

Research Provides Golden Opportunity for Physicians

An overview of clinical trials and how to conduct them

By Ruth Ann Nylen, PhD

CONDUCTING CLINICAL research trials as a physician investigator represents a multi-faceted opportunity for practicing physicians.

It allows physicians to gain first-hand experience with novel therapies and provides patients with treatment options that may be available only in a clinical trial.

The 2001-2002 annual report of the Pharmaceutical Research and Manufacturers of America shows that U.S. pharmaceutical companies will spend more than 30 billion dollars on research and development this year.

The majority is spent on clinical trials.¹ Physicians are needed by pharmaceutical sponsors (drug companies) to serve as principal investigators and conduct trials on their patients.

What is clinical research?

Pharmaceutical clinical research integrates medical practice, compliance with regulatory requirements and a research-based evaluation of drug therapy.

Clinical research is a process of conducting clinical studies overseen by an investigator. Most investigators for new drug therapies in the U.S. are physicians with active medical practices.

Clinical research is a component of the drug research and development process that occurs in sequential phases.

The drug development process

The discovery phase may encompass isolation of a potential compound from an organic source or organic

IN THIS ARTICLE...

Conducting clinical trials at your practice can help you increase your medical knowledge, allow you to contribute to valuable scientific study and create a new revenue stream. Take a look at how to get involved in clinical research.

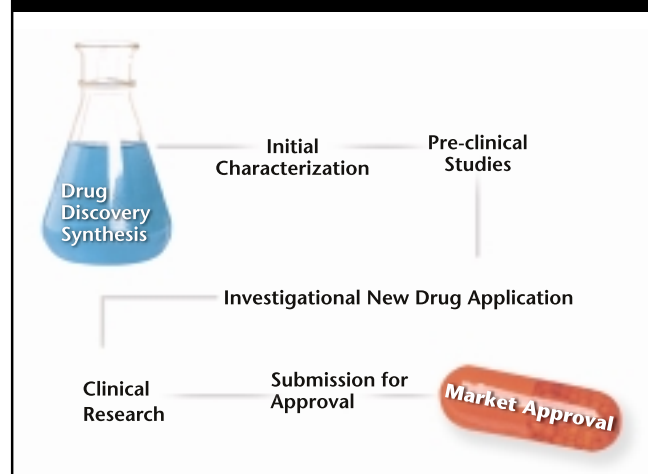
chemical synthesis of a specific new molecule.

Once identified and initially characterized, patent application typically follows. The pre-clinical research phase includes both chemical and biological characterization, as

well as assessment of teratogenic, mutagenic and carcinogenic activity in whole animal models, isolated tissues or cell lines.

Once adequate data exist to substantiate the risk of introducing a compound into human subjects, an Investigational New Drug (IND) application is filed with the Food and Drug Administration (FDA).

Figure 1:
The Drug Research and Development Process





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in clinical research trials
is to conduct phase III
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Figure 2. Phases of Clinical Trials



Phase I

- Establishes initial safety of a drug within humans, beginning with administering a single dose of the investigational drug, progressing to multiple or higher doses
- Defines a pharmacokinetic profile of the drug
- Establishes maximum tolerated dose (MTD) and preliminary human profile of potential toxicity
- Conducted by board-certified, subspecialists with experience in clinical pharmacology and previous experience in phase II or III trials
- Generally conducted at in-patient clinics with 10-35 normal, healthy volunteer subjects

Phase II

- Employs multiple and/or escalating doses in patients (as opposed to normal healthy volunteers) to identify the minimum effective dose(s)
- Seeks to establish an acceptable balance between benefit and risk, as evidenced by adverse events and other measures of safety
- Conducted by board-certified, physician specialists with previous experience as a PI in phase III trials
- Conducted at either inpatient or outpatient clinics (study-dependent) with 50-200 subjects

Phase III

- Establishes the safety and efficacy of a drug in humans, based on optimal doses identified in phase II
- Encompasses several hundred to several thousand patients, most often including placebos and other active compound(s) as controls, forming the basis on which the FDA makes a safety and efficacy determination
- Conducted by subspecialists and primary and secondary care physicians

Barring any concerns by the FDA, clinical research commences.

Clinical research occurs in sequential phases (I, II and III) each of which occurs before submitting an NDA for marketing approval. The characteristics of each phase are summarized in Figure 2.

The role of the physician

Physicians with active medical practices are needed to conduct clinical trials sponsored by private pharmaceutical companies, as well as federally funded programs supported by the National Institutes of Health, the Centers for Disease Control and prevention and the Veteran's Administration.

The greatest need for Physicians in clinical research trials is to conduct phase III safety and efficacy trials. Opportunities for physicians in single-site medical practices are often equal to those of a multi-site practice.

Here's a look at the various entities involved in clinical trials.

The sponsor

A sponsor is responsible for initiating a clinical trial.

A sponsor may be an individual or an organization. Private industry sponsors include pharmaceutical and biotechnology companies. The NIH is the primary sponsor of federally funded clinical research.

The sponsor's role typically includes:

- Filing the IND application
- Preparing a protocol and case report form (CRF)
- Selecting clinical investigators and filing their credentials with the FDA
- Providing study drug
- Monitoring the trial
- Closing investigator sites (retrieving all data and supplies, and reviewing records)

- Collecting, analyzing and reporting the study data

The investigator

The investigator is responsible for conducting a clinical trial.

Investigators are most often, but not exclusively, physicians working in private, hospital, academic or government-sponsored clinical settings. The investigator's role includes:

- Obtaining institutional review board (IRB) approval of the research
- Recruiting and enrolling subjects in the study
- Performing protocol-defined procedures
- Collecting and reporting all study information
- Reporting the study results to the sponsor and the IRB

In addition, the investigator is responsible for the subject's medical care and treatment while the subject is participating in the study. The investigator interacts directly, or indirectly, with everyone involved in a clinical trial.

The clinical research coordinator

While not specifically defined or referenced in the FDA regulations, the clinical research coordinator (CRC) plays a critical role in most clinical trials.

The CRC's role is to accept responsibility for and perform clinical study functions, as delegated by the investigator.

A strong word of caution is offered to physicians. While investigators may delegate their responsibilities to a research coordinator or sub-investigator, those responsibilities are not abdicated.

The investigators retain full responsibility and liability for all activities and compliance when they are the principal investigators.

The IRB

The IRB reviews and approves human clinical drug trials prior to initiation by an investigator.

The FDA and the Department of Health and Human Services' regulations and guidelines define membership requirements and activities of an IRB. The IRB's role in clinical trials includes initial review of human drug research to evaluate the risks to study subjects and ethical issues associated with the proposed research.

The IRB reviews the investigator's qualifications, the study protocol and informed consent form to make its assessment of the research. The IRB is also responsible for the continuing review of previously approved research, including an ongoing evaluation of safety data such as serious adverse event reports.

IRBs are required by federal regulation to have written operating procedures that demonstrate their compliance with the regulation and clarify expectations of investigators.

While an IRB's procedures must minimally comply with regulations, they may have additional requirements. As such, the requirements for investigator submissions for review of research, interactions with the IRB and reporting to the IRB may vary.

The study subject

The study subjects voluntarily consent to participate in a study and comply with the protocol requirements to the best of their ability. Under certain circumstances, a legally authorized representative may give informed consent for a subject with impaired decision-making abilities.

Institution

An institution may be involved administratively in a clinical trial if an investigator is employed by or affiliated with an institution.

An institution's role most often involves the contractual and financial areas of a clinical study.

Investigators working in academic and government settings are usually required to involve their institution in the study contracting process.

Very few schools teach clinical research

FDA

The FDA is the official U.S. agency that defines regulations and guidelines to begin development of a new drug (IND) and for the evaluation of drugs in human subjects. The FDA receives and reviews applications submitted to it for marketing approval of a drug (NDA).

The rules of the game

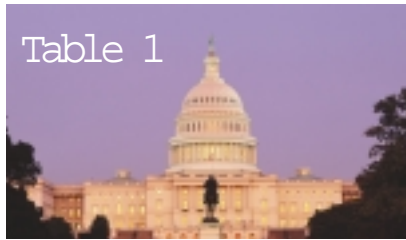
Clinical trials must be conducted in compliance with good clinical practices.

It is critical that physicians understand that the term "good clinical practice," or GCP, is different in the practice of medicine than it is in clinical trials.

In the practice of medicine, good clinical practice is generally understood to encompass professional behaviors including employing the accepted standard of care to patients.

Conducting clinical trials in compliance with good clinical practices includes behaviors accepted in medical practice, but additionally requires sound knowledge of and compliance with specific FDA and international regulations and guidelines.

The essential guidelines that physician investigators must be knowledgeable of to ensure GCP



Federal Regulations Essential to Clinical Trials

Regulation or Guideline	Summary of essential content
21 CFR 11 Electronic records; electronic signatures	Controls and requirements for electronic data
21 CFR 50 Protection of Human Subjects	Informed consent requirements
21 CFR 54 Financial Disclosure by Clinical Investigators	Requirements for investigators to disclose financial relationships with sponsors
21 CFR 56 Institutional Review Boards	Requirements for independent review of human research
45 CFR 46 Protection of Human Subjects	Note: Applies only to investigators conducting federally funded research. Includes human subject protection requirements as well as institutional review board requirements
21 CFR 312 Investigational New Drugs	Defines the scope of human research under jurisdiction by the FDA; outlines the responsibilities of investigators and sponsors in clinical trials
The ICH (International Conference on Harmonization)	GCP Guideline Outlines all Good Clinical Practice requirements for IRBs, investigators, sponsors, including protocol requirements, and documentation requirements for clinical trials
The FDA Information Sheets for Clinical Investigators and Institutional Review Boards	Provides a detailed explanation of the FDA's interpretation of the requirements in clinical trials

Note: "CFR" refers to the United States Code of Federal Regulations

compliance include those listed in Table 1.

Compliance with these federal regulations must be taken seriously. Non-compliance or violation of these federal statutes may result in disqualification by the FDA, as well as civil or criminal prosecution.

Essential qualifications of a physician investigator

Sponsors are required by the FDA and international regulations and guidelines to evaluate and select physician investigators to conduct clinical trials. Typical areas/items assessed include:

- Investigator and staff qualifications
- Availability of protocol-eligible subjects
- Equipment and facilities
- Knowledge of GCP requirements
- Familiarity with clinical research requirements, including previous experience with an IRB
- Willingness to provide financial disclosure
- Interest, motivation and cooperation

6 steps to get involved with clinical trials

1. Educate yourself

To be successful in clinical research, physicians must be trained. Medical schools effectively teach clinical therapeutics and the practice of medicine. Very few schools teach clinical research. Being assigned to serve as a sub-investigator during a residency is a far cry from the actual responsibilities of being a principal investigator. You must seek training in good clinical practices, either through a live seminar or course, an online course or other study. The risk of being untrained in clinical research is too great to assume.

2. Define the research capabilities of your site

This should include an objective assessment of your interests, availability of your time, experience, support staff and the other items the sponsor will assess.

3. Hire a consultant to help you prepare

A quality clinical research consultant will have worked for a pharmaceutical company for at least 10 years and been responsible for selecting investigators and running multiple protocols for the sponsor. A typical one-day onsite assessment, plus pre-visit conference call and follow-up report and recommendations, should cost about \$5,000-7,500, if the consultant knows what he or she is doing. This may be the single best investment you make.

4. Join clinical research industry organizations

These organizations are great for networking, education and professional liaison. They include the Association of Clinical Research Professionals (ACRP) www.acrpnet.org, and Drug Information Association (DIA) www.diahome.org. Medical specialty organizations may also have sections of physicians with interests in clinical trials. These organizations continually sponsor educational programs at regional, national and international conferences.

5. Hire an experienced clinical research coordinator (CRC)

Contact the ACRP, or the Society of Clinical Research Associates (SOCRA) www.socra.org. Each association includes many CRCs as members and sponsors certification programs for CRCs. An experienced CRC's salary will range from \$40,000-\$80,000. The CRC will be

worth 10 times this much the first year or two that they run trials with you.

6. Expect to make an investment

The investments involve both time and money to adequately prepare yourself and your organization to conduct successful clinical trials. Remember that the initial investment in preparation will most likely be completely recouped in your first or second successful clinical trial, depending on the type of trial and number of patients studied.

As with any new endeavor, participating in clinical trials has both challenges and opportunities. Challenges include:

- More paperwork than you ever imagined
- An initial investment of time and money
- Re-organization or restructuring issues to ensure the trials are a success

But clinical research also affords physicians with opportunities not available elsewhere:

- Expanding your research knowledge
- Making a scientific contribution to the body of therapeutic knowledge
- Generating information that, when approved, becomes the prescribing information for all physicians

While clinical research can enhance diminished revenue streams due to the massive restructuring of the health care dollar in the past decade, it is not a place to make a fast buck.

An investment in education, time and personnel is essential to be successful, and clinical research is not the same as daily medical practice. ●

Reference:

1. Annual Report of the Pharmaceutical Research and Manufacturers of America, 2002-2002.



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