CHAPTER

2

Ethical Considerations in Clinical Research

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CHAPTER OBJECTIVES

- Explain the clinical phases of the drug approval process
- Understand the guiding ethical principles in clinical research
- Understand the regulatory framework governing clinical research, including informed consent and data confidentiality
- Explore key ethical challenges involved in clinical research

KEY TERMINOLOGY

Belmont Report
Beneficence
Common Rule
Conflicts of interest
Data and Safety Monitoring Board
Ethical principles
Human subjects research
Informed consent
Institutional review board
Justice
Phase I trials
Phase II trials
Phase III trials
Phase IV trials or post-marketing studies
Respect for persons
Therapeutic misconception

INTRODUCTION

Clinical research, which involves testing interventions in humans to establish their effectiveness and safety, must involve careful design and implementation to ensure the protection of the human subjects. When applied to drug development, the focus of clinical research is on establishing the efficacy and safety of the new drug. Clinical research trials are tightly controlled for both inclusion and exclusion of the participants and design of the protocol, with strict control over study procedures and interventions. It is important to recognize that the overall goal of clinical research is to develop or contribute to generalizable knowledge, which is hoped to be useful to future patients and providers. Clinical research involves actual patients with a disease; consequently, actual effects in terms of benefits and risks to these individuals also become relevant. In clinical practice, the clinician has an obligation to always act in the best interest of the patient. In clinical research, conflicts may arise as the clinician/researcher may have dual goals: to protect the patient/subject and to maintain research integrity.

A case example may help illustrate some of the conflicts that can arise.[1] In the late 1990s, researchers at the University of Pennsylvania were developing a gene transfer intervention that was intended to target the underlying pathology causing ornithine transcarbamylase (OTC) deficiency syndrome, which is a rare metabolic disorder that leads to the accumulation of ammonia in the blood. An 18-year-old man with partial OTC deficiency was recruited and consented to research. He received an infusion of the study agent and, after a short course, died. His family was distraught, claiming that they were never informed of the possibility of death from the study. A variety of disturbing facts came to light as part of the investigation of the death, including issues involving study design, consent, and conflict of interest. It was uncovered that the researcher held patents on the technology being tested, and he had founded and held significant equity in the biotech company that stood to benefit from the clinical trial. The university also held significant equity in the company. Troubling questions were raised about the researcher's conflicting interests and whether the young man had been inappropriately enrolled in the trial. In addition to the death of this young man, this tragedy has been a devastating blow to the gene transfer scientific community as a whole. This case also illustrates a conflict for the clinician (ensuring the well-being of the patient) and the researcher (striving to get research results that may lead to a future product).

In their editorial in the *American Journal of Health-System Pharmacists*, Cobaugh and Allison[2] call on pharmacists to recognize their responsibility to thoroughly understand the evidence supporting therapy choices as part of the patient care provided. This chapter provides the ethical and regulatory framework for overseeing clinical research. Specifically, it reviews the drug development process in the United States, discusses the ethical principles in human subjects research, discusses the regulatory framework in which clinical research takes place, and explores several key ethical challenges that confront those involved in the clinical research enterprise. By understanding these principles, clinicians will be better equipped to evaluate the ethical validity of research studies that may influence prescribing and drug therapy selection.

THE DRUG DEVELOPMENT PROCESS

The drug development process involves a long and expensive series of trials that are intended to lead to a commercial agent marketed for a particular indication or indications. Drug development begins with preclinical studies, which involve laboratory testing and animal testing. Suitable drug candidates identified in the laboratory are tested

in animal models of the disease for pharmacologic effects, and toxicity studies are also conducted in these models. If a drug candidate is found to be promising after preclinical testing, then clinical research, which involves human testing, proceeds. See **Table 2-1** for an overview of the clinical drug testing process.

Clinical trials are conducted in phases that are sequential. **Phase I trials** involve testing a drug in humans with the intent of establishing the initial toxicity profile of the substance. The flip side of this concept is to establish the safety of the drug or, as it is sometimes phrased, show that the drug is safe for human use. Safety is a rather elusive term, however. Perhaps a more accurate term is "tolerability," which better reflects the fact that adverse effects do occur as a matter of course, but subjects (and then, eventually, patients) are able to tolerate the agent. All types of adverse effects are monitored for, reported, and compiled in the information developed about the agent. Typically, phase I trials are carried out in a cohort (group) of normal, healthy volunteers, although this is not always the case. Notably, phase I oncology trials are carried out in patients with cancer, often end-stage cancer. Phase I trials usually involve small numbers of subjects who receive the drug in a dose-escalation-by-cohort fashion. That is, the first enrollees will receive a low dose of the agent (such that the dose is not expected to have much effect) and will be monitored for toxicity. If these subjects (typically 3–6 subjects) tolerate that dose, then the next cohort of 3–6 subjects will be given a higher dose. This dose escalation and monitoring for toxicity continues until dose-limiting toxicity (DLT) is encountered. At that point, the previous dose level administered is called the maximum tolerated dose (MTD), and this is the dose that is generally recommended for the next phase of testing. The first time a drug crosses from the laboratory or animal testing into the human testing realm, the trial is referred to as a "first in human trial" (FIHT). For many drugs, there can be several phase I trials, testing different dosage forms and beginning to generate pharmacokinetic data as well.

TABLE 2-1 Clinical Drug Testing Process

Features of Clinical Trials	Phase I	Phase II	Phase III	Phase IV
Primary Interest[a]	Toxicity (tolerability)	Preliminary efficacy and safety	Efficacy and safety	Long-term data
Target Population[b]	Healthy volunteers or subjects with the disease in question	Subjects with the disease in question	Subjects with the disease in question	Possibly subjects with other diseases
Study Design[c]	Dose escalation in cohort of patients, generally unblinded, often uncontrolled	Randomized, double-blind, placebo, or active controlled	Randomized, double-blind, placebo, or active controlled	Various depending on intent—experimental/observational designs
Duration[d] **(subject/overall)**	About 1 month/less than a year	Months/a year or two	One to two years/several years	Variable
Numbers Enrolled[e]	Small about 50	Medium about 100	Large 100s to 1,000s	Varies

[a] Phase I trials are intended to establish tolerability and focus primarily on toxicity. All phases, however, include reporting of toxicity data to build the profile of the drug.
[b] Phase I trials usually enroll healthy volunteers, although sometimes patients are enrolled, as in oncology phase I trials, and often in studying new drugs for Alzheimer's disease.
[c] A variety of designs can be and often are used. Placebo-controlled trials are considered strongest by the FDA.
[d] Duration is variable for each phase, but these are averages.
[e] Numbers of enrollees vary in each phase, but these are typical. Overall, it is not uncommon for a drug to be approved for marketing after having been studied in fewer than 5,000 subjects.

Once a tolerated dose is determined, a phase II trial may proceed. **Phase II trials** involve subjects with the disease in question, as these trials are designed to give initial data on efficacy and continued safety/toxicity data. This phase is also designed to collect data on pharmacokinetics, pharmacodynamics, minimum effective dose, and dose ranges that might be effective. Phase II trials are randomized trials involving fairly small numbers of subjects, about 100, and generally are short-term studies with a usual duration of months to less than a year. This phase is designed to provide preliminary evidence of efficacy and safety before large-scale trials can be conducted.

Phase III trials are designed to demonstrate efficacy in a statistically-powered sample of subjects with the disease in question. The goal of phase III trials is to generate efficacy and safety data to allow evaluation of the overall risk-to-benefit relationship of the drug. Well-done phase III trials that generate statistically significant results can be used to secure marketing approval for a given indication. Generally, phase III trials are large, enrolling hundreds or thousands of subjects, and may be long-term, extending for many months or years. The usual trial is set up as a randomized controlled trial (RCT) often involving blinding and placebo controls. Although establishing efficacy is the purpose, monitoring for safety/toxicity remains critical and will shape the eventual approval and labeling of the drug.

New drug substances for human use are under the regulatory oversight of the Food and Drug Administration (FDA), governed by the Investigational New Drug (IND) regulations in the Code of Federal Regulations (CFR) at title 21 part 312.[3] There are also regulations for biological substances at 21 CFR 600.[4] The regulations govern processes for submitting an investigational new drug application, responsibilities of sponsors and investigators, special processes for drugs intended to treat life-threatening and severely debilitating diseases, and expanded access for use of investigational drugs for treatment. All accumulating data for a particular investigational drug are compiled in an investigator's brochure, beginning with laboratory and animal data, which serves as an encyclopedia of accumulating data about the new drug. Agents that are tested in humans must be filed under an IND application with the FDA, and each protocol that is developed is submitted as part of the IND filing. When a sponsor believes data are adequate to support approval, all these data are submitted as part of a New Drug Application (NDA) for FDA approval.

Sometimes, as part of the FDA approval process, additional data collection is required by the FDA. This generally takes place as **phase IV trials or post-marketing studies** and is often intended to generate longer-term safety/toxicity data. Rarely occurring adverse effects of a drug may not have been noted during the earlier phases, but may become noticed as a new drug is prescribed to millions of patients. Collecting phase IV post-marketing safety data may help to establish the toxicity profile of the drug in a more robust fashion. At times, a phase IV trial may involve cost-effectiveness comparisons that will help in therapeutic selection among members of a drug class.

The RCT is recognized as the gold standard for conducting clinical research, as it is the strongest design to allow conclusions about causality to be drawn.[5] Randomization works to minimize bias in selection of therapeutic arm for a given subject. Strict control in the protocol procedures, and the inclusion and exclusion of subjects, serves to allow deduction about causality of the research intervention. The drug development process is a long and costly enterprise (**Figure 2-1**). According to Kaitin,[6] the average cost to bring one product to market, including failures, is $1.32 billion in 2005 dollars. For an excellent, more in-depth overview of the drug development process in the United States, consult Moore's (2003) review in *Southern Medical Journal*.[7]

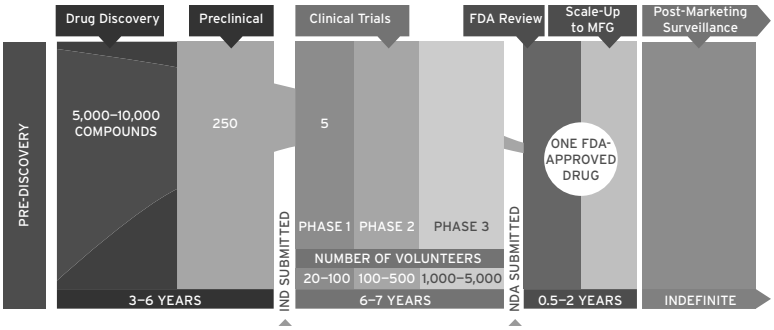

FIGURE 2-1 Research and development process in the pharmaceutical industry.
Reproduced from 2013 Profile: Biopharmaceutical Research Industry, PhRMA 2013.

Data and Safety Monitoring

It is essential that data generated during the course of a clinical trial be monitored closely, especially data related to adverse effects of the drug. Routine monitoring is a requirement because each clinical protocol must have a data and safety monitoring plan, which stipulates the responsibility for routine review, frequency of review, reporting responsibilities, and authority for modifying or stopping the study. In many large clinical trials, these responsibilities are assumed by a formal **Data and Safety Monitoring Board (DSMB)**. The DSMB reviews aggregate data that either have been unblinded or are separated by study arm to allow ongoing oversight of emerging trends in the data. Silverman[8] provides an in-depth analysis of the need for ongoing attention to ethical issues during the conduct of the clinical trial.

ETHICAL PRINCIPLES IN HUMAN SUBJECTS RESEARCH

The complex environment of clinical research and clinical drug development in particular highly depends on the participation of humans in clinical trials. However, a key fundamental concept is that participation in research is expected to be voluntary, not forced. Over the decades, there have been many examples of researchers forcing participation or deceiving participants about the true nature of the research and the risks entailed therein. During World War II, Nazi physicians performed life-threatening experiments on unwilling concentration camp detainees. Worldwide outrage over these atrocities led to development of the Nuremberg Code,[9] which emphasizes that participation in research must be *voluntary* and should never cause deliberate harm. In the United States, beginning in the 1930s, Public Health Service physicians followed the natural history of syphilis over several decades in a cohort of African-American men, who subsequently were denied antibiotic use once it was shown penicillin could be an effective treatment for syphilis. This trial became known as the Tuskegee Syphilis Study. National outrage over this reckless behavior by government-funded researchers, once exposed in 1972, led to passage of the National Research Act in 1974, which required institutions wishing to do federally-funded research to set up an institutional review board. The **institutional review board (IRB)** is charged with protecting the rights

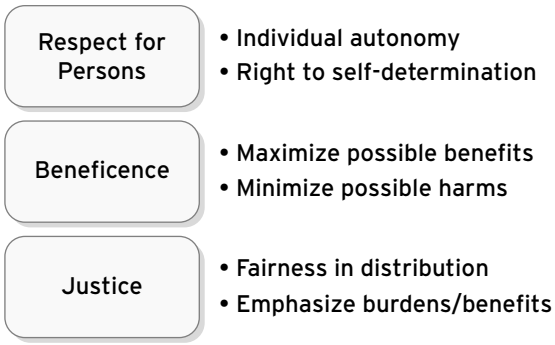

FIGURE 2-2 Ethical principles in human subjects research.

and welfare of human subjects of research, and ensuring that research is conducted in accordance with accepted ethical standards.

The National Research Act also established the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research, which met over several years and, in 1979, issued a report titled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," known as the Belmont Report.[10] The **Belmont Report** articulates the fundamental **ethical principles** that must be the underpinnings of all research with human subjects: respect for persons, beneficence, and justice (**Figure 2-2**).

Respect for Persons

This is a concept based on Western philosophy that values individual autonomy and the individual's right to self-determination. As the Belmont Report states,

> **Respect for persons** incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and, second, that persons with diminished autonomy are entitled to protection.[10]

The principle of respect for persons is demonstrated through the **informed consent** process, which should be an ongoing dialogue intended to provide sufficient information so that the individual can make his/her own decision about research participation. The process involves conveying information in language that the subject can understand, assessing the comprehension of the subject, and securing voluntary agreement to participate. A written consent form is used to provide information and allow subjects to indicate agreement by signing. Consent forms must explain the purpose of the study, procedures that will be used, potential risks and benefits, economic considerations, the voluntary nature of the study and the subject's right to withdraw at any time, and an explanation of what will happen and who will pay in case the subject is injured in the study.

There is a real struggle in clinical research when developing consent documents. While their intent is to inform subjects, they often are viewed as legal documents that must contain every procedure and every risk ever possibly associated with the investigational agent. In this fashion, consent forms for investigational drug studies have become very long, very technical, and potentially overwhelming to research subjects. Ethical concerns involving the consent process focus on possibilities that subjects may not fully comprehend what is involved in the study or what risks they are willingly assuming by agreeing to participate.

In addition to those concerns inherent in clinical research with autonomous adults, it must be recognized that not every human being is capable of self-determination. Persons

with diminished autonomy require special safeguards to prevent their exploitation in research. Such safeguards might involve limiting the degree of risk exposure that could be allowed, or providing for a consent monitor or advocate who would ensure the individual's welfare is protected. An example is the enrollment of adults with decisional impairment. In addition to seeking consent from the subject's legally authorized representative, limits might be placed on the acceptable levels of risk that a protocol may entail, especially if the protocol will not be of direct benefit to enrollees.

Beneficence

According to the Belmont Report,

> Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. . . . In this document, **beneficence** is understood, in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.[10]

Application of this ethical principle generally takes place by doing a risk–benefit analysis, such that benefits must exceed the risks to undertake the research. Of course, such an analysis is imperfect, because research by its very nature has unknown risks and benefits. Part of the risk–benefit analysis includes deciding with imperfect knowledge when it is justifiable to seek certain benefits despite the risks involved, versus when the potential benefits are so small that the risks outweigh the benefits. It is important for each protocol that risks and benefits be monitored over time via an adequate data and safety monitoring plan. Researchers need to plan to detect and manage adverse effects as they occur and consider the need to modify or stop the research protocol. It must be recognized that research by its very nature involves risk, and indeed, subjects may be exposed to risk and may be harmed. The ethical obligation is to minimize probability of harm, while maximizing potential benefits, and to never knowingly cause (permanent) injury. Researchers are obligated to identify risks and objectively estimate their magnitude and likelihood. Both the risks and the benefits should be presented to prospective subjects in the consent form.

Several important features will influence how a protocol minimizes the risk: start with a highly competent research team and a well-designed study that incorporates procedures that have the least likelihood of harm. Build in adequate monitoring so that adverse events are quickly identified, managed, and reported. Incorporate provisions to protect privacy and confidentiality. Because clinical research, especially phase II and III trials, involves patients as research subjects, there are concerns that the research subject may suffer from the "**therapeutic misconception**."[11] That is, these research subjects may be prone to misunderstanding the risks and potential benefits associated with research participation and may have unreasonable expectations about potential individual benefits. This misunderstanding may lead to discounting of risks and overestimating personal benefits, and can be especially problematic when the treating physician is the researcher as well. Strict attention needs to be paid to accurately describing a benefit only as a potential, not a guarantee.

Justice

According to the Belmont Report, there must be a sense of fairness in distributing the burdens and benefits of research. The ethic of **justice**

> . . . gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.[10]

Researchers have an obligation to make certain that no group inappropriately bears the burdens of research for the benefit of others. In the 1990s, this protectionist perspective underwent a paradigm shift when it was recognized that at times, clinical trials might be the best possibility of getting access to promising new drugs. An example was during the early days of the acquired immunodeficiency syndrome (AIDS) epidemic, when no drugs were yet approved to treat AIDS. Activist groups lobbied to expand access to clinical trials, not from a protection perspective, but from a perspective of fairness in distribution of potential benefits. Thus, justice requires that researchers strive to balance distribution of both the burdens and the benefits of research.

The Belmont principles remain the essential ethical principles in place to guide human research. Their application to individual research protocols involves the need to understand the principles and deal with some situations in which conflicts arise among or between them. This is the ongoing work of the IRB. It is important to note that one ethical principle does not "trump" the others. Weighing and prioritizing conflicting ethical norms is a difficult task that must involve discussion, debate, and often struggle.

REGULATORY FRAMEWORK FOR HUMAN SUBJECTS RESEARCH

In addition to the previously discussed Nuremberg Code and Belmont Report,[9,10] a number of other ethical codes exist and provide rich resources for researchers. Professional societies and special interest groups should be consulted for codes of conduct specific to specialties. In addition, several worldwide ethical guidelines exist, including the *Declaration of Helsinki*[12] and the international ethical guidelines for biomedical research issued by the Council for International Organizations of Medical Sciences (CIOMS).[13]

In the United States, the regulations for the protection of human subjects in research took shape largely after exposure of the problems associated with the Tuskegee Syphilis Study. The National Commission for the Protection of Human Subjects of Research issued the Belmont Report,[10] which provided the ethical underpinnings of human research protection regulations in the United States. These principles became codified as law in the Code of Federal Regulations (CFR) at title 45 CFR 46.[14] This set of regulations, adopted by 15 federal agencies, became known as the **Common Rule**. Notably, the FDA did not adopt these regulations wholesale, but rather, has similar regulations regarding informed consent and the IRB structure at 21 CFR 50 and 56, respectively.[15,16] The Office for Human Research Protections (OHRP)[17] provides oversight of human subjects research for the Department of Health and Human Services. The mission of the OHRP is to provide leadership in the protection of subjects involved in research by providing guidance and educational sessions for the research community. In the international setting, drug regulatory bodies have collaborated on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (known as ICH).[18] This is a collaboration of Europe, Japan, and the United States to achieve harmonization in regulatory approaches to oversight of the drug approval process in an efficient manner. While largely focused on drug regulatory standards, ICH also incorporates the requirement for ethical review and approval of clinical research protocols before beginning the research.

Human Subject Research and Institutional Review Boards

Human subjects research is defined in the Common Rule as research on:

> . . . a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individuals or (2) identifiable private information.[14]

Although most researchers who interact or intervene with living individuals recognize that they are doing human subjects research, those who only work with identifiable private information often do not and may inadvertently fail to comply with applicable human subjects regulations. For example, conducting medical records reviews for research purposes and recording identifiable private information involves the need for review and approval of the research by the institutional review board (IRB). Although not strictly required by the regulations, most IRBs require that researchers submit proposals so that the IRB can evaluate whether the proposal involves human subject research.

IRBs are charged with protecting the rights and welfare of research subjects and ensuring sound ethical research design. By regulation, an IRB must comprise at least 5 members, at least one of whom is a scientist and one a non-scientist. In addition, there must be at least one member who is not otherwise affiliated with the institution. Membership is required to be diverse, including multiple scientific disciplines, genders, and races. The diversity of perspectives is what makes the IRB review valuable. In many IRBs for biomedical research, a pharmacist serves as a member who adds value because of his/her understanding of good research design and how to evaluate risks and benefits.

Researchers must submit information in sufficient detail in the IRB application to allow IRB review and approval. Typically, for clinical trials, this will involve submission of a detailed clinical protocol, a consent form, a sponsor's protocol, and an investigator's brochure. To approve research, an IRB must make determinations that the following criteria are met:[14]

- Risks to subjects are minimized.
- Risks to subjects are reasonable in relation to anticipated benefits to subjects, if any, and the importance of the knowledge that may reasonably be expected to result.
- Selection of subjects is equitable.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
- Informed consent will be appropriately documented.
- The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

In addition to initial review and approval of protocols, IRBs are required to provide continuing review at appropriate intervals for the degree of risk associated with the protocol, but not less than once a year. If approval of a given protocol ends, all research activities must cease until reapproval is secured from the IRB. Approved research must

be conducted according to the approved protocol. Any changes to the protocol must be reviewed and approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject(s).

In clinical drug trials, monitoring for and assessing and managing adverse events or adverse drug reactions takes a central role. All clinical drug trials must be vigilant in soliciting adverse event information from subjects and reporting these events to the sponsor, who then reports to the FDA. Only a subset of the large constellation of adverse events must be reported to the IRB: those with unanticipated problems involving risks to subjects or others.

There are various types of review that an IRB may use, including exemption determination, expedited review, or review by the full board. The Common Rule notes six exemption categories, all involving minimal risk, such as surveys/interviews, use of existing data, or specimens without identifiers. If the IRB determines the project is exempt, it does not undergo full review and may be carried out without IRB oversight. For other minimal risk protocols that do not meet one of the exemptions, it is possible that the IRB may conduct an "expedited" review, meaning it may be reviewed by the IRB chair or designee. Such protocols need to meet the full approval criteria as outlined above. For all protocols involving greater than minimal risk, review and approval by a full board must be secured before starting the research. Byerly[19] provides an in-depth review of the review types and IRB functions to help the practicing pharmacist understand these issues.

Around the turn of 21st century, institutions wishing to strengthen protections for research subjects began to form human research protection programs (HRPPs). These programs seek to create a culture of respect for, and awareness of, the rights and welfare of human research participants at the institution level while advancing scientific knowledge and facilitating the highest quality research. Such goals transcend traditional personnel and departmental jurisdictions, so the program involves integration of review and oversight functions from a number of key stakeholder groups essential to the research enterprise. In addition to protocol review and approval by IRBs, the HRPP establishes a formal process to monitor, evaluate, and continually improve the protection of human research participants. This involves oversight of research protection at the institution, as well as education of investigators and research staff about their ethical responsibility to protect research participants.

DATA CONFIDENTIALITY

Since its inception, the Common Rule required that research must include adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data (see above). Research interactions with human subjects should be conducted privately, and the data generated should be held confidentially. Because of electronic record keeping, data security measures to ensure confidentiality have increased, including use of secure servers and encryption software. In addition to the Common Rule requirements, the standards for protecting patient health information are described in the federal law known as the Health Insurance Portability and Accountability Act (HIPAA). HIPAA limits how health information can be used and disclosed to a set of activities that mainly encompass activities related to treatment, payment for treatment, and healthcare operations. Use of protected health information for research requires that the participant consent to its use through a research authorization that spells out the purpose of the research and how the data will be secured and shared.

KEY ETHICAL CHALLENGES IN CLINICAL RESEARCH

Although underlying ethical principles have been elucidated and regulations have been implemented, challenges remain in the conduct and oversight of clinical research. Some ongoing challenges involve knowing when it is appropriate to use a placebo control, how to ethically conduct phase I trials, how to avoid or manage investigator conflicts of interest in clinical research, how to differentiate research from quality improvement activities, how best to inform participants when genetic research is done, how to ensure appropriate registration of clinical trials, and dealing with myriad issues involved in clinical trials conducted in foreign countries.

Placebo use: Although the RCT, which often includes a placebo control, is considered the gold standard for clinical research, the use of a placebo control is not without ethical controversy. A placebo is generally considered an inactive or inert substance that is made to appear identical to the investigational drug being tested. According to the FDA's Robert Temple,[20] placebo-controlled trials generate the strongest efficacy data with fewest numbers of subjects. Concerns arise, however, regarding the ethics of enrolling subjects with a disease in a placebo (or no real treatment) arm. When is this justified? According to the *Declaration of Helsinki*,[12] "the benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:"

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where, for compelling and scientifically sound methodological reasons, the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

Researchers wishing to use a placebo arm must provide a justification in terms of the above factors for the IRB to consider in approval of the study.

Phase I trials: Phase I trials themselves may raise ethical concerns. If phase I trials are done in healthy volunteers, they cannot bring direct benefit to these participants. If phase I trials enroll subjects with disease (such as oncology phase I trials), then perhaps a direct benefit may result, but it is recognized that phase I trials are not designed to be of direct benefit to the participants but, rather, are designed to test safety and establish a possibly tolerable dose for future study. So why do people enroll in phase I studies?

The answer is complex and not well elucidated. Both types of subjects may enroll for altruistic reasons, in that they want to help others in the future who may suffer from debilitating disease. But as an incentive to enroll and assume the risks associated with new drug testing, healthy subjects are generally paid rather handsomely. This raises the concern that some subjects, especially those with limited means, may discount the potential risks to reap the financial reward. Conversely, patients with the disorder being studied usually are not paid and, indeed, may be subject to additional copays or other charges from a clinical trial. Although there is not much empirical data that address their reasons for participating, Glannon[21] examined this and found several motivators, such as altruism, wanting to fight as long as possible, or "therapeutic optimism" (weighing the low potential for benefit against risk when the person is facing near certain death), at play in decisions to participate in phase I trials.

Conflicts of interest: Another thorny issue at play in conducting human clinical trials involves the potential for **conflicts of interest** (COI) to affect study results. A COI is a situation in which a researcher's financial or other personal considerations may compromise, or appear to compromise, the investigator's professional judgment in conducting or reporting research. Financial interests held by those conducting research may compromise or appear to compromise the fulfillment of ethical obligations regarding the well-being of the research subjects.[22] Financial conflicts of interest, where the researcher receives large sums of money from the research sponsor, or has equity interest in a sponsor, raise the specter of concern about possible undue influence on subjects to participate in the research or bias in analysis of the data toward favorable results. Either of these behaviors will lead to concern about subject safety or concern about validity of results. Conflicts of interest are ubiquitous. The challenge is to recognize, identify, and manage them. The IRB will need to understand when a researcher's personal financial interests might have the ability to distort or affect the safety and rights of the human subjects of research or the integrity of the research, such that disclosure of the COI to research subjects or management of the conflict is necessary.

Quality improvement (QI): Another area that is often surrounded by controversy and confusion involves questions about quality improvement projects, especially in clinical settings where patients and their therapy may be involved. As QI practices have evolved to become more rigorous and controlled, they can begin to look like research studies and it becomes difficult to differentiate between the two. It is important to differentiate between human subjects research, which entails a commitment to the concept of voluntariness in participation, and QI, which explicitly is not done on a voluntary basis but rather is an operational implementation on the part of healthcare organizations.[23] Consumers as patients should have an expectation that the healthcare organization is committed to constantly improving its operations. As such, implementation of a QI project is not an optional process, but rather part of the healthcare operations. IRB review requirements are not in place for these types of projects, as they are not considered human subjects research.

Genetic research: In the age of genomics, most clinical drug research studies include a component that tests samples such as blood, saliva, cerebrospinal fluid, or tissues, such as biopsy tissues, for a variety of biomarkers or genetic makeup and mutations. Often these studies are done on leftover samples, such as samples drawn for clinical purposes, or an additional draw is added to that done for clinical reasons. These procedures generally involve minimal risk of physical harm. Instead, the primary concern is with informational risks, such as discrimination, psychological harm, or harm to family relationships if the results of the genetic testing became known to outsiders in case of a failure to keep the information secure. Another concern involves controversy over whether the results of the research testing will be shared with the participants. Because the testing involves research, which does not necessarily yield results of known validity, much research of this type does not share results with participants. However, as certain genetic mutations are becoming better associated with disease prediction, many argue that researchers and, in particular, biobanks must find a mechanism to ethically share clinically actionable information with research participants.[24]

Public registration of clinical trials: Proponents advocate the development of clinical trial registries for a variety of reasons. Originally, registries were proposed to let investigators and reviewers know about all trials, whether published or not.[25] In 2004, the International Conference of Medical Journal Editors (ICMJE) made registration of certain trials a condition of publication in an effort to encourage publication of both negative and positive trial results. More recently, there is a new FDA Amendment Act requirement for public registration of trials prior to subject enrollment, as well as

a requirement to post results. The overall goals are to increase access to trials and create transparency in access to results (both positive and negative). ClinicalTrials.gov is an example of a registry, although many others exist. Although the goals of increasing public access to trials and making results available publicly may seem, on the surface, to be good, several concerns arise in how these registries perform. In 2012, Dickersin and Rennie[25] noted that ClinicalTrials.gov is coming up short in that most posted trials are not posting results. But concerns arise in simply posting results without commentary, interpretation, or context. This remains an area of interest for both researchers and the public funding the research.

Globalization of clinical research: In the 21st century, due to a burgeoning global research enterprise, there have been efforts to streamline regulatory approval in many countries. Numerous ethical concerns come into play, including whether there is adequate infrastructure for oversight/monitoring of clinical research in foreign countries; whether there are cultural differences that may make acceptance of Western ethical principles difficult; and concerns about exploitative "parachute research,"[26] where research is conducted in an ethically suspect fashion by researchers swooping into an underdeveloped country, yet once the research is concluded, the resultant pharmaceutical product is marketed in the wealthier nations and never becomes available in the locale where it was tested. IRBs are often confronted with diverse cultural practices, and it can be difficult to decide whose principles apply. There is a general recognition of the need for local review to evaluate the research project for cultural, political, and legal issues. There is also a heightened awareness about some sponsors who may use vulnerable foreign populations for risky research with little potential for future benefit.

SUMMARY AND CONCLUSIONS

Clinical research in the 21st century holds much promise for the alleviation of pain and suffering associated with many diseases. Along with such promise comes the responsibility to respect the human participants in the research and make rigorous efforts to protect their rights and well-being. This chapter provided a review of the drug approval process in the United States and the regulatory and ethical principles that guide research with human subjects. Pharmacists who are involved in the drug prescribing/selection process need to understand the clinical drug development process and the implications of ethical responsibility in the conduct of clinical research. Ethical challenges that confront the practitioner need to be considered thoughtfully as research projects are contemplated, developed, reviewed, conducted, and published.

REVIEW QUESTIONS

1. What are the fundamental ethical principles detailed in the Belmont Report and how are they implemented in clinical research?
2. In what phase of clinical trials does the evaluation of safety data take place?
3. Informed consent is a concept critical to enrollment of human subjects in clinical trials. Is there an ideal way to convey the information needed for consent?
4. Placebo controls lead to the best scientific data but may lead to ethical concerns. What are these concerns and how should they be handled?
5. What factors are necessary for an IRB to approve a protocol?

ONLINE RESOURCES

Bioethics Resources on the Web, National Institutes of Health: http://bioethics.od.nih.gov/
Collaborative Institutional Training Initiative (CITI): https://www.citiprogram.org/
Food and Drug Administration: http://www.fda.gov/
Office for Human Research Protections: http://www.hhs.gov/ohrp/
Protecting Human Subject Research Participants: http://phrp.nihtraining.com/
Yale University Human Research Protection Program: http://www.yale.edu/hrpp/

REFERENCES

1. Savulescu J. Harm, ethics committees and the gene therapy death. *J Med Ethics*. 2001;27:148–150.
2. Cobaugh DJ, Allison JJ. Understanding research principles: giving our patients the care they deserve. *Am J Health-Syst Pharm*. 2009;66:1265.
3. FDA Part 312 Investigational New Drug Application. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=312. Accessed October 11, 2012.
4. FDA Subchapter F-Biologics. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=600. Accessed October 11, 2012.
5. Hartung DM, Touchette D. Overview of clinical research design. *Am J Health-Syst Pharm*. 2009;66:398–408.
6. Kaitin KI. Deconstructing the drug development process: the new face of innovation. *Clin Pharmacol Ther*. 2010;87(3):356–361.
7. Moore SW. An overview of drug development in the United States and current challenges. *South Med J*. 2003;96(12):1244–1255.
8. Silverman H. Ethical issues during the conduct of clinical trials. *Proc Am Thorac Soc*. 2007;4:180–184.
9. Nuremberg Code. *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*. Washington, DC: U.S. Government Printing Office; 1949;2:181–182. Available at http://www.ushmm.org/research/doctors/Nuremberg_Code.html. Accessed October 7, 2012.
10. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, April 18, 1979*. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html. Accessed October 7, 2012.
11. Miller FG, Brody H. A critique of clinical equipoise: therapeutic misconception in the ethics of clinical trials. *The Hastings Center Report*. 2003;33(3):19–28.
12. World Medical Association. *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and as revised by the 59th WMA General Assembly, Seoul, Korea, October 2008. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed October 7, 2012.
13. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva, Switzerland, 2002. Available at http://www.cioms.ch/. Accessed October 9, 2012.
14. Code of Federal Regulations. Title 45 Public Welfare Department of Health and Human Services; Part 46 Protection of Human Subjects; June 23, 2005. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html. Accessed October 7, 2012.
15. US FDA Protection of Human Subjects. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=50. Accessed October 12, 2012.
16. US FDA Institutional Review Boards. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=56. Accessed October 12, 2012.
17. Office for Human Research Protections (OHRP). Available at http://www.hhs.gov/ohrp/. Accessed October 12, 2012.
18. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Good Clinical Practice E6 May 1996. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. Accessed October 9, 2012.
19. Byerly WG. Working with the institutional review board. *Am J Health-Syst Pharm*. 2009;66:176–184.
20. Temple R, Ellenberg SS. Placebo-controlled trails and active-control trials in the evaluation of new treatments. Part I: ethical and scientific issues. *Ann Intern Med*. 2000;133:455–463.

21. Glannon W. Phase I oncology trials: why the therapeutic misconception will not go away. *J Med Ethics*. 2006;32:252–255.
22. Financial Conflicts of Interest, Public Health Service, effective August 24, 2012. Available at http://grants.nih.gov/grants/policy/coi. Accessed October 10, 2012.
23. Siegel MD, Alfano SL. The ethics of quality improvement research (Editorial). *Crit Care Med*. 2009;37:791–792.
24. Wolf SM, Crock BN, Van Ness B, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet Med* 2012:14(4):361–384.
25. Dickersin K, Rennie D. The evolution of trial registries and their use to assess the clinical trial enterprise. *JAMA*. 2012;307:1861–1864.
26. Bastida EM, Tseng TS, McKeever C, et al. Ethics and community-based participatory research: perspectives from the field. *Health Promot Pract*. 2010;11(1):16–20.