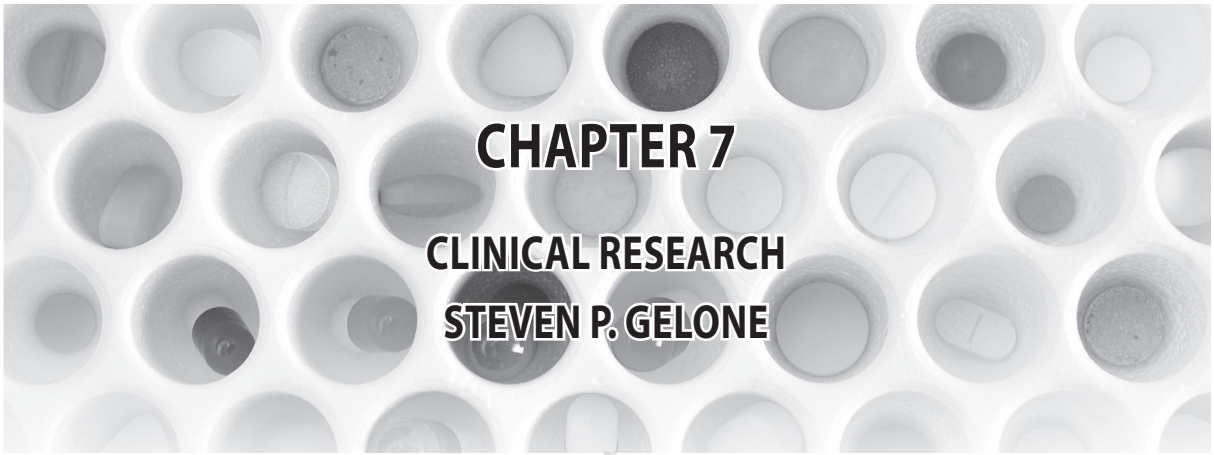

# CHAPTER 7

# CLINICAL RESEARCH

STEVEN P. GELONE



## WHAT IS CLINICAL RESEARCH?

In 1999, the American Medical Association and the American Association of Medical Colleges (AAMC) Task Force on Clinical Research convened a clinical research summit. The output of this summit was a national call to action that included a working definition for clinical research that states that clinical research is

> a component of medical and health research intended to produce knowledge essential for understanding human diseases, preventing and treating illness, and promoting health. Clinical research embraces a continuum of studies involving interaction with patients, diagnostic clinical materials or data, or populations, in any of these categories: disease mechanisms; translational research; clinical knowledge; detection; diagnosis and natural history of disease; therapeutic interventions including clinical trials; prevention and health promotion; behavioral research; health services research; epidemiology; and community-based and managed care research.

## HISTORICAL PERSPECTIVE ON CLINICAL RESEARCH

The beginnings of clinical research date back to the Old Testament in the Book of Daniel (Daniel 1:11–16) in the Bible, where a comparative protocol of diet and health is documented and to Hippocrates (460–370 BC), considered to be the father of modern medicine, who exhibited the strict discipline required of a clinical investigator. The first modern clinical trials were conducted in the 1700s to address the growing problem of scurvy in the British Navy, and in the late 1800s Robert Koch established "Koch's postulates" to prove that an infectious agent causes disease. The 20th century brought with it amazing advances in the medical sciences, the establishment of medical colleges in Europe and the Untied States, and the discovery of such drugs as penicillin and insulin. In 1925 Abraham Flexner, a noted medical educator, wrote, "Research can no more be divorced from medical education than can medical education be divorced from research."

Like many advances, progress in clinical research also brought with it troubling events including human experimentation by the Nazis and the Tuskegee syphilis experiments in African American men that lasted more than 30 years. These events led to the enactment of several key measures to ensure ethical

clinical research, including the Nuremberg Code (1949), the Harris Kefauver amendment to the Food and Drug Act in 1962, the Declaration of Helsinki in 1964, and the Belmont Report in 1979. Implicit in the conduct of all clinical research are ethical principles and integrity that are discussed in greater detail in Chapter 6 of this text. The remainder of this chapter focuses on clinical research involving drug products intended for use in humans.

## WHY IS CLINICAL RESEARCH NEEDED?

Given the uncertain nature of diseases and the potentially large variation that exists in biological systems and measures, it is extremely difficult to determine whether a new treatment or intervention makes a difference on a patient's outcome on the basis of uncontrolled observation. In addition, a true risk versus benefit analysis cannot be conducted outside the context of a controlled situation. Although the controls that are sometimes employed in clinical research may not exactly mimic clinical practice, they do provide a standardized manner in which to evaluate the safety and effectiveness of interventions to treat or prevent disease. The types of evaluations of medicines or interventions are outlined in Table 7-1.

## THE PHASES OF DRUG DEVELOPMENT

The development of drug products is generally divided into four phases. Phase 1 studies are exploratory clinical research designed to evaluate the safety of new medicines to determine whether further investigation is appropriate. Phase 1 studies involve the first administration of a new therapy to humans (the so-called first-in-man studies) and are often conducted on normal, healthy subjects. In addition to evaluating safety, Phase 1 studies are commonly designed to describe the clinical pharmacology of a new drug. They may evaluate single versus multiple dose exposure, establish a maximum tolerated dose (MTD), describe drug–drug or drug–food interactions, or evaluate the pharmacokinetics of a drug in special patient populations such as those with renal insufficiency. Phase 1 investigations are conducted throughout the development lifecycle of a drug, the earliest of which evaluate safety and pharmacokinetics, whereas drug–drug interaction studies and special patient population studies may be conducted later in the development cycle.

Phase 2 studies are the first attempt to evaluate the safety and efficacy of a drug in patients with the disease to be diagnosed, treated, or prevented. The overall objectives for Phase 2 evaluations are to acquire information on dose-response relationship, estimate the incidence of adverse reactions, and provide additional insight into the pathophysiology of disease and the potential impact of new therapy. Some have divided Phase 2 studies into Phase 2a, which are small pilot studies, and Phase 2b, which are larger studies and may be considered a pivotal trial (key studies used for submission to regulatory

**TABLE 7-1** Types of Evaluations of Medicines

| |
|---|
| Safety |
| Efficacy |
| Pharmacokinetic/pharmacodynamic |
| Mechanism of action |
| General population |
| Clinical methodology |
| Clinical pharmacology |
| Post marketing |

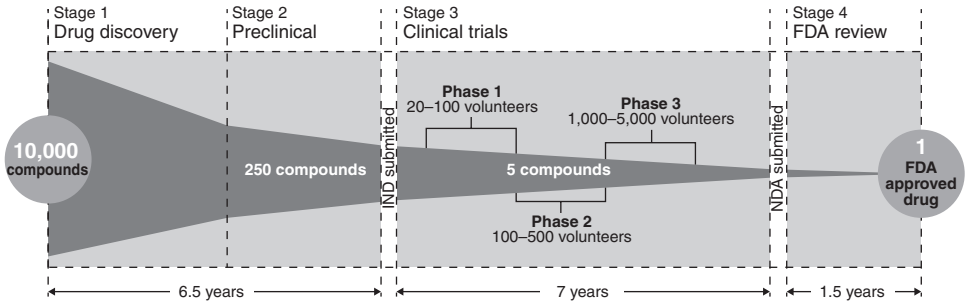


**FIGURE 7-1**

authorities). Regardless of whether Phase 2a or 2b, this phase of clinical research often evaluates dose-response or different patient types (e.g., young versus old or different ethnicity).

Phase 3 studies are considered the definitive evaluation of a new therapy to determine the safety and efficacy of new medicines in patients with the disease to be diagnosed, treated, or prevented. These clinical investigations most commonly compare a new therapy to the standard of practice at the time and involve large numbers of patients, including special patient populations. Phase 3 studies are often called "pivotal" or "registration trials" (also called Phase 3a studies) because they are the clinical research backbone of a New Drug Application (NDA) or biologics license application (BLA) to the Food and Drug Administration (FDA) and will ultimately provide the basis for labeling of a new medicine. Phase 3b studies are clinical trials conducted after the submission of an NDA or BLA and may supplement earlier studies and add new information to the labeling of a medicine.

Phase 4 studies are trials conducted after a medicine has been approved and marketed. These studies monitor the use of a new therapy in clinical practice and are designed to gather additional information on the impact of a new therapy on the treatment of disease, the rate of use of a new therapy, and a more robust estimate of the incidence of adverse events of a new therapy. Phase 4 trials are sometimes referred to as postmarketing surveillance studies and may be required by a regulatory authority as a condition of approval of a new product. Phase 4 research can be observational in nature and is often not as well controlled as investigations in phases 1 through 3. A summary of the phases of the drug development lifecycle is presented in Figure 7-1.



## WHERE CLINICAL RESEARCH BEGINS

All clinical research begins with an unanswered question and the development of a concise and specific primary objective. The objective is the springboard for all of the analysis to occur from the data generated from the clinical research study. Although one can theoretically change the primary objective of a clinical research study after initiation, this usually results in major problems with analysis and interpretation of the data obtained as well as the acceptability of the data by the medical community. As such, it is critical that prior to initiating a clinical research study one invests the time upfront to explore and develop a primary objective that will allow for the most robust analysis to occur.

## CRITICAL CONCEPTS IN CLINICAL RESEARCH

The two fundamental aspects of all clinical research are whether the results are valid and generalizable. The most compelling evidence in research is the ability to replicate the outcome of an investigation.

Because not all studies undergo replicate analysis, one should critically evaluate the study design and analysis utilized as a surrogate marker of the validity of a study. If one concludes that a study result is valid, it is equally important to consider whether the findings of the study are applicable to multiple clinical practice settings. Again, replication of a study is very helpful in this assessment but often is not conducted.

In the absence of a replicate study, one should evaluate the inclusion and exclusion criteria utilized in the clinical study to assess the generalizability of the results. Researchers from McMaster University have developed a series of questions that are useful in interpreting the results of clinical research studies:

Are the results of the study valid?

- Primary guides:
  Was the assignment of patients to treatments randomized?
  Were all patients who entered the study properly accounted for at its conclusion?
  Was follow-up complete?
  Were patients analyzed in the groups to which they were randomized?
- Secondary guides:
  Were patients, clinicians, and study personnel blinded to treatment?
  Were the groups similar at the start of the trial?
  Aside from experimental intervention, were the groups treated equally?
  What were the results?
- How large was the treatment effect?
- How precise was the treatment effect (confidence intervals)?
- Will the results help me in caring for my patients?
- Does my patient fulfill the enrollment criteria for the trial? If not, how close is the patient to the enrollment criteria?
- Does my patient fit the features of a subgroup analysis in the trial report? If so, are the results of the subgroup analysis in the trial valid?
- Were all the clinically important outcomes considered?
- Are the likely treatment benefits worth the potential harm and costs?



## APPROACHES TO THE DESIGN OF CLINICAL RESEARCH STUDIES

As noted previously, the design of a clinical study is critical to the analysis, interpretation, validity, and generalizability of clinical research. Although an in-depth review of statistical approaches to clinical trial design and all of the permutations which a clinical research study can take on are beyond the scope of this text, the following represents an overview of the approaches to clinical research design.

Clinical research design can be divided into one of a couple of broad categories: retrospective versus prospective studies, and those involving a single group versus multiple groups. In short, retrospective studies evaluate events that occurred in the past and as such are limited by the data that were collected. As a result, retrospective studies are unable to definitively answer research questions. Although these limitations are a reality, retrospective studies are easier to conduct, usually require less resources and time than prospective studies do, and are very useful for hypothesis generating. Prospective studies evaluate events in the present time and forward. As such, these studies' greatest strengths are the ability to control bias more effectively and have more robust data collection than retrospective studies. A timeline for clinical studies is presented in Figure 7-2.

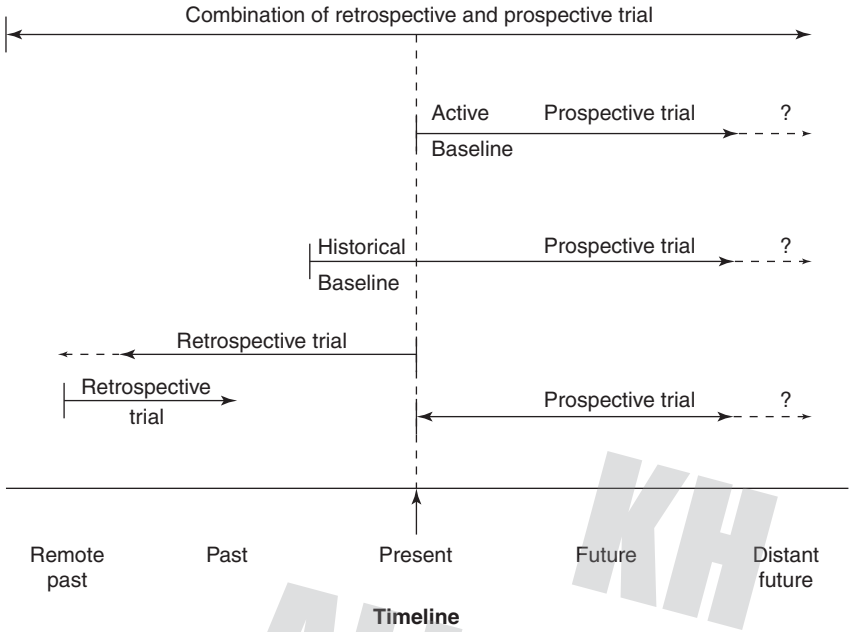


**FIGURE 7-2**



In single-group studies, all subjects are treated with the same intervention or medicine. In multiple-group studies, subjects in each group are treated with different interventions and the results are compared between groups. The major study designs employed for two groups of subjects are cross-sectional and longitudinal trials. Cross-sectional studies are usually short-term trials (weeks) in which a cross-section of the patient population is evaluated and data obtained from each group are compared. Most safety and efficacy studies conducted are cross-sectional trials. Longitudinal trials are typically longer in duration (months), and patients' data are generally compared with the patients' baseline data to identify any changes. Many epidemiological studies and Phase 4 studies are longitudinal trials.

The two most commonly utilized designs comparing two groups of subjects are the parallel and crossover designs. In the parallel design, subjects are randomized into one of two groups and typically receive one of two potential treatments as assigned for the entire duration of the study. These studies are applicable to most experimental situations. In crossover studies, subjects receive both treatments being compared. To effectively utilize a crossover design, subjects should have a stable, chronic condition during both treatment periods and a similar baseline condition at the start of each treatment. Examples of diseases for which a crossover-designed study may be conducted include migraines, epilepsy, and glaucoma. For the same sample size, the parallel design is less sensitive in detecting differences between the two groups. The analysis of crossover studies is more greatly affected by patient dropouts and missing data.

Two other designs comparing two groups of subjects are matched pairs and historical control studies. Neither is as robust as parallel or crossover studies. Matched pair design is a type of parallel design in which subjects who are identical with regard to relevant factors are identified. One subject within each matched pair receives one treatment, while the other receives the other treatment. The obvious limitations of this design are the difficulty in identifying well-matched pairs and that all relevant factors to match pairs may not be known.

In historical control trials, all subjects receive the same treatment and the control group is composed of a similar group of subjects who were previously treated, often by different investigators. The advantage of historical control trials is that enrollment may be easier, but this must be counterbalanced by the fact that it is very difficult to have an adequately controlled historical group with all the relevant information required.

Phase 4 study designs can be divided into five broad categories, including descriptive studies, cross-sectional studies, case-control studies, cohort studies, and controlled clinical research studies.

Descriptive studies provide information on the pattern of disease occurrence in populations. The data used in descriptive studies is often collected passively to describe rare events or generate hypotheses. Cross-sectional studies involve data from a random sampling of a target population and data are classified based upon exposure and observed outcomes. This type of study can provide the prevalence of an event and as such is a snapshot in time. Case-controlled studies are retrospective research in which the cases have the disease in question and the controls do not. Each case is matched based on relevant factors to a control subject, which is often difficult. Case-controlled studies can evaluate multiple exposures and uncommon diseases, and are logistically easy. A cohort study follows forward in time a group of subjects who have been exposed to an event or intervention. The outcomes in the cohort are then compared retrospectively with a control group that was not exposed to the event or intervention. Cohort studies can evaluate multiple outcomes and uncommon exposures. Last, controlled clinical trial designs have been presented previously and are the most convincing clinical research design.



## BIAS IN CLINICAL RESEARCH

Bias is errors that enter into a clinical research study that distort the data collected. Bias may be introduced by anyone involved with the design, conduct, or analysis of clinical research. Because the introduction of various forms of bias into a clinical research study may significantly affect the validity and generalizability of a study, one of the primary goals in designing a clinical research study is to eliminate or minimize the introduction of bias. As described earlier, some clinical research designs inherently introduce bias (e.g., case-control or retrospective designs), but the best way to avoid bias is to identify its potential during the design of a clinical research study. The types of bias to be considered in clinical research are summarized in Table 7-2.

The main methods used to control bias in clinical research include blinding, randomization, and when possible the administration of placebo to the control population in the study. Blinding is a method

**TABLE 7-2** Types of Bias in Clinical Research

| Type of Bias | Description |
|---|---|
| Selection bias | Occurs during recruitment and selection of potential subjects |
| Information bias | Information collected directly from subjects can be biased based on beliefs or values |
| Observer bias | Clinical investigator objectivity for measuring outcomes varies greatly |
| Interviewer bias | The expectation of the interviewer may influence how information is collected |

**TABLE 7-3** Types of Blinding in Clinical Research

| Type of Blinding | Description |
|---|---|
| Open-label | No blinding is used. Both patient and investigator know the identity of the treatment being used. Least rigorous design. |
| Single-blind | Patient is unaware of the treatment being used. |
| Double-blind | Neither the patient nor the investigator is aware of what treatment is being used. |
| Full-double-blind | The patient and anyone who interacts with the patient group is unaware of the treatment being used. |
| Full-triple-blind | The patient, the investigator, and anyone who interacts with the patient or investigator are unaware of the treatment being used. |
| Full-clinical-trial-blind | The patient and anyone who interacts with the patient or the data are unaware of the treatment being used. |

**TABLE 7-4** Randomization Methods

| Method | Description |
|---|---|
| Simple randomization | Uses a predetermined code to assign patients to one of two or more treatments |
| Block randomization | A block size is chosen and the number of patients assigned to each treatment is proportional (e.g., 1:1, 2:1, 3:1) |
| Systematic randomization | Patients are assigned to receive treatment based on a random order in the first block, whose pattern is repeated in subsequent blocks or by a sequential assignment to treatment |



used to keep the identity of the treatment used in a group unknown. Groups that can be blinded include patients, investigators, data review committees, ancillary personnel, statisticians, and monitors. With regard to blinding, clinical research studies can be described as outlined in Table 7-3.

Randomization is a process by which patients in a clinical research study are randomly assigned to receive one of the potential treatments using a predetermined randomization code. Randomization decreases the effect of interjecting an investigator's bias(es), allows for breaking a blind on one patient while keeping it on the remaining subjects, and permits statistical testing conducted on resulting data in a valid manner. Examples of randomization methods are provided in Table 7-4.

## CHALLENGES IN CONDUCTING CLINICAL RESEARCH

After a clinical research idea is developed more fully into a study protocol, one must consider the complexity and various moving parts that are critical to the efficient conduct of a clinical research study. The two major groups include a coordinating group and a support group. These groups can be further

subdivided into their functional units, all of which are critical to the successful completion of a clinical research study.

The overall roles of the functional groups are to provide intellectual and scientific leadership for the study (e.g., investigators, medical directors), selection and management of investigational sites (e.g., clinical operations, study managers, research associates), data gathering and analysis (e.g., data management, programming, biostatisticians), and infrastructure support (e.g., finance, human resources, information technology). It is only with the collaboration of all of these functional groups that one can efficiently conduct clinical research that is scientifically and ethically sound.

## THE INTERPRETATION AND INTEGRATION OF CLINICAL RESEARCH INTO CLINICAL PRACTICE

The ultimate goal of conducting clinical research is to improve patient care. To this end, the results of clinical research must be integrated into clinical practice. The interpretation of the results of clinical research studies is therefore a critically important part of the process and must be undertaken with great care. In an effort to adequately synthesize empirical information, a variety of methods are currently used to aid clinicians in effectively integrating clinical research study results into clinical practice (Figure 7-3).

In particular, national and international societies and other organizations, most notably the Centers for Disease Control and Prevention, the Cochrane Collaborative Group, and the World Health Organization, regularly prepare evidenced-based guidelines derived from the available clinical research results to aid clinical decision making and improve patient care.

Ultimately, for the results from a clinical research study to influence medical practice they need to be published in a peer-reviewed journal, be interpreted by clinicians as positive, and must be generalizable to the clinician's specific patient population. It is worth noting that many well-designed trial results have had little effect on medical practice and many poorly designed studies have had a major influence. In the



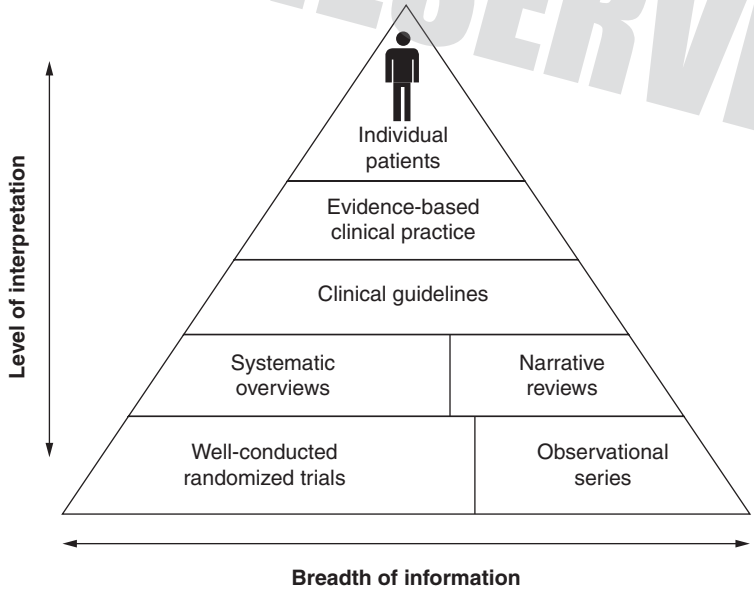


**FIGURE 7-3**

end, it is the responsibility of each clinician to make his or her own assessment of new clinical research data. Critical evaluation of such studies requires one to pose questions related to the endpoints, methodology, and data obtained from the study. Only after answers to these questions are generated and an understanding of the strengths and limitations of a study is obtained can a clinician proceed to integrate the results into clinical practice.

## WHAT DOES THE FUTURE HOLD FOR CLINICAL RESEARCH AND WHAT OPPORTUNITIES EXIST FOR ALLIED HEALTH PROFESSIONALS?

The clinical research summit conducted by the Association of American Medical Colleges (AAMC) in 1999 identified several issues that are critical to the conduct of clinical research, including: (1) a general lack of understanding by the general public of what clinical research is and what its potential value is to patient care; (2) a lack of data on funding for clinical research and productivity; (3) a lack of interest and funding in some types of clinical research; (4) a lack of sufficiently trained clinical researchers; (5) an insufficient emphasis on incorporating clinical research into clinical practice; (6) inadequate coordination among research centers and disciplines; (7) significant impact of fiscal concerns at academic centers that may negatively affect clinical research; and (8) the lack of a comprehensive clinical research agenda.

Subsequently, the AAMC published a follow-up report in 2006 directed at addressing many of the issues identified, in particular recommending that all future physicians receive as part of their education and training instruction in the basic principles of clinical research. In the author's opinion, it would be beneficial if this goal were extended to all future healthcare professionals.

A variety of training programs (both certificate and degree conferring) are currently available that provide an in-depth exposure to the various aspects of clinical research. As identified by the AAMC report in 2006, there is a shortage of well-trained clinical research professionals. Opportunities for allied health professionals in the field of clinical research are numerous and exist in academia, foundations, government, and industry. The 21st century has brought with it incredible advancement in the medical sciences. These advancements have been the by-product of basic science and clinical research efforts. Patient care will continue to improve only through the combined efforts of educational institutions and well-trained translational and clinical researchers, skilled in research design and interpretation.



## SUGGESTED READING

Association of American Medical Colleges. *Clinical Research: A National Call to Action.* November 1999. Washington, DC.

Association of American Medical Colleges. *Promoting Translational and Clinical Science: The Critical Role of Medical Schools and Teaching Hospitals*. May 2006. Washington, DC.

Association of American Medical Colleges. *Task Force on Clinical Research*. November 1999. Washington, DC.

Fletcher AJ, et al. *Principles and Practice of Pharmaceutical Medicine*. West Sussex, UK: John Wiley; 2002.

Gallin JI. *Principles and Practice of Clinical Research*. San Diego, Calif: Academic Press; 2002.

Kelley WN. *Careers in Clinical Research: Obstacles and Opportunities*. Washington, DC: Committee on Addressing Career Paths for Clinical Research, Institute of Medicine, National Academy Press; 1994.

Spilker B. *Guide to Clinical Trials*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

United States Government Accountability Office. *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts.* Washington, DC: US GAO; November 2006.