

Clinical Trials: The Basics of Operation and Participation

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WITH CARL D. REGILLO, MD, FACS; JOEL A. PEARLMAN, MD, PHD; AND DAVID S. BOYER, MD



Clinical research is vital to the advancement of medicine. Before new therapies become available to patients, a lengthy experimental process is undertaken, including evaluation of treatments on human subjects. If a therapy seems promising, phase 1, 2, and 3 clinical trials are performed to assess the safety and pharmacodynamics of a therapy or drug, dosing requirements, efficacy, and comparison to the standard of care in a randomized controlled fashion.

Patient recruitment can be time-consuming, as inclusion and exclusion criteria are quite specific, and large numbers of patients are typically required to adequately assess the safety and efficacy of a therapy before approval by the US Food and Drug Administration (FDA). For this reason, clinical trials require a large number of physicians to evaluate and treat the number of patients necessary to properly complete a study. Physician participation in clinical research is ever-expanding, and it is our role to become involved in trials to perpetuate the growth of scientific knowledge. We interviewed Carl Regillo of the Wills Eye Institute (Philadelphia, PA), Joel Pearlman of the Retinal Consultants Serving Northern California (Sacramento, CA), and David Boyer of the Retina-Vitreous Associates Medical Group (Los Angeles, CA) for a variety of perspectives on what young retina specialists need to know to participate in clinical trials. For more information regarding trials, please visit clinicaltrials.gov.

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HOW DO I INITIATE PARTICIPATION IN CLINICAL TRIALS?

Carl D. Regillo, MD, FACS: Clinical trials are usually sponsored by drug companies, although some studies, such as the recent CATT (Comparison of AMD Treatments Trial), are government funded. The best way to initiate contact with a pharmaceutical company is to keep informed as to which trials are currently recruiting and which companies are involved. You should find out who the scientific research personnel in the company are (typically not the people involved in marketing) and approach them directly. If you have a particular idea for a project using their therapies, the scientific personnel are typically the best people to discuss the feasibility of this idea with. In addition, trials may be performed with FDA-approved treatments for off-label use, and the pharmaceutical company can help provide the medication.

If a company is interested in your participation, you will often be asked to fill out a questionnaire or survey, includ-

ing the numbers of patients you are seeing with the diseases that the company is interested in and what you are treating them with. Pharmaceutical companies want to get indicators that you will be able to recruit an adequate number of patients in a timely fashion for their study before they invest in funding your site, which can be quite expensive.

Young physicians who are interested in research can benefit by joining a group with prior research experience. Often, practices have already built relationships with particular drug companies, making it easier to initiate contact or to begin participation in active trials. If a given practice has already participated successfully in previous trials, sponsors are more likely to fund the same group for their study, as they are more assured that an adequate number of patients will be recruited.

Joel A. Pearlman, MD, PhD: Before becoming involved in clinical trials, you must be assured that you are pursuing

research because of your passion for the advancement of medicine and a desire to change the field. Clinical research can be extremely time-consuming, burdensome to the overall function of a private clinic, and a general pain in the you-know-what, so financial gains or the appeasement of an upper-level colleague or chairman will ultimately not be adequate incentive. Once you have assured yourself that you are pursuing clinical research for the right reasons, there are 4 main types of trials: large company-sponsored trials which are usually randomized controlled studies, smaller investigator-sponsored trials (ISTs), large government-sponsored trials which are also usually randomized and controlled, and small physician-sponsored trials.

Company-sponsored trials are most of the big studies we hear about, such as the MARINA and ANCHOR trials. For these trials, the companies have already applied for Investigational New Drug (IND) approval through the FDA and have recruited physician scientists to oversee the trial. ISTs are smaller trials that can be designed by individual physicians and are also important to both patients and companies, as they may help expand the indications for a particular therapy. In an IST, the physician may have to apply for an IND and/or perform some additional legwork to get the trial up and running.

To become involved in company-sponsored trials and ISTs, the best person to speak to is the medical science liaison (MSL) of a particular company. One can discover who a particular pharmaceutical company's MSL is by asking other physicians who have done research with the company, by asking pharmaceutical representatives, or by researching the company in a variety of other ways. To participate in a government-sponsored trial, the best person to speak to is the principal investigator (PI) of the study. Physician-sponsored trials are more self-explanatory; they are usually run by a group of colleagues who decide to pursue and fund a specific research idea for the benefit of medical practice.

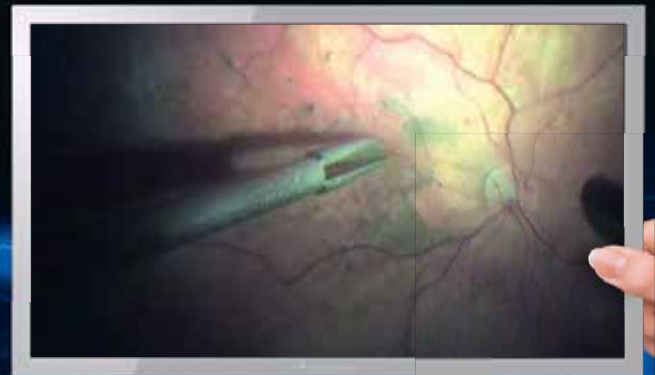
David S. Boyer, MD: As Dr. Pearlman mentioned, you must first understand what the undertaking means to become involved in clinical research. You should know what becoming a clinical investigator entails. The PI of a study is in charge of all the workings and personnel in a trial, including subinvestigators, photographers, and research staff, as well as the proper maintenance of data. Clinical research is extremely time-consuming, and your primary goal should be the advancement of medicine and love of science.

To start participation in trials, it is helpful to contact representatives from a particular drug company. Clinical research organizations (CROs) may also be contacted directly. Government-sponsored trials are often easier to

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become a participant in; however, they are often more time-consuming as they are typically quite complex and require investigators to attend courses and conferences. To determine the feasibility for a particular center to participate in any given trial, clinicians often must initially complete questionnaires detailing the number of patients with a particular disease being seen, and what type of equipment and personnel the clinic has.

HOW DO I ASSURE THAT I'M CONDUCTING RESEARCH PROPERLY?

Dr. Regillo: Before becoming involved in clinical research involving human subjects, it is crucial for the investigator to become familiar with the Good Clinical Practice (GCP) guidelines. GCP is the worldwide consensus standard for conducting clinical research in human subjects. The FDA has also laid out a number of regulations and guidance documents for the conduct of clinical trials, which the investigator must familiarize him/herself with. Human subject participation (HSP), including informed consent, is highly regulated by the FDA.

Every study must be approved by an investigational review board (IRB). If the study is being performed in an institution, the institutional IRB is used, and if the trial is performed in a private setting, a centralized IRB can be used. It is important for the clinician to learn how to submit a project proposal to their IRB. Fellowship is a great time to figure out how an IRB works, how to submit to an IRB, and what it takes for a study to be approved at a given institution.

Once a study is under way, a research site is always subject to auditing, either by the FDA or by the trial sponsor. It is therefore imperative that your site maintain proper order of all documents and health records. Investigators are subject to a number of adverse legal actions if studies are improperly conducted. The FDA also frowns upon financial incentives for patient recruitment.

It is important for all patients recruited in a study to understand all possible treatment options and for the researching physicians to make sure informed consent is conducted properly. Particularly in placebo-controlled trials, the patients must understand that a particular treatment may not benefit them specifically. Rather, the goal of many studies is to benefit other patients in the future. Patients must also realize that there may be a substantial time commitment, sometimes requiring frequent visits over multiple years.

The PI is the person responsible for all materials and patients in a study. The PI oversees the proper conduct of the study, patient recruitment, and data collection and handling. Investigators and research coordinators are often asked to participate in investigator meetings, which are often 1 or 2 days long. Investigator meetings are often

important to review the trial protocol and to assure that proper inclusion and exclusion criteria are being met.

Once you start participating in a clinical trial, most of your contact with the company is through a CRO. A CRO provides the pharmaceutical company with support in managing clinical trials and contacting the FDA for approval of the research and ultimately approval of the drug for human use. Members of the CRO are typically the people who come to your site to make sure the study is being conducted properly.

Dr. Boyer: It is helpful to become involved in clinical research during fellowship, in order to understand how clinical research is run and how to report to an IRB. Patient safety is the most important, as you are dealing with investigational treatments that may have side effects not immediately apparent. It is easy to sign people up for trials, but often difficult to keep them in studies because they did not realize the time commitment to the research and the potential lack of benefit to them if they are receiving a sham or placebo; therefore the informed consent process should be lengthy and detailed.

WHAT KIND OF INFRASTRUCTURE IS NEEDED TO PERFORM CLINICAL RESEARCH?

Dr. Regillo: Performing successful clinical research requires physical space and equipment as well as adequate personnel. The office location should be sufficiently busy to recruit patients, but not so busy that research becomes difficult to perform. Trials usually use ETDRS vision testing, including proper refraction; therefore a phoropter, lenses, and ETDRS chart are needed. Sufficient space for vision testing is also needed; some trials require an extended vision lane. Ophthalmic technicians must be properly trained to perform vision testing. If multiple trials are being performed, a technician specifically devoted to clinical research may be necessary.

Often, studies require photographic documentation, including fundus photos, fluorescein angiography, and optical coherence tomography. A reading center is often used to assess the images, and the ophthalmic photographer typically must be certified by the reading center for the images to be used. In some instances, intravenous infusions or blood testing is also part of the study, and a registered nurse may be necessary to perform some of these functions.

With the wealth of data and paperwork obtained during a trial, a clinical research coordinator is also required to ensure that all patients are receiving the appropriate treatment and follow-up and that the data are recorded properly. In some instances experienced coordinators can manage more than 1 study, but often 1 research coordinator is necessary for each busy study (more than 6 patients enrolled).

Dr. Pearlman: In addition to what Dr. Regillo mentioned, some trials require the presence of both a masked and unmasked physician on the same day. Often, the masked physician is the PI and is primarily involved in evaluation of the patient, while the unmasked physician delivers the treatment, placebo, or sham. For these trials, therefore, 2 physicians must be in close proximity on the same day. The trial may also require both masked and unmasked staff, so additional staff may become necessary.

Physical space and equipment can also become an issue. In some trials, a particular type of OCT machine may be required. If your practice does not own that particular OCT device, you would not be able to participate in the study. Some trials require a 4-meter vision lane, which may not be available in some locations. If you want to run a trial in a separate office, additional research equipment and personnel are required. For example, we recently opened a research unit in another office and had to hire a contractor to create a vision lane for research and beg our clinical research coordinator to drive more than an hour to the office on designated research days.

Dr. Boyer: To start, it may be best to participate in smaller prospective trials and chart reviews. You might find that you do not have the time, resources, or personnel to conduct proper research. Even if you theoretically have the proper personnel, you will find that certain elements of trial research, such as photography, are much more time-consuming than you initially imagined. It is very important to have good staff who are capable of becoming certified for research and participating in trials. Adequate research coordinators and staff are crucial. The feasibility of trials in your clinic often depends on how many patients are recruited and how long the trial lasts: 6 months, 12 months, or even several years. If a number of patients are recruited in a time-consuming trial, coordinators are often kept busy inputting data and making sure that patients have properly scheduled appointments for that trial alone.

HOW DO I MAKE A CLINICAL TRIAL FINANCIALLY FEASIBLE?

Dr. Pearlman: Again, it is important to remember that financial reimbursement is not the primary goal when it comes to research. In our practice, the motivation for a physician to recruit patients in a study is for the advancement of medicine. We do not separate research from insurance monies in our practice, and each partner receives the same share of research funds. Once a culture of altruism is created in practice, the ability to recruit patients falls into place. Patients are often eager for the

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chance to advance medical care for others. We use the rationale behind the study design to explain to patients why the study is important for both them and future patients.

That being said, to make a trial financially feasible, you should choose a study that pays sufficiently for your time, effort, and resources. Do not be afraid to negotiate with the sponsor if you are participating in a company-sponsored trial. Companies often create an itemized budget for your reimbursement, but these budgets are usually negotiable. For example, the company may not factor individualized prices for things such as fluorescein angiography, which may cost much more than the normal rate of reimbursement as photographers must spend the time it takes to become certified for a reading center.

In company-sponsored trials, reimbursement per patient is often much higher than standard insurance rates. Remember that you are doing work for a pharmaceutical company that may reap enormous financial success from the research that you are performing. It is important, however, to remember the huge amounts of money it takes to bring a drug to market. It costs around \$100 million to bring a pharmaceutical agent to phase 2/3 trials, and only one-tenth of those agents make it to market, so each drug brought to market costs the company approximately \$1 billion. Conversely, for government-funded studies, reimbursement is often at the Medicare level.

Another important point is to make sure not to overstaff your research unit, but rather to hire excellent staff that can fulfill multiple roles. Study coordinators are crucial to the smooth running of clinical trials. Coordinators often must manage study monitors, data collection, and a host of other responsibilities, and therefore must be proficient multitaskers. For this reason, it is better to pay a good coordinator well than to hire several mediocre people to perform the same tasks. Along the same lines, it can be possible to be involved in too many clinical trials. If you have several trials looking at exudative macular degeneration, for example, each trial may take away from patient recruitment from the other.

Dr. Regillo: Funds for a study are usually carefully laid out based on the specific requirements per each patient enrolled. The drug company typically assigns particular monetary values for personnel and equipment used, which can sometimes be negotiated with the investigator depending on your site requirements. Each patient recruited at a particular site allows the study to become more financially feasible for both the clinician and the sponsor.

To help with patient recruitment, if a number of different studies are being conducted in a practice simultane-

ously, it is helpful to have basic inclusion and exclusion criteria posted in the clinic rooms and to remind participating physicians to enroll patients. In our practice, we set aside research income separately from our standard income, and we use a point system with points given to each physician based on the number of patients recruited in a study. Those with more points for a given study will therefore receive that amount of compensation from the research income, which is a fair way to be properly reimbursed as an individual investigator.

Clinical research is very time-consuming. Informed consent for a clinical trial is much more involved than that for other standard treatments for a given condition. The clinical investigator should assume that some of his or her time will be sacrificed to participate in a study. This may initially mean sacrificing income as well; however, once a clinical research infrastructure is in place, financial sacrifices for a clinical researcher can be minimized.

Dr. Boyer: It is often impossible to make clinical trials financially rewarding, so the most important reason to participate is for the love of research. Although time-consuming and difficult to perform in a busy clinical setting, clinical trials are extremely rewarding. Clinical research allows us as clinicians to participate in the advancement of medical therapies that ultimately can greatly benefit our patients. ■

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