejection fraction <30% after MI had improved survival after defibrillator placement
SIRIUS ⁹	2003	1058	Marked reduction of in-stent restenosis with rapamycin-coated stent

LRC indicates Lipids Research Clinic; MI, myocardial infarction; GISSI-1, Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico; ISIS-2, International Study of Infarct Survival 2; AMI, acute myocardial infarction; CAST, Cardiac Arrhythmia Suppression Trial; SOLVD, Studies of Left Ventricular Dysfunction; NINDS, National Institute of Neurological Disorders and Stroke trial; MADIT-II, Multicenter Automatic Defibrillator Implantation Trial II; and SIRIUS, Sirolimus-Eluting Stent in Coronary Lesions.

interest of the principal investigator that motivates colleagues and associates who work with him or her. Without the passion of the study group leader, the trial may not succeed.

A clinician who is interested in participating in clinical research should have a clear understanding of ethical issues involved in human experimentation; we discuss this in more detail in the "Protecting Patient Rights" section below. Also important is an understanding of the regulatory environment.

The investigator must be knowledgeable in the area being studied. Although this may seem self-evident, it is entirely possible to be presented with a study protocol that sounds interesting but involves therapeutics or management in an unfamiliar area. Without practical experience with the disease or condition being investigated, signs and symptoms might be misinterpreted or go unrecognized, and patient care can suffer.

Knowledge of study design and statistics is helpful but not essential; basic concepts in these areas are addressed in Appendices 1 and 2, with relevant references for more in-depth information.

Barriers to Participating in Clinical Trials

Although a newcomer to clinical research may be concerned by his or her lack of trial experience,¹⁶ a practitioner transitioning into investigator can learn the regulations and understand the procedures related to the primary responsibility of maintaining patient safety. Often there are organizational meetings before the initiation of a study that thoroughly review the study protocol and procedures. There is generally a detailed manual of operations for reference, and telephone assistance is usually available. Thus, interested individuals who are willing can "learn by doing," especially in a trial with a simple intervention and/or limited data collection. Additionally, courses dealing specifically with conducting clinical trials are offered by several academic institutions and other organizations for interested clinicians and their staffs.

Potential investigators may be seriously concerned by time constraints, because there are time commitments both at the startup and during the conduct of a study. The completion of initial regulatory and study-related documents, possible site visits, meetings and support staff training, and institutional review or other committees may require physician involvement at the outset. Screening patients, explaining the study, and obtaining informed consent all take time and will prolong an office or hospital visit. There may be a need for attendance at follow-up institutional review committee meetings and interim investigator meetings. Nonetheless, physician time commitment can usually be kept manageable with planning and efficient use of a study coordinator and other staff.

The amount of reimbursement for participation in a trial is another consideration. There is a wide range of reimbursement and a large variation in responsibilities among trials, but one should expect remuneration to be commensurate with the amount of work involved. In trials organized by smaller groups or centers, there may be no payment or only a token payment. In this case, the individual must decide whether other factors—the subject under investigation, the group involved, the experience, possibility of coauthorship of an article, etc—would justify the time spent on the project. Certainly, trial reimbursement should

cover one's expenses; this subject is dealt with in more depth in the "Financial Issues" section.

Investigators also express concern that the degree of recognition for their contribution to the study may appear to be insufficient. In general, functioning as an investigator adds a degree of prestige to your practice and/or institution. Colleagues can be kept informed at staff meetings. Local media might also find the project of interest, adding to local recognition. Most multicenter trials will acknowledge participating investigators in the article that reports the main study results. Finally, many studies will encourage investigators to participate in writing groups, and in these instances, the investigator may ultimately become a coauthor of an article.

Finally, issues with regard to one's legal liability as an investigator must be considered. Few legal actions have been brought against physicians who participate in clinical trials, although there is concern this may be changing.¹⁷ In most studies, the sponsor agrees to assume the legal defense of the investigator and his or her study staff (indemnifying the investigator and staff) in the event of litigation, providing there was no gross negligence and the study protocol was followed. This should be included in any clinical trial agreement. Investigators must carefully read and understand the contract agreement. It may be prudent to have an attorney review study agreements before signing them, although this cost will likely not be covered by the study sponsor. If the investigator is organizing the trial, he or she should look for legal backup from his or her own institution, if appropriate. Financial arrangements have come under increasing scrutiny from government investigators; great care needs to be taken to ensure that reimbursement arrangements are proper, ethical,¹⁸ and appropriate to the work performed.

These issues might limit physician interest or willingness to participate in clinical trials.¹⁶ With proper forethought and preparation, however, none of these should prove to be insurmountable, even for an individual in a busy private practice.

Physician as Investigator: Managing Conflicts of Interest

Once a physician considers enrolling a patient in a trial, a new relationship between that patient and physician develops with the potential for conflict with the traditional doctor-patient relationship.¹⁹ It is most important for the investigator to remember that as the treating physician, one's principal responsibilities remain to avoid harm to one's patients and to help them. Therefore, a condition called "equipoise" is required before one may deem it morally appropriate to enroll patients in a clinical trial.²⁰ This means that when considering the various treatment arms of a trial (including any placebo arms), one should be in a state of uncertainty about whether one arm or the other is more effective. If a proposed study is asking a question that, to the best of one's knowledge, has not yet been answered, it would be ethically appropriate to propose the trial to one's patients and to enroll those who consent. Although one may have a personal belief that one arm or another will turn out to be more effective, most ethicists now argue that the state of equipoise necessary to justify enrolling patients in a clinical trial need only reflect a state of uncertainty in the medical and scientific community, not one's own individual beliefs.²¹ For example, if a trial were proposed that administered *d*-sotalol to patients after myocardial

infarction²² at a time when there was already concern in the scientific community about the proarrhythmic effects of antidysrhythmic drugs, one might suspect there was a potential risk to participation based on current evidence and that one could not ethically recruit patients for the study. Although some have raised questions about the necessity of clinical equipoise in all cases,²³ for a physician to be on ethically “solid ground,” to the best of his or her knowledge, there should be reasonable uncertainty about whether any of the various treatment arms of the trial is either superior or inferior to the others.

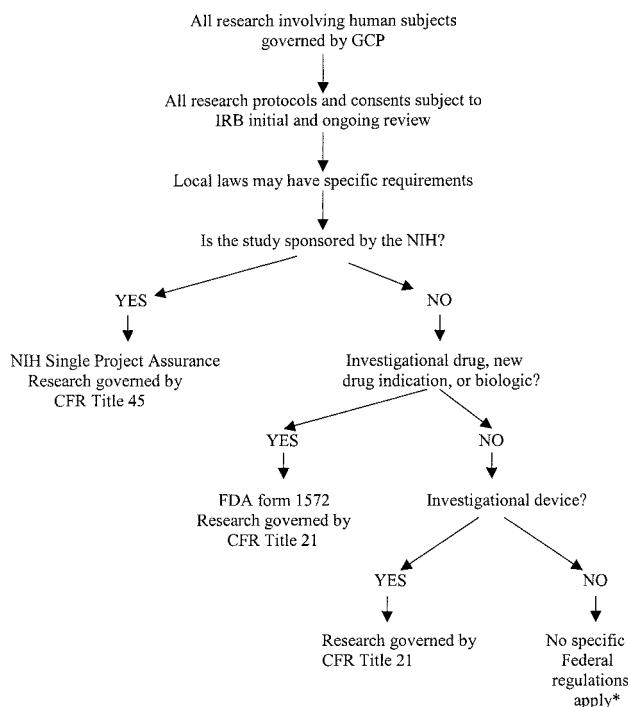
As a general rule, placebo arms should not be used in clinical trials if there is already an effective standard treatment for the condition. In 2002, the World Medical Association revised the Declaration of Helsinki to allow exceptions to this rule for minor conditions in which the temporary omission of the treatment would not cause serious harm to the patient or if there were “compelling and scientifically sound methodological reasons” to use a placebo.²⁴ The former exception is widely accepted, but the latter remains deeply controversial, even though regulatory agencies (such as the US Food and Drug Administration [FDA]) still often require placebo controls.²⁵

Local standards of care should also, of necessity, be taken into account. The potential risk-to-benefit ratio of any planned intervention needs to be considered carefully before patients are enrolled into a trial.

When recruiting patients into a study, treating physicians must tell them that their participation or lack of participation will in no way affect their future care. Although this is explicitly stated in the informed consent document, there is a responsibility to avoid any sense of coercion when the study is presented to a patient, because patients often develop a sense of trust with their physician and can feel obligated to participate in a study if asked. Because there can be blurring of the roles of physician as caregiver and physician as investigator, particular attention must be paid when a trial is described so that the patient clearly understands that the intervention is not simply a part of his or her continuing care.²⁶

Financial incentives might also threaten the doctor-patient relationship. Reimbursement should simply be commensurate with the investigator’s effort involved, but there are times when financial pressures that must be dealt with arise. In response to a cash incentive, an investigator or study coordinator might be tempted to enroll patients into a study he or she might not otherwise consider, or to enroll patients who do not strictly meet entry criteria. Both examples illustrate unethical behavior, with the former violating the principle of avoiding harm to study subjects and the latter spoiling the integrity of the data being collected. The investigator must be scrupulous in avoiding circumstances in which it appears the trial is being performed for financial gain rather than scientific merit.

In situations in which an investigator could benefit directly from the outcome of the trial (testing a new device or a new biotechnological agent for which the investigator holds a patent), that individual should not be involved in the recruitment and consent phase of the study, given the powerful incentives to enroll patients.¹⁹ An investigator who is a major shareholder or who has a large financial interest (defined variously as more than \$10 000 to more than \$50 000)²⁶ in the company sponsoring or otherwise involved in the trial has a clear conflict of interest and



*Federal regulations may apply to Veteran’s Administration (VA) and Department of Defense (DOD) institutions or studies receiving their support

Figure 1. Overview of regulations governing human research. GCP indicates good clinical practice; CFR, Code of Federal Regulations; and NIH, National Institutes of Health.

should either avoid direct participation in the study or disclose his or her financial involvement clearly to potential enrollees and to the appropriate Institutional Review Board (IRB).²⁷

Financial or other pressures may tempt an investigator to falsify data, an illegal and unacceptable action. The investigator must hold himself or herself, along with the trial staff, to the highest ethical standards to maintain the integrity of the study. The investigator’s conduct must be able to withstand external scrutiny with respect to the scientific questions being addressed, the ethics of the intervention (and the control arm of the trial), and the financial aspects of the study.

Protecting Patient Rights: Informed Consent and IRBs

There are laws and regulatory agencies that are specifically concerned with protecting the rights of patients involved in a clinical trial. The investigator must understand his or her moral and legal obligations throughout the course of the trial and must conduct the trial according to the principles of good clinical practice,²⁸ a general term that encompasses federal regulations, guidelines, and local laws that may be applicable to clinical trials in a specific area. The organizations that have jurisdiction over various types of research, and their applicable regulations, are outlined in Figure 1. Investigators must also comply with new Health Insurance Portability and Accountability Act (HIPAA) regulations that aim to enhance the protection of patient privacy.

Informed consent is the process by which potential subjects are fully informed of the nature of their participation in the study,

indicate comprehension of the procedures involved, and sign an agreement to participate. These individuals cannot be coerced, lured by false promises of cures or benefits, or otherwise inappropriately enticed. Vulnerable patient groups, such as prisoners, are usually excluded outright from participating in trials, whereas others (children or the mentally ill) are afforded special protection. Potential participants (or their surrogates, if the patient is unable to provide informed consent on his or her own behalf) should have time to review the consent form, which can be lengthy, and should be able to discuss the project fully with the investigator before they agree to participate.

Language barriers provide another challenge to informed consent. If the concepts of the trial cannot be fully understood by the patient, enrollment should not be considered unless a competent interpreter is present. If non-English-speaking individuals are to be considered as potential study subjects, the consent document must be available in the appropriate language; consent documents in languages other than English are often available in international multicenter studies or in trials that target specific ethnic groups.

In most cases, no study intervention can be performed until the study procedures are understood and agreed to and the informed consent is signed. There are rare instances, involving emergency care in life-threatening circumstances,²⁹ for which informed consent is presumed and the need for a signed consent is waived. Trials of this nature are very closely supervised by their responsible IRBs.

In the United States, the FDA regulates the development and marketing of drugs, devices, and biologics. The FDA has outlined the scope and responsibilities of each institution's IRB and can review the activities of particular IRBs. These committees, composed of healthcare professionals and nonclinicians, aim to protect human subjects involved in research at their particular institution. They review the ethics of proposed research projects, ensure that consent forms are appropriate, and monitor the safety of ongoing trials. An IRB can recommend changes to study protocols or consent forms and can order a trial to be stopped at their facility if there are alarming safety or other issues. The IRB must approve any modification to the originally approved study protocol. Every institution conducting research must have an IRB; outpatient studies conducted from an office or clinic can be reviewed by an IRB from a local institution or a central location. In studies funded by the National Institutes of Health (NIH), investigators are required to have completed an approved online course in ethical conduct of research before the study can commence. Useful information on research ethics and IRBs is available from the Office for Human Research Protections at the Department of Health and Human Services (available online at <http://ohsr.od.nih.gov>).

As noted, institutions that conduct research have their own IRBs to review study protocols and monitor the progress of trials at their location. Smaller hospitals may not have active IRBs, and trials conducted with outpatients will usually not fall under the jurisdiction of an institutional IRB. To deal with these situations, many trials offer the option of utilizing a central IRB, which is a properly convened body that will perform the duties of an IRB for centers unable to find an IRB to review the trial locally. Investigators participating in outpatient trials can otherwise request the IRB from a local institution, if available, to

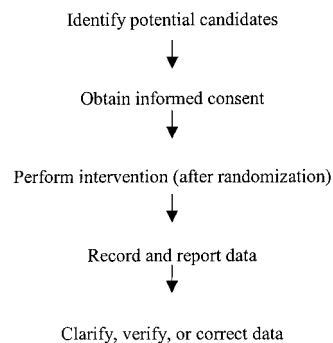


Figure 2. Steps in conduct of clinical trial.

review and monitor their studies, although some local IRBs may charge a fee for this service.

Multicenter studies usually have a Data and Safety Monitoring Board that is independent of the organization conducting the trial. This committee reviews study data as the trial progresses to detect significant benefits or risks of a study intervention before the trial's scheduled completion date. If they detect a highly significant trend of risk or benefit, they have the power to unblind the intervention and prematurely terminate the study; it is unethical to continue a randomized trial once it is clear there is a major risk or benefit of an intervention. An excellent reference that covers the conduct of clinical trials with special emphasis on protecting patient rights and the regulatory environment is available from the Duke Clinical Research Institute.³⁰

Although these regulations are important, one should be aware that they may represent more of a moral floor than a moral ceiling. In the final analysis, the best safeguard for patients who enroll in clinical trials is the character and virtue of those physicians who conduct the research and have sworn oaths that they will act in the interest of their patients.³¹

How to Conduct the Trial: Role of the Study Coordinator

Several steps are involved with each patient entered into a clinical trial (Figure 2). A competent study coordinator is central to the satisfactory conduct of a trial and is involved with most of the steps. A study coordinator is usually a nurse but may be a nurse practitioner, a physician's assistant, or a trained individual with a medical background. The study coordinator must be an organized individual, meticulous about data, responsive to deadlines, familiar with the clinical issues, and aware of relevant regulations, including the new HIPAA privacy requirements. He or she may also train individuals who might play roles in the trial: office staff to screen for study candidates or hospital nurses to administer the study drug. Resources and training programs for study coordinators are available through professional societies such as the Society of Clinical Research Associates, which can be contacted online (<http://www.socra.org>). Patients often develop a special relationship with the study coordinator because they usually interact with that person most frequently; this relationship is very helpful in maintaining compliance with an intervention and in ensuring complete follow-up with patients.

Inclusion and exclusion criteria for the study need to be well known by individuals likely to encounter candidates. Once an

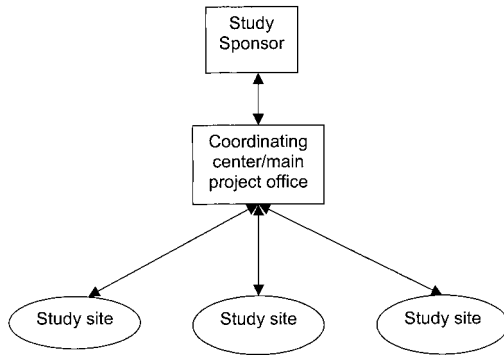


Figure 3. Simplified organizational structure of clinical trial.

eligible patient agrees to participate in the trial and provides consent, the patient is then usually subjected to a randomization process in which his or her treatment is assigned. Most trials use a computer-based randomization process, accessed via telephone or directly by computer using the Internet. The appropriate intervention is performed, which may be the administration of a drug, scheduling a test or a procedure, or the initiation of an outpatient medication.

Timely recording and submission of data to the central office are keys to the success of a trial. Here is where the efforts of a skilled and dedicated study coordinator are most appreciated. The data required can vary widely, depending on the nature of the study: There may be a single Case Report Form or a multipage booklet for data submission. Blood samples or other specimens might also need to be shipped centrally. Data may be mailed, faxed, or submitted directly by computer over the Internet. Some data will subsequently need correction or review, either because of missing information or simple errors in data entry or because of a need for clarification. Missing or faulty data reduce the likelihood that a study will have statistical power to reach an accurate conclusion.

The actual organization of a clinical trial can vary substantially, depending on such things as the nature and size of the study, whether or not there is federal (eg, NIH) or industry support, and whether an academic institution is involved (Figure 3). Generally, the study sponsor finances the trial. In an evaluation of a new drug or device, the study sponsor is often a pharmaceutical company or a device manufacturer, frequently paired with an academic institution or other organization providing the scientific input and expertise to establish the study protocol. Indeed, an academic institution often develops the study and then seeks industry or other support to help finance the trial. The actual conduct of the trial (ie, distributing the experimental drugs, conducting the randomizations, collecting the data, collecting and analyzing adverse events, verifying the accuracy of the data, and monitoring the study sites) is performed by the central project office/coordinating center. The coordinating center may be an academic institution or one of several commercial organizations that specialize in conducting clinical research. In small studies and some trials run by academic consortia, the sponsor and the coordinating center may be the same group. The clinical coordinator is generally the liaison between the study site and the trial coordinating center.

Most trials have mechanisms to report adverse events (AEs) to the central office. AEs must be shared promptly with other investigators so that the safety of the trial can be ensured. In new drug studies, AE reporting is mandated by federal regulations, besides being necessary for the construction of a safety profile for the drug. Serious AEs must be reported within a 24-hour period to the central office and to the local IRB. Many trials, particularly those involved in a new drug evaluation, will require reporting of all AEs, even if there is no clear relation to the study intervention. The reason for this is that a pattern of unusual AEs may not be apparent to an individual study site but may become clear when viewed in the aggregate trial data.

Before a trial can commence at a particular location, the principal investigator and the study coordinator must fully understand the study protocol in terms of eligibility, exclusions, and the actual intervention(s) and follow-up. There may be a teleconference, Internet-based training, or an investigator's meeting at a central location. They, in turn, will instruct other staff in the study protocol. In trials of several years' duration, there are frequently periodic investigator meetings, at which staff and investigators can ask questions, learn more about the study, learn about progress in related areas, and meet other participants. Other review or refresher programs may be conducted by teleconference or on the Internet.

Financial Issues in Conducting a Trial

Most trials compensate the investigator on a per-patient basis: a certain sum of money is provided for each patient completing the protocol with "clean" data (ie, complete and without error) transmitted to the study center. Payment for each subject is usually made in portions over the course of the study, either at a particular calendar interval (eg, quarterly) or at specific stages of a patient's progress through the protocol (ie, a certain percentage at randomization, a certain percentage after each follow-up visit, and a certain percentage after completion of the protocol).

Some studies, especially registries, require little additional effort beyond routine clinical care and may not place an extra burden on staff if the paperwork is simple. Reimbursement may only be a token sum per patient. There have been large trials of thrombolysis (eg, ISIS-3) that did not reimburse investigators at all. Paperwork for those trials was very simple, however, and thrombolytics were supplied, which provided an indirect financial benefit for the involved hospital.

Compensation should depend solely on the time and effort spent by the investigator and the support staff; details of reimbursement will vary depending on the nature and size of your organization. Finder's fees for referring patients to clinical trials are a form of fee splitting and are unethical.³² In practices without a full-time research nurse, study-related work might simply be considered part of an employee's regular duties, with compensation included in his or her basic salary. Study payments made to the practice can be paid directly to the investigator, into the practice revenue stream, or into a separate fund for current or future study-related expenses. A study coordinator can be paid either a fixed salary (which would require a fairly steady stream of trials) or an hourly or per-patient rate from ongoing study reimbursement. Enthusiasm on the part of other employees might be stimulated by salary adjustments based on their degree of participation in the trial. Other physicians in the practice may

be remunerated for work related to the recruitment of their patients into studies.

Hospital-based studies present different challenges. Hospital staff may not at first be amenable to the extra work involved with a study, but they can also be kept motivated by the prestige and intellectual satisfaction of participating in a trial or by update luncheons or other meetings. Hospital personnel cannot be paid directly by the investigator, but payments can be made to the appropriate hospital units as part of an education fund or to the hospital on their behalf. If study payments are made directly to the hospital, arrangements must be made in advance with regard to how they are apportioned and how the investigator and staff (if necessary) will receive their reimbursement. Hospitals may want to deduct a portion of any trial payment as a cost of supporting the trial (institutional overhead); this must be negotiated before the receipt of any payments. Hospital administrators should understand that their institution may receive indirect financial benefit from participating in a trial: expensive drugs or devices may be supplied as part of the study intervention, decreasing the hospital's cost of caring for the patient.

Whether a trial is conducted in an office or hospital setting, the prestige of being involved in a clinical trial, as well as the possibility of key personnel being sent to study meetings, should be considered as part of the remuneration. This generally will lead to further physician education, improved staff training and education, and improved patient care.

Other costs may be involved in conducting a study. Some supplies, such as dry ice for shipping samples, may not be directly covered by the study payments. Laboratory tests might need to be obtained as part of patient management, although if tests are specified by the protocol, their cost should be covered by the trial reimbursement. If there is a likelihood of noncovered study-related laboratory expenses, such as might be involved in pretrial eligibility screening, the investigator can often negotiate a discounted rate with a laboratory or other provider for these services. These and other miscellaneous expenses can then be covered by a "research fund" established with surplus funding from earlier or ongoing trials. Investigators should be aware of any noncovered expenses before participating in a study.

If an investigator sees a patient solely for follow-up in a study, it is inappropriate for that physician to bill the patient for an office or a hospital visit. A benefit for patients' participating in a clinical trial is the understanding (explicitly stated in the informed consent) that there will be no cost for participation. In trials for which there is long-term follow-up and for which study visits are considered incidental to regular visits scheduled for ongoing care, it is ethical to bill the patient for an office visit while still receiving remuneration from the study for the data processing involved. Any procedures required as part of the study, however, are paid for by the trial and should not be billed to the patient. The trial should cover research costs, whereas patients may be billed for ongoing medical care.

Selecting a Trial

Clinical trials are constantly being organized. The following institutions/corporations can be consulted to find out about studies that are looking for investigators: large academic institutions involved in multiple multicenter trials (eg, the Brigham and Women's Hospital, the Cleveland Clinic, the Duke Clinical Research Institute, the

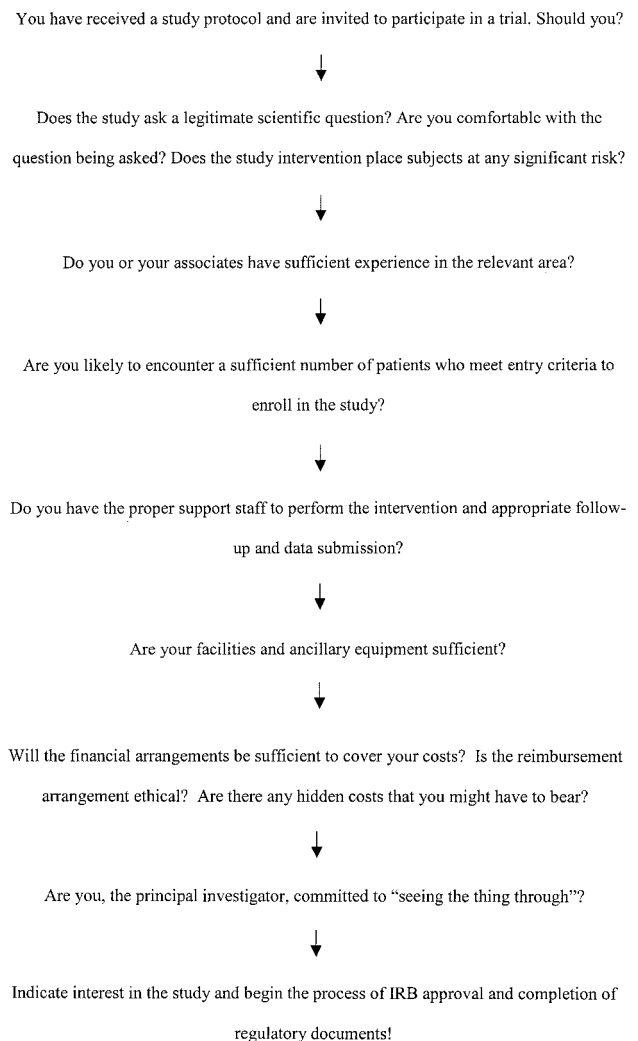


Figure 4. How to decide whether to participate in clinical trial.

Mayo Clinic, and McMaster University), commercial study management organizations, the NIH World Wide Web site (<http://www.nih.gov>) or publications, and local pharmaceutical or medical device representatives.

The National Institutes of Health (NIH) recognizes the need for developing new partnerships of research with organized patient communities, community-based physicians, and academic researchers. The importance of this concept is echoed in the recently released NIH Roadmap initiative (<http://nihroadmap.nih.gov>), within the "Re-engineering the Clinical Research Enterprise" theme. NIH will establish a cadre of National Clinical Research Associates, composed of community-based practitioners receiving specialized clinical research training. The National Clinical Research Associates will participate in national studies, facilitate the sharing of data and resources, and augment clinical research performance and analysis through a clinical research informatics network: the National Electronic Clinical Trials and Research Network (NECTAR), another Roadmap initiative.

Once an invitation to participate in a clinical trial has been received, there is a series of questions to address (Figure 4), which we have discussed above. Personal commitment to the

study may be the single most important factor; if the leader is lackadaisical, recruitment will likely lag, and data may be incomplete or inaccurate.

The importance of having a dependable, experienced, and well-trained study coordinator cannot be overestimated. Before committing to participate in a trial, staff should be aware of the nature of expected time commitments. If the trial will take place in a hospital, the hospital staff must be willing to fulfill their potential roles in the study.

There may be special facilities or equipment issues to consider. Study drugs and records will need to be kept in a secure, locked area. Some trials require certain apparatus such as a centrifuge, a special freezer for storing blood samples, or a source of dry ice for shipping specimens. Blood samples or other specific tests may be required. An onsite catheterization laboratory may be necessary for certain interventional studies. All of these issues need to be carefully considered before one agrees to participate in a trial.

The contract with the study sponsor or research organization should be reviewed carefully. Investigators and their staff should be indemnified, confidentiality clauses should be reasonable, and there should be a commitment to publish the study data regardless of the results. When a trial is selected carefully and appropriately, participation will be an exciting and rewarding experience for the investigator, the patients, and the staff members involved.

Conclusions

Practicing physicians need to enlist as investigators in the rapidly growing number of trials evaluating new drugs, devices, and treatment strategies to ensure the continued development of knowledge and improvement of patient care. The data they generate may be immediately applicable to the unselected, general population, an advantage not necessarily shared by trials conducted at tertiary centers. With the proper background, experience, support staff, and commitment, physicians in private practice can keep themselves on the cutting edge of a therapy while making a contribution to modern medicine.

Acknowledgment

The authors thank Lawrence Friedman, MD, NHLBI Acting Deputy Director, for reviewing this manuscript and John Daniel for editorial assistance. The authors also thank Laura Cramer, ScM, for her help with the statistical appendix.

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