Clinical Research 2021

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KEYWORDS

• Clinical research • Clinical trials • Regulation • Protocol

KEY POINTS

- Clinical research is of great benefit to patients and rewarding to clinicians.
- Clinical research in the United States is highly regulated.
- There are significant penalties for violating protocols.
- Clinical research requires a good infrastructure in each practice.

MANAGING A RESEARCH PROGRAM IN 2021

Why Do It and What Are Benefits of Doing It?

During residency and fellowship programs, most urologists have an opportunity for clinical and/or basic science research. When choosing private practice, however, many urologists believe this opportunity would be lost. Doing research in private practice is extremely rewarding and uses skills not used routinely in the course of clinical practice. It is an opportunity to be on the cutting edge of urology treatment and to use pharmaceutical agents before they are approved by the Food and Drug Administration (FDA). Common research trials in recent years have included studies of drugs and devices for benign prostatic hyperplasia, erectile dysfunction, stress urinary continence, bladder cancer, prostate cancer, kidney cancer, overactive bladder, and other conditions. It is an opportunity to offer patients who have failed traditional therapy a new option, and it can help retain patients who often might have to travel a great distance to an academic medical center to have access to these agents. In addition, it can be rewarding and enjoyable for clinicians when a drug ultimately is approved, and the urologists concerned then are experts among their peers because they have been using a drug/device for several years prior to FDA approval. It also can be a source of revenue for the practice, but financial gain should not be a reason for establishing a clinical research program in private practice. In summary, a clinical research program directly benefits patients by giving them access to drugs and devices when the patients have failed or cannot tolerate traditional therapy; a clinical research program allows a practice to retain patients instead of referring them to an academic medical center that might require the patients to travel a great distance; it can be a source of revenue; and it allows a urologist to become a credible expert on a new treatment by having used the therapy prior to FDA approval.

The Research Landscape in 2021

The research landscape has changed dramatically over the past decade. The clinical trials in urology are focused more on oncology than on other areas, and these trials often require recruitment of patients with very specific characteristics, making it difficult to have high-volume recruitment for any single trial. The devices also are more sophisticated and require specific inclusion criteria. In addition, there has been significant consolidation in the contract research organization (CRO) business, so relationships with the current CROs are important. Finally, sponsors, institutional review boards (IRBs), and the FDA have been exercising more oversight, so it is important that every research site be prepared for a time-consuming audit.

Practice Support

One physician cannot drive a successful research program. Research must be an initiative that the entire practice supports, because it requires all of the providers to understand the trials and to participate in recruitment. The primary investigator (PI) for the trial must be given time during the day

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to perform the clinical visits, meet with research staff, and meet with the clinical monitors. If the practice compensates its providers on a productivity model, then the PI must be compensated appropriately.

Types of Clinical Trials

Phase I trials often require an inpatient research facility and are the most difficult trials to conduct because a drug is being tested in a small group of humans, often for the first time, and the full range of side effects is unknown. In phase I trials, the subjects and the researchers know the drug and the dosage that they are receiving, and the dose usually is escalated until such time as the subjects experience significant side effects.

In phase II trials, the experimental drug or treatment is given to a larger group of people at a specified dose or several doses to test its efficacy and monitor side effects. Sometimes, if the drug is being tested in a rare disease state that has limited opportunity for recruitment, a phase II trial actually can lead to FDA approval in certain circumstances.

Phase III trials are the most common trials conducted in a private practice clinical research program. These usually are double-blind trials conducted across many sites in large numbers of patients at specified doses to truly measure efficacy and safety of a new drug.

Phase IV trials are postmarketing studies conducted after a drug has been approved for treatment by the FDA and provide additional information about a drug's risks and benefits.[1]

These are the accepted 4 phases of clinical trials, but the studies themselves can be classified by category:

Treatment research—involves drugs, devices, or new therapies to effect a cure for a disease state

Prevention research—looks for therapies to prevent disorders from developing or recurring

Diagnostic research—looks for new ways to identify a disorder or condition

Screening research—finds the best ways to identify a disorder or condition

Quality of life research—seeks to find ways to improve the quality of life for patients with chronic conditions

Genetic studies—seek to understand how genes and disorders are related. These studies are becoming much more common, particularly in oncology.

Epidemiologic studies—try to identify patterns and causes of disease[2]

Note that some clinical trials are designed to gather a substantial amount of data and can overlap in several of these categories, particularly in oncology.

Clinical Research Organizations

Many trial sponsors do not have the resources to conduct a clinical trial, so they hire professional CROs to recruit sites, conduct the trials, and in some cases analyze the data. A CRO may provide services, such as biopharmaceutical development, biologic assay development, commercialization, preclinical research, clinical research, clinical trials management, and pharmacovigilance.

Staffing

Principal investigator/medical director

Once a practice decides to embark on a clinical research program, it needs to hire dedicated staff who are assigned exclusively to the program. The PI, who usually serves as the medical director for the program, needs to have time carved out of the normal work week to oversee the program, conduct patient visits, review results, and monitor patient compliance and side effects. The FDA regards the PI as the individual who is responsible for the conduct of the trial at the study site, and, although the PI may delegate responsibilities, ultimately the PI is responsible for everything that happens at the site.

Subinvestigators

In a large practice, the PI has other clinical responsibilities, so other physicians and advanced practice providers are able to serve as subinvestigators to ensure compliance with the research protocol and to help recruit patients into the trials.

Lead clinical coordinator

The lead clinical coordinator leads the research team on a day-to-day basis. It helps, greatly, if this person is a registered nurse or licensed practical nurse so that they have the skills to draw blood, start intravenous lines, administer medications, and perform electrocardiograms and other clinical tasks. They should be experienced, to understand the importance of meticulous documentation and how to handle an FDA audit. This individual is responsible for training the other coordinators and should have a reasonable knowledge of reviewing and negotiating research budgets. In short, this person is the key member of the team.

Clinical coordinator

Clinical coordinators are delegated tasks by the PI and, like the lead coordinator, should be dedicated to research and not have other responsibilities in the practice. They need to have good clinical skills and great rapport with patients because some of the research visits can be quite long. An experienced coordinator, depending on the complexity of the trial, typically can handle 1 to 2 trials in the active recruiting phase, 1 to 2 trials in the clinical visit stage, and 2 to 3 trials in the follow-up stage after most of the visits have been completed.[3]

Resources

Data and information technology support

Although many sponsors of clinical research trials provide an advertising budget to recruit patients from outside the practice, most patients who are enrolled into trials are patients of the practice, so maintaining a good database and being able to use analytical tools to scan the electronic medical record system are extremely important. It is important for a site to take a clinical trial only if it has the staffing and resources to conduct the trial properly. Also, because it is expensive for a sponsor to initiate a site, if a site performs poorly by having multiple protocol violations during monitoring visits or fails to meet its recruitment goals, the site could be blacklisted and not given any more trials in the future by the sponsor or CRO.

Standard operating procedures

Every research site should have a handbook of standard operating procedures (SOPs) for all tasks that could be required of site personnel. Every member of the team should sign the book, indicating that they have read it and agree to comply with the SOPs. It should be updated on a regular basis. Although SOP binders are available for purchase, it is better if they are developed in house and reflect the actual practices of the site.

Regulatory and Compliance

Form 1572

FDA Form 1572 as well as a financial disclosure form should be completed by all individuals at the research stie for each clinical trial. The form is published by the FDA and should be updated on an annual basis or if circumstances change where a site member has a significant financial or other conflict in performing the trials.[4]

Good Clinical Practice

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials. It also serves to protect the rights, integrity, and confidentiality of trial subjects. Most sponsors of clinical trials require site personal to be GCP certified and the certification to be updated on a regular basis. GCP courses are available online.[5]

Code of Federal Regulations

The FDA, having been given Congressional authority, creates the rules and regulations for conducting clinical research. These regulations, although technically not laws, have the force of law and are codified in the Code of Federal Regulations (CFR), and there are serious penalties for not following them, including being banned from conducting clinical research.[6]

Institutional review board

An IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities. Most academic institutions that conduct clinical research have their own IRBs, whereas clinical research conducted at private practice sites often uses a nationally recognized central IRB. The members of an IRB usually include clinicians, researchers, clergy, ethicists, and members from the community at large. The job of the IRB is not to write or rewrite a protocol but to protect the rights and welfare of all patients enrolled in the trials, to monitor the studies for adverse events (AEs) and serious adverse events (SAEs), and to review and approve all amendments to the protocols. Members are obligated to recuse themselves if they have a conflict of interest.[7]

Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment (**Box 1**).[8] This is a broad definition and is designed to capture anything that a patient reports as different while participating in a clinical trial. The sponsor provides a timeline for the reporting of AEs and requires the PI to decide if the AE is related to the treatment that the patient is receiving in the trial. The AEs are reported to the IRB, and the IRB has the power to halt or to terminate the trial in order to protect the patients enrolled in the trial. AEs are graded (see **Box 1**).

Serious Adverse Events

An SAE is an AE that results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect.[9] An SAE usually must be reported to the sponsor and IRB

Box 1
Grading of adverse events

Grade 1: mild or minimal symptoms. Intervention rarely is indicated.

Grade 2: moderate symptoms. Minimal or noninvasive intervention is required.

Grade 3: severe symptoms requiring medical intervention, but not life threatening

Grade 4: life threatening event requiring urgent care

Grade 5: death

within 24 hours of the event occurring. Failure to do so could result in the closing of the research site. Ultimately, it is the decision of the PI at the site to decide if an SAE has occurred and to determine the causality to the trial.

Monitoring Visits

During the conduct of the trial, the sponsor or CRO managing the trial conducts regular visits to the site to ensure compliance with the protocol.[10] There usually is a visit to the site before site selection, a start-up visit to review the protocol, a visit after the first subject is enrolled, regular visits during the trial, and then at least 1 close-out visit. It is important that the study coordinator in charge of the trial be available during these visits to the study monitor as well as the lead coordinator. The monitor usually wants to meet with the PI to discuss the findings of the visit and usually sends a formal letter discussing any deficiencies found during the visit, which must be reviewed and corrected, if possible. It is important that the monitor finish the visit feeling that the PI truly is involved in supervising the trial and is aware of the enrolled subjects, has conducted the visits, and has reported any AEs.

Budget Development and Accounting

Research can be a profit center for the practice, but money should not be the motivating factor to establish a clinical research program. Many programs believe they are profitable when in fact they are losing money. It is important to negotiate a start-up fee from the sponsor that covers the fixed costs of the trial and to negotiate an archiving fee when the trial is done, because most sponsors want the records stored on site for at least 6 months and then off site in perpetuity. When calculating budgets, be sure to include rent; utilities; depreciation on equipment, such as refrigerated centrifuges; and costs of performing examinations, blood draws, and other diagnostic tests, including radiologic studies. Shipping containers, dry ice, wet ice, and packing materials also should be budget line items. In short, if a site is not attentive to every detail in the study and the time required from each member of the research team, the trial could result in a substantial financial loss even if enrollment was good.

Sources of Clinical Trials

Industry

Industry-sponsored trials are one of the most common sources of clinical trials and typically have the best budgets because the sponsor intends to sell the drug or device for a profit after receiving FDA approval.[11] Often, the trials are managed by CROs, and the sponsors review their databases to see which sites have performed well in past trials. It is important for a site to decline a trial if they do not have the resources or patient population that has been requested. Advertising well yields some new patients but advertising cannot be relied on predominantly to fill the trial slots. Budget negotiations take place with the CRO or the industry sponsor directly, who has a record of what the site was paid in the past. If costs have increased or the trial is more complex and requires more resources, a case usually can be made for an increased budget, especially if the site has performed well in the past. Medical science liaisons who visit the practice often are knowledgeable about upcoming clinical trials for their company and can recommend sites.

Cooperative groups

Cooperative groups include the Society of Urologic Oncology Clinical Trials Consortium, the Southwest Oncology Group, the Radiation Therapy Oncology Group, the Eastern Cooperative Oncology Group, the Comprehensive Unit-based Safety Program, and others. The National Cancer Institute funds these groups to study adult cancers. Membership usually is required to participate in the trials, and most of the members are academic centers. The budgets for these trials are not lucrative and often barely cover costs. The trials, however, usually are well designed, and participation in them is considered prestigious.

Investigator-initiated trials

Most pharmaceutical companies encourage investigator-initiated trials (IITs). The process to approval can be laborious, and the budgets usually are limited. Conducting an IIT can be rewarding but requires a lot of resources from the site, which essentially serves as its own CRO and must follow GCP and FDA regulations. Only

sites that have an experienced PI with experienced staff should undertake IITs.

Academic center

If a private practice site has a good relationship with the local academic medical center, then the academic center may reach out to the private site to help with patient recruitment because private groups often see a higher volume of patients. These trials usually are funded by industry or federal grants, so the budgets are limited but can provide an opportunity for patients to have access to a novel treatment.

Subject Recruitment

Site databases are the best way to recruit subjects for clinical trials. It is good practice to keep a log of all patients who are screened for a particular disease state, because they may screen fail for a specific trial but might meet criteria for another trial.[12] Also, sometimes patients who complete a trial and have had a good experience may be willing to participate in future trials. Using the electronic medical record, it also is possible to search for patients with specific conditions who might consider enrolling in a trial.

Most sponsors provide IRB-approved signs that can be placed in waiting rooms advertising for a specific trial. Radio, television, and newspaper advertisements also can be helpful. Clinical research trials also can be advertised on a practice Web site.

Staff members, such as medical assistants and nurses who interact with patients, can suggest to patients that they speak with the doctor about a clinical trial. Urodynamics nurses often know if a patient is a candidate for a clinical incontinence trial and can discuss the options with the patient.

Patient support groups for various disease states, including prostate cancer, bladder cancer, interstitial cystitis, and incontinence, should be notified about new clinical trials and opportunities for patients who have failed traditional therapies.

It is important to let the referring physicians know that about the research and, although a practice may not have an IRB-approved recruitment letter for every trial, it certainly is acceptable to let referring physicians know that a practice does clinical research and the broad disease characteristics of the ongoing trials. Patients in clinical trials also may refer friends to the site.

Audits

Audits can be conducted by the sponsor, the CRO, the IRB, or the FDA.[13] Sometimes the audit is for a specific cause, if a deficiency is suspected, and sometimes it is a random audit, particularly if a site is high enrolling in a clinical trial. An FDA audit is a serious and time-consuming affair, so most sponsors require that if a site is served notice by the FDA of an impending audit, the site must contact the sponsor so that they can send in a team to help the site prepare for the FDA visit. Depending on the number of visits and length of the clinical trial, an FDA audit can last days, weeks, or even months, so the entire research team should be available while the FDA is on site.

According to the FDA, the "FDA conducts clinical investigator inspections to determine if the clinical investigators are conducting clinical studies in compliance with applicable statutory and regulatory requirements. Clinical investigators who conduct FDA-regulated clinical investigations are required to permit FDA investigators to access, copy, and verify any records or reports made by the clinical investigator with regard to, among other records, the disposition of the investigational product and subjects' case histories. See 21 CFR 312.68 and 812.145. The FDA investigator typically performs this oversight function through on-site inspections designed to document how the study was actually conducted at the clinical investigator's site. For investigational drug studies, clinical investigators must retain study records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified. See 21 CFR 312.62(c)."

There are several outcomes that can result from an FDA audit. The best action is no deficiencies as the inspector finds that the site was in total compliance. The next level is a written 483 form. The 483 describes any inspectional observations that, in the opinion of the FDA investigator conducting the inspection, represent deviations from applicable statutes and regulations. A FDA Form 483 usually results when there are protocol violations, documentation deficiencies, informed consent issues, or accountability of the investigational product. The FDA also can issue a warning letter to the site if more significant violations are found, and, finally, the FDA can close a research site and bar the investigator and subinvestigators from doing research in the future.

DISCLOSURES

The author has nothing to disclose.

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