CHAPTER

2

Ethical Principles in Clinical Research

CHRISTINE GRADY

Section on Human Subjects Research, Department of Clinical Bioethics, National Institutes of Health Clinical Center, Bethesda, Maryland

Clinical research has resulted in significant benefits for society, yet continues to pose profound ethical questions. This chapter describes ethical principles that guide clinical research and briefly considers the history of clinical research ethics and particular ethical challenges in randomized controlled trials.

1. DISTINGUISHING CLINICAL RESEARCH FROM CLINICAL PRACTICE

Clinical research involves the study of human beings in a systematic investigation of human biology, health, or illness, designed to develop or contribute to generalizable knowledge. Clinical research includes a set of activities meant to test a hypothesis, permit conclusions to be drawn, and thereby contribute to generalizable knowledge useful to others. The goal of clinical research is to generate knowledge useful to improving medical care or the public health and thus serve the common or collective good. The individual subject participating in clinical research may or may not benefit from participation.

Clinical research is distinct from clinical practice in that the purpose and goals of each, although not mutually exclusive, are quite different. The purpose of clinical practice is to diagnose, prevent, treat, or care for an illness or condition in a particular individual or group of individuals with the goal of meeting the needs of and benefiting that individual(s). Clinical practice is a set of activities designed to enhance the patient's well-being and has a reasonable expectation of success. In some cases, participation in clinical research does meet the health needs of, and benefit, individual patient-participants. In fact, through participation in good clinical research, an individual may receive a very high quality of patient care and treatment, yet that is not the goal of research, and much research does not directly benefit individual participants.

2. WHAT DOES ETHICS HAVE TO DO WITH CLINICAL RESEARCH?

Broadly, ethics is a systematic method of inquiry that helps us answer questions about how we ought to live and behave and why. With respect to clinical research, there are two fundamental ethical questions: (1) Should we do research with human subjects? Why or why not? and (2) If yes, how should it be done? In addressing the first question, two competing considerations are recognized. On the one hand, clinical research is valuable in generating practical knowledge useful for advancing or improving medical care and health. On the other hand, respect for the inviolability, safety, dignity, and freedom of choice of each individual is indispensable. Advancing or improving medical care and/or the public health is desirable as a public good—good for society. Such knowledge is knowledge in "the service of action, [because] health professionals seek knowledge in order to know how to best serve."[1] The pursuit of knowledge through research should be rigorous because false knowledge applied in practice can be harmful. Rigorous clinical research is an important means to the end of progress in medical and health care—progress that would not be possible without research. It has been claimed that conducting clinical research designed to understand human health and illness may be more than a social good; it may be a social imperative.[2] In contrast, it also has been asserted

that although progress in medical care and health is good, it is an optional good[3] and that other considerations, such as the primacy of the individual, should take precedence. Even if one accepts that improvement in medical care or health is a social good, and that clinical research is an essential means to that end, limits are necessary as progress is achieved through research with human beings. Human subjects who participate in research are the means to securing practical knowledge. Because human beings should never be used "merely as means to an end, but always as ends in themselves,"[4] the need to respect and protect human participants in research is paramount.

The primary ethical tension in clinical research, therefore, is that a few individuals are asked to accept some burden or risk as research subjects in order to benefit others and society. The beneficiaries of research may sometimes include the subjects themselves but also will include others with similar disorders or risk profiles, as well as future persons and society. Asking human subjects to bear any risk of harm or burden for the good of others creates a potential for exploitation. Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not "merely used" but are treated with respect while they contribute to the social good, and their rights and welfare are protected throughout the process of research. Through history, the perception and acceptance of the methods, goals, and scope of clinical research have shifted significantly along with attention to and appreciation of what respecting and protecting research subjects entails. A brief detour through the history of clinical research illustrates these changing perspectives.

3. HISTORY OF ETHICAL ATTENTION TO CLINICAL RESEARCH

3.1. Benefit to the Individual

For hundreds of years, research was done sporadically. There was little basis for a distinction between experimentation and therapy because most therapy was experimental. Systematic evidence of the effectiveness of medical interventions was rare. Experimental therapy was often used to try to benefit ill patients, but such "therapy" frequently contributed to or caused morbidity or mortality. Most researchers were medical practitioners, motivated to do what they thought best for their patients, and trusted to do the right thing. Fraud and abuse were minimized through peer censorship because there were no specific codes of ethics, laws, or regulations governing the conduct of research. Early regulations, such as the Pure Food and Drug Act of 1906 in the United States, prohibited unsubstantiated claims on medicine labels. Yet, research began to grow as an enterprise only after the development of penicillin and other early antibiotics and the passage of the Food, Drug, and Cosmetic Act in 1938 that required evidence of safety before a product was marketed.

3.2. Benefit to Society

Around World War II, there was a dramatic shift in clinical research with tremendous growth in research as an enterprise. Pharmaceutical companies were established; large amounts of both public and private money were devoted to research; and research became increasingly centralized, coordinated, standardized in method, and valued. Human subjects research entered what has since been described as an "unashamedly utilitarian phase."[5] During this period, individuals were often included as research subjects because they were available, captive, and possibly considered unimportant, but they were seen as making a contribution to society. Infectious diseases were a significant problem for the armed services. The federal government and the pharmaceutical industry supported intensive research efforts to develop vaccines and antibiotics for infectious diseases to help the soldiers.

A large part of this effort was accomplished through research conducted in prisons, orphanages, homes for the emotionally or developmentally disturbed, and with other institutionalized groups. There was a fairly clear distinction between research and therapy; subjects not necessarily in need of therapy were accepting a personal burden to make a contribution to society. A utilitarian justification was the basis of claims that some individuals could be used for the greater common good. Revelations of the Nazi medical experiments and war crimes raised concerns about research with human subjects.

3.3. Protection of Research Subjects

In the late 1960s and early 1970s in the United States, shock and horror at stories of abuse of human subjects led to intense scientific and public scrutiny and reflection, as well as debate about the scope and limitations of research involving human subjects. A renowned Harvard anesthesiologist, Henry Beecher, published a landmark article in the *New England Journal of Medicine* in 1966[6] questioning the ethics of 22 research studies conducted in reputable U.S. institutions. Accounts of and debate about the hepatitis B studies at Willow-

brook, the U.S. Public Health Service Tuskegee syphilis studies, and others all generated intense public attention and concern. Congressional hearings and action led to the passage in 1974 of the National Research Act (EL. 93-348) and the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This extremely influential body authored multiple reports and recommendations about clinical research, including reports on research with children and institutional review boards (IRBs). Included in their legacy is the Belmont Report, in which ethical principles underlying the conduct of human subjects research and their application are explicated.[7] The emphasis of the commission's work was the need to protect individuals participating in research from potential exploitation and harm. The commission's work provided the basis for subsequent federal regulations codified in 1981 in Title 45 U.S. Code of Federal Regulations, Part 46, titled "Protection of Human Subjects." These regulations in 1991 became the currently operative Common Rule (45CFR46).[8] The Common Rule governs the conduct of human subjects research funded through any one of 17 U.S. federal agencies. The major thrust of these federal regulations and many of the existing codes of research ethics is protection of subjects from the burdens and harms of research and the possibility of exploitation.

3.4. Research as a Benefit

Events in the late 1980s and 1990s altered some public perspectives on clinical research. Certain very articulate and vocal activists claimed that participation in research can be a benefit that individuals should not be denied rather than a harm to be protected from.[9] According to this perspective, espoused by activists for individuals with the human immunodeficiency virus and breast cancer, among others, participation in research is a benefit, protectionism is discrimination, and exclusion from research can be unjust. Empirical studies have demonstrated that oncology patients, for example, who participate in clinical trials benefit through improved survival.[10,11] Activism and changes in public attitudes about research led to substantive changes in the way research is done and drugs are approved.

In addition to the possible benefits of participation, it was also claimed that certain groups of people traditionally underrepresented in research were being denied the benefits of the application of knowledge gained through research.[12] Since 1994, the U.S. National Institutes of Health requires those who receive research funding to include certain groups of traditionally underrepresented subjects, such as women and ethnic minorities.[13] Since 1998, NIH guidelines emphasize the importance of including children in research.[14]

3.5. Community Involvement in Research

In recent years, the growth of genetics research and of international collaborative research, in particular, has highlighted an ethical need for more community involvement in research. Clinical research does not occur in a vacuum but is a collaborative social activity that requires the support and investment of involved communities, and it comes with inherent risks and potential benefits for communities. As such, involvement of the community in helping to set research priorities, planning and approving research, evaluating risks and benefits during and after a trial, and influencing particular aspects of recruitment, informed consent, and the form of community benefits demonstrates respect for the community and is likely to promote successful research.

4. CODES OF RESEARCH ETHICS AND REGULATIONS

Throughout this history several influential documents have helped to shape our sense of the contours of ethical research (Table 2-1). Most were written in response to specific crises or historical events, yet all have accepted an underlying assumption that research as a means to progress in medical care or health is good. The Nuremberg Code, a 10-point code on the ethics of human experimentation, was written as the concluding part of the judgment at the Nuremberg Trials (1949).[15] Established in response to Nazi experimentation, the Nuremberg Code recognized the potential value of research knowledge to society but emphasized the absolute necessity of the voluntary consent of the subject. The Nuremberg Code established that to be ethical, the conduct of research must

TABLE 2-1 Selected Codes and U.S. Regulations Guiding Research with Human Subjects

- The Nuremberg Code (1949)
- The Declaration of Helsinki (2000)
- The Belmont Report (1979)
- CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002)
- International Conference on Harmonization Guidelines for Good Clinical Practice (1996)
- Title 45 US CFR, Part 46–The Common Rule
- Title 21 US CFR, Parts 50 and 56

have the rights and welfare of the subject as its utmost priority. Most subsequent codes and guidelines for the ethical conduct of research have maintained this emphasis and incorporated the necessity of informed consent. The Declaration of Helsinki was developed by the World Medical Assembly in 1964 as a guide to the world's physicians involved in human subjects research.[16] The Declaration of Helsinki recognizes that some, but not all, medical research is combined with clinical care and emphasizes that patients' participation in research should not put them at a disadvantage with respect to medical care. The Declaration of Helsinki also recognized as legitimate research with people who cannot give their own informed consent but for whom informed permission would be obtained from a legal guardian. Recognized as "the fundamental document in the field of ethics in biomedical research,"[17] the Declaration of Helsinki has had considerable influence on the formulation of international, regional, and national legislation and regulations. The Declaration of Helsinki has been revised several times (1975, 1983, 1989, 1996), and most recently in 2000. Additions to the 2000 version of the declaration, especially those related to the use of placebo controls and obligations to assure post-trial access to tested interventions, have been the subject of continued debate among international researchers.

The Belmont Report, published by the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, described three broad ethical principles that guide the conduct of research and form the "basis on which specific rules could be formulated, criticized, and interpreted."[7] The three principles are respect for persons, beneficence, and justice. Respect for persons requires respect for the autonomous decision making of capable individuals and protection of those with diminished autonomy. Informed consent is the application of this principle in clinical research. Beneficence requires not deliberately harming others, as well as maximizing benefits and minimizing harms. This principle is applied to clinical research through careful risk–benefit evaluation. Justice requires a fair distribution of the benefits and burdens of research. The application of justice described in the Belmont Report is to the selection of research subjects.

The Council of International Organizations of Medical Sciences (CIOMS) in conjunction with the World Health Organization (WHO) issued *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, first in 1982 and revised in 1993 and 2002,[17] that explored the application of the Helsinki principles to the "special circumstances of many technologically developing countries." The CIOMS guidelines, noting an increase in international research, acknowledge differing circumstances in developing and non-Western countries, where there is generally less of a focus on the individual. CIOMS adopts the three ethical principles spelled out in the U.S. National Commission's Belmont Report and maintains most of the tenets of Nuremberg and Helsinki but provides additional and valuable guidance and commentary on externally sponsored research and research with vulnerable populations.

United States federal regulations found in Title 45 of the U.S. Code of Federal Regulations, Part 46 (45CFR46)[8] were first promulgated in 1981 for research funded by the Department of Health and Human Services (formerly the Department of Health, Education, and Welfare). These regulations were extended in 1991 as the Federal Common Rule, applicable to research funded by any of 17 U.S. federal agencies. Based on the recommendations of the National Commission, the Common Rule stipulates both the membership and the function of IRBs and specifies the criteria an IRB should employ when reviewing a research protocol and determining whether to approve it. The Common Rule also delineates the types of information that should be included in an informed consent document and how consent should be documented. Subparts B, C, and D of 45CFR46 describe additional protections for DHHS-funded research with fetuses and pregnant women, prisoners, and children, respectively.

The U.S. Food and Drug Administration (FDA) regulations[18] found in Title 21, USCFR, Part 50, "Protection of Human Subjects," and Part 56, "Institutional Review Boards," contain regulations that are similar, but not identical, to those found in the Common Rule. Compliance with FDA regulations is required for research that is testing a drug, biologic, or medical device for which FDA approval will ultimately be sought.

5. ETHICAL FRAMEWORK FOR CLINICAL RESEARCH

Based on a synthesis of guidance found in the various ethical codes, guidelines, and literature, a systematic framework of principles that apply sequentially to all clinical research was proposed.[19] According to this framework, clinical research must satisfy the following requirements to be ethical: social or scientific value, validity, fair subject selection, favorable risk–benefit ratio, independent review, informed consent, and respect for the enrolled subject[19] (Table 2-2).

TABLE 2-2 Ethical Framework for Clinical Research

Principles of Ethical Clinical Research	Description
Value	Research poses a clinically, scientifically, or socially valuable question that will contribute to generalizable knowledge about health or be useful to improving health. Research is responsive to health needs and priorities.
Validity	Study has an appropriate and feasible design and end points, rigorous methods, and feasible strategy to ensure valid and interpretable data.
Fair subject selection	The process and outcomes of subject and site selection are fair and based on scientific appropriateness, minimization of vulnerability and risk, and maximization of benefits.
Favorable risk–benefit ratio	Study risks are justified by potential benefits and value of the knowledge. Risks are minimized and benefits are enhanced to the extent possible.
Independent review	Independent evaluation of adherence to ethical guidelines in the design, conduct, and analysis of research.
Informed consent	Clear processes for providing adequate information to and promoting the voluntary enrollment of subjects.
Respect for enrolled participants	Study attends to and shows respect for the rights and welfare of participants both during and at the conclusion of research.

5.1. Value and Validity

The first requirement of ethical research is that the research question be worth asking—that is, have potential social, scientific, or clinical value. Research has value when the answers to the research question might offer practical or useful knowledge to understand or improve health. Critical to value is the usefulness of the knowledge gained, not whether the study results are positive or negative. Value is a requirement because it is unethical to expend resources or to ask individuals to assume risk or inconvenience for no socially valuable purpose.[20] A valuable research question then ethically requires validity and rigor in research design and implementation in order to produce valid, reliable, interpretable, and generalizable results. Poorly designed research—for example, studies with inadequate power, insufficient data, or inappropriate or unfeasible methods—is harmful because human and material resources are wasted and exposed to risk for no benefit.[19]

5.2. Fair Subject Selection

Fair subject selection requires that subjects be chosen for participation in clinical research based first on the scientific question, balanced by considerations of risk, benefit, and vulnerability. As described by the National Commission in the Belmont Report, fairness in both the processes and the outcomes of subject selection prevents exploitation of vulnerable individuals and populations and promotes equitable distribution of research burdens and benefits. Fair procedures means that investigators should select subjects for scientific reasons—that is, related to the problem being studied and justified by the design and the particular questions being asked—and not because of their easy availability or manipulability, or because subjects are favored or disfavored.[7] Extra care should be taken to justify the inclusion in research of vulnerable subjects, as well as to justify excluding those who stand to benefit from participation. Since exclusion without adequate justification can also be unfair, eligibility criteria should be as broad as possible, consistent with the scientific objectives and the anticipated risks of the research. Since distributive justice is concerned with a fair distribution of benefits and burdens, the degree of benefit and burden in a particular study is an important consideration. Scientifically appropriate individuals or groups may be fairly selected consistent with attention to equitably distributing benefits and burdens as well as minimizing risk and maximizing benefit.

Persons are considered vulnerable if their ability to protect or promote their own interests is compromised or they are unable to provide informed consent. Although there remains some disagreement about the meaning of vulnerability in research and who is actually vulnerable,[21] there is support for the idea that among scientifically appropriate subjects, the less vulnerable should be selected first. So, for example, an early drug safety study should be conducted with adults before children, and with consenting adults before including those who cannot consent.

Certain groups, such as pregnant women, fetuses, prisoners, and children, are protected by specific regulations requiring additional safeguards in research. According to U.S. regulations governing research with children, a determination of the permissibility of research with children depends on the level of research risk and the anticipated benefits. Accordingly, research that poses minimal risk to children is acceptable, research with more than minimal risk must either be counterbalanced by a prospect of direct therapeutic benefit for the children in the study, or by the importance of the question in children with the disorder

under study, or be approved by a special panel convened by the U.S. Secretary of DHHS.[22] Permission for the research participation of children is sought from their parents or legal guardians, and the child's assent is also sought whenever possible.

Fair subject selection also requires considering the outcomes of subject selection. For example, if women, minorities, or children are not included in studies of a particular intervention, then the results of the study may be difficult to apply to these groups and could actually be harmful. Therefore, study populations recruited for research should be representative of the populations likely to use the interventions tested in the research.[23]

Similarly, it has been argued that justice requires subjects to be among the beneficiaries of research. This means that subjects should be selected as participants in research from which they or others like them can benefit and not be asked to bear the burdens of research for which they can reap no benefits. This understanding of justice has raised important and challenging questions in the conduct of collaborative international research. Some have argued that if a drug or vaccine is tested and found effective in a certain population, there should be prior assurance that that population will have access to the drug or vaccine.[24] Alternatively, subjects or communities should be assured of and involved in negotiation about fair benefits from research that are not necessarily limited to the benefit of available products of research.[25]

5.3. Favorable Risk–Benefit Ratio

The ratio of risks to benefits in research is favorable when risks are justified by benefits to participants or society and research is designed in a way that minimizes risks and maximizes benefits to individual subjects. The ethical principle of beneficence obligates us to (1) do no harm and (2) maximize possible benefits and minimize possible harms. It is a widely accepted principle that one should not deliberately harm another individual regardless of the benefits that might be made available to others. However, as the Belmont Report reminds us, offering benefit to people and avoiding harm requires learning what is of benefit and what is harmful, even if in the process some people may be exposed to some risk of harm. To a great extent, this is what clinical research is about (i.e., learning about the benefits and harms of unproven methods of diagnosing, preventing, treating, and caring for human beings). The challenge for investigators and review groups in clinical research is to decide in advance when it is justifiable to seek certain benefits in research despite the risks, and when it is better to forego the possible benefits because of the risks. This is called a risk–benefit assessment.

The actual calculation and weighing of risks and benefits in research is complicated. Investigators in designing a study consider whether the inherent risks are justified by the expected value of the information and benefit to the participants. Studies should be designed in a way that risks to participants are minimized and benefits are maximized. When reviewing a study, an IRB must first identify the possible risks and benefits and then weigh them to determine if the relationship of risks to benefits is favorable enough that the proposed study should go forward or should instead be modified or rejected. When reviewing studies with little or no expected benefit for individual subjects, the IRB has the sometimes formidable task of deciding whether the risks or burdens to the subjects in the study are justified only by the potential value of the knowledge to be gained, sometimes a particularly difficult risk–benefit assessment. Prospective subjects do their own risk–benefit assessment to decide whether the risks of participating in a given study are acceptable to them and worth their participation.

Many kinds of risks and benefits may be considered in a risk–benefit assessment, including physical, psychological, social, economic, and legal. For example, in a genetics study, the physical risks may be limited to a blood draw or buccal swab, and assessment of the potential psychological and social risks may be more important. Investigators, reviewers, and potential subjects may not only have dissimilar perspectives about research but also are likely to assign different weights to risks and benefits. For example, IRBs consider only health-related benefits of the research in justifying risks, whereas subjects are likely to consider access to care or financial compensation as important benefits that may tip the balance for them in favor of participation. Acknowledging that risk–benefit assessment is not a straightforward or easy process does not in any way diminish its importance. Careful attention to the potential benefits to individuals or society of a particular study in relation to its risks, as well as consideration of the risks of not conducting the research, is one of the most important steps in evaluating the ethics of clinical research.

5.4. Independent Review

Independent review allows evaluation of the research for adherence to established ethical guidelines by individuals with varied expertise and no personal or business interests in the research. For most clinical research, this independent review is carried

out by an IRB or research ethics committee. Using criteria detailed in the U.S. federal regulations,[18] IRBs evaluate the benefits of doing the study, the risks involved, the fairness of the subject selection, and the plans for obtaining informed consent and decide whether to approve a study, with or without modifications, table a proposal for major revisions or more information, or disapprove a study as unacceptable. (See also Chapter 5.)

Independent review of the risks of proposed research by someone other than the investigator has been described as a "central protection for research participants."[26] Nonetheless, many believe the current system of IRBs in the United States is inadequate for protecting subjects, outdated given the current profile of clinical research, beset with conflicts, and in need of reform.[27]

5.5. Informed Consent

Once a proposal is deemed valuable, valid, and acceptable with respect to risks and benefits and subject selection, individuals are recruited and asked to give their informed consent. Through the process of informed consent, prospective subjects are given the opportunity to make autonomous decisions about participating and remaining in research. Respect for persons and their autonomy requires respect for the choices people make and no interference with these choices unless they are detrimental to others. We show lack of respect for persons when we repudiate their considered judgment, deny them the freedom to act on their judgments, or withhold information necessary to make a considered judgment. Inviting people to participate in research voluntarily and with adequate information about the research (i.e., informed consent) demonstrates respect for persons. Informed consent is a process involving three main elements: information, comprehension, and voluntariness.[28] Information provided to subjects about a research study should be adequate, according to a "reasonable volunteer" standard, balanced, and presented in a manner that is understandable to the subject. Information should be provided in the language of the subject, at an appropriate level of complexity given the subject's age and educational level, and culturally appropriate. Attention to the manner and setting in which information is presented is an important aspect of informed consent. The U.S. federal regulations detail the types of information that should be included in informed consent; these essentially include what a reasonable person would need to know to make an informed decision about initial or ongoing research participation. In addition to receiving the necessary information, individuals should be able to process and understand it in the context of their situation and life experiences. Investigators assess the degree to which an individual subject comprehends the particular information provided about a research study and can deliberate and make a choice. After deliberating about information provided, a research subject is asked to make a "voluntary" choice about participation (i.e., a choice about participation free from coercion or undue influence). Informed consent, therefore, is a process that involves presentation of information, discussion and deliberation, assessment of understanding, a choice about participation, and ultimately some form of authorization (Table 2-3).

TABLE 2-3 The Process of Informed Consent

Elements of Informed Consent	Description	Considerations and Challenges
Disclosure of information	Information about the study is disclosed that is based on a "reasonable" person standard. Disclosure takes into account subjects' language, education, familiarity with research, and cultural values. Both written information and discussion are usually provided.	There is a need to balance the goal of being comprehensive with that of attention to the amount and complexity of information in order to give participants the information they need and facilitate understanding.
Understanding	Understanding of the purpose, risks, benefits, alternatives, and requirements of the research.	Empirical data show that participants often do not have a good understanding of the details of the research.
Voluntary decision making	Free from coercion and undue influence. Free to choose not to enroll.	Many possible influences affect participants' decisions about research participation. Avoid controlling influences.
Authorization	Usually given by a signature on a written consent document.	For some individuals or communities, requiring a signature reflects lack of appreciation for their culture or literacy level.

Informed consent is a process that continues throughout someone's participation in research. The process of initial informed consent in research usually culminates with the signing of a document that attests to the fact that the volunteer has given consent to enroll in the study. However, respect for persons requires that subjects continue to be informed throughout a study and are free to modify or withdraw their consent at any time.

Although widely accepted as central to the ethical conduct of research, in reality, achieving true informed consent is challenging. Deciding how much information is adequate is not straightforward. In a complicated clinical trial, written consent documents can be long and complex, and it is not clear the extent to which large amounts of information enhance or hinder subject understanding. The appropriate mix of written and verbal information and discussion varies with the complexity of the study and the individual needs of each subject. Scientific information is often complex; research methods are unfamiliar to many people; and subjects have varying levels of education, understanding of science, knowledge about their diseases and treatments, and are dissimilar in their willingness to enter into dialogue. Besides the amount and detail of information, understanding may be influenced by who presents the information and the setting in which it is given. In some cases, information may be more accessible to potential subjects if presented in group sessions or using print, video, or other media presentations.

Determining whether a subject has the capacity to consent and understands the particular information is also challenging. Capacity to provide consent is study specific. Individuals who are challenged in some areas of decision making may still be capable of consenting to a particular research study. Similarly, individuals may not have the capacity to consent to a particular study, even if generally capable in their lives. Assessing capacity might take into account an individual's educational level and familiarity with science and research, as well as evidence of cognitive or decisional impairment. In some cases, but certainly not all, mental illness, depression, sickness, desperation, or pain may interfere with a person's capacity to understand or process information. Empirical research in informed consent has demonstrated that research participants who give their own consent to participation do not always have a good understanding of the purpose or the potential risks of their research studies.[29]

Informed consent to research should also be voluntary. Life circumstances and experiences provide a context for all decisions, such that decisions are never free from other influences. The expectation in clinical research is that a subject's decision to participate should be free from *controlling* influences.[30] Terminal or chronic illness, having exhausted other treatment options, or having no health insurance may limit a participant's options but do not necessarily render decisions involuntary. Payment and other incentives, trust in health care providers, dependence on the care of clinicians, family pressures, and other factors commonly influence decisions about research participation. Determining the point at which these otherwise acceptable influences become controlling is not straightforward. Given these multiple factors, it is important to ensure that the individual has the option to say no to research participation and to do so with impunity.

Research has demonstrated that active and ongoing dialogue and discussion between the research team and subjects, opportunities to have questions answered, waiting periods between the presentation of information and the actual decision to participate, the opportunity to consult with family members and trusted others, clear understanding of alternatives, and other strategies can serve to enhance the process of informed consent.[31,32]

5.6. Respect for Enrolled Subjects

After enrollment, research participants deserve continued respect throughout the duration of the study and after it is completed. Respect for subjects is demonstrated through appropriate clinical monitoring throughout the study and attention to their well-being. Adverse effects of research interventions and any research-related injuries should be treated. Private information collected about subjects should be kept strictly confidential, and they should be informed about the limits of confidentiality. Research subjects should be reminded of their right to withdraw from the research at any time without penalty. Reevaluation of a decision to participate may be stimulated by a change in clinical status or life circumstances. Information generated by the study or other studies that might become available and could be relevant to a person's decision about continued participation should be expeditiously shared with subjects. Investigators should make plans regarding how to help ensure continued access to successful interventions and to study results after the study is finished.

In summary, ethical clinical research is conducted according to the seven principles in Table 2-2. The exact application of the principles to specific cases will always involve some judgment and specification on the part of investigators, sponsors, review boards, and others involved in clinical research.

6. ETHICAL CONSIDERATIONS IN RANDOMIZED CLINICAL TRIALS

Randomized clinical trials (RCTs) remain the principal method and "gold standard" for demonstrating safety and efficacy in the development of new drugs and biologics, such as vaccines, surgical interventions, behavioral interventions, and systems interventions. An RCT has several characteristic features. It is controlled, randomized, and usually blinded; also, the significance of the results is determined statistically according to a predetermined algorithm. An RCT typically involves the comparison of two or more interventions (e.g., Drug A versus Drug B) to demonstrate the equivalence or the superiority of one intervention over the other in the treatment, diagnosis, or prophylaxis of a specific disorder. Although few existing codes of research ethics, guidelines, or regulations specifically speak to particular issues of moral importance in the conduct of RCTs, the design of the RCT presents a spectrum of unique ethical problems (Table 2-4). "In considering the RCT, the average IRB member must be baffled by its complexity and by the manifold problems it represents."[33]

The ethical justification to begin an RCT is usually described as that of "an honest null hypothesis,"[33] also referred to as equipoise or clinical equipoise.[34] In an RCT comparing intervention A and B, clinical equipoise is satisfied if there is no convincing evidence available to the clinical community about the relative merits of A and B (e.g., evidence that A is more effective than or less toxic than B). The goal of an RCT is by design to disturb this state of equipoise by providing credible evidence about the relative value of each intervention. Equipoise is based on the idea that even in research, patients should receive treatment with a likelihood of success, not one known to be inferior, and they should not be denied effective treatment that is otherwise available. Assigning half or some portion of subjects to each treatment in an RCT is ethically acceptable because patients are not assigned to known inferior treatment. Doubt about which intervention is superior justifies giving subjects an equal chance to get either one. There are many controversies regarding equipoise. Some argue that equipoise is based on a mistaken confluence of research with therapy and therefore should be abandoned.[35]

There are other controversies in RCTs. Universal agreement, for example, about what counts as "convincing" evidence does not exist. The common acceptance of statistical significance at the $p = 0.05$ level, indicating that there is <5% chance that differences noted between interventions in an RCT are due to chance, potentially discounts clinically but not statistically significant observations. There is also disagreement about the extent to which preliminary data, data from previous studies, data from uncontrolled studies and pilot studies, and historical data influence the balance of evidence. In some cases, the existence of these other types of data may make equipoise impossible. However, data from small, uncontrolled studies can also lead to false or inconclusive impressions about safety or efficacy, which likewise can be harmful.

Lack of convincing evidence about which of two or more interventions is superior in terms of long-term outcomes for a group of patients does not necessarily preclude judgments about what is best for a particular patient at a particular time. An individual's unique symptoms, side effects, values, preferences, etc. may suggest that one intervention is better for him or her

TABLE 2-4 Selected Ethical Considerations in Randomized Controlled Trials (RCTs)

Features of RCTs	Description	Questions/Considerations
Equipoise	No convincing evidence that one intervention is better, i.e., more effective or less toxic than the other.	How to factor in early evidence? Is a requirement for equipoise conflating research and therapy?
Choice of control	Appropriate choice of control is necessary for scientific validity and generalizability.	Choice of control is not simply a scientific decision. Placebos as controls require ethical justification.
Randomization	Random assignment decreases bias and controls for many factors.	Random assignment does not allow for autonomous preferences.
Blinding	Either single or double blinding is often used to decrease bias.	Research participants consent to temporarily suspend knowledge of which intervention they are receiving. A blind may need to be broken to treat some clinical problems.
Sharing preliminary information	As evidence accumulates, information about risks and benefits may change and equipoise may be disturbed.	Study monitors, independent data and safety monitoring boards, and others carefully monitor data to help determine when the study should be stopped or information should be shared with participants.

than the other, and if so, the individual may not be a good candidate for participation in an RCT. Clinicians responsible for the care of patients should take these factors into account. When the clinician is also serving as the investigator of a study in which the patient is a subject, tension and role conflict can occur. Being aware of this tension, clearly informing the patient, relying on other members of the team, or, in some cases, separating the roles of clinician and investigator may be necessary so that the patient's needs are not overlooked.[36]

Another important scientific and ethical consideration in RCTs is the selection of outcome variables by which the relative merits of an intervention will be determined. Different conclusions may be reached depending on whether the intervention's efficacy is a measure of survival or of tumor shrinkage, symptoms, surrogate end points, quality of life, or some composite measure. The choice of end points in a clinical trial is never simply a scientific decision.

In an RCT, subjects are assigned to treatment through a process of randomization. This means that each subject has a chance of being assigned to treatment randomly by a computer or the use of a table of random numbers rather than based on individual needs and characteristics. The goal of random assignment is to control for confounding variables by keeping the two or more treatment arms similar in relevant and otherwise uncontrollable aspects. In addition to random assignment, RCTs are often either single blind (subject does not know which intervention he or she is receiving) or double blind (both subject and investigator are blinded to the intervention). Random assignment and blinding are methods used in clinical trials to reduce bias and enhance study validity. Although compatible with the goals of an RCT, random assignment to treatment and blinding to treatment assignment are not necessarily compatible with the best interests or autonomy interests of the patient-subject. It has been shown that in some placebo-controlled blinded studies, both subjects and investigators can guess (more frequently than by chance) whether they are on active drug or placebo.[37] Therefore, the necessity and adequacy of blinding and randomization should be assessed in the design and review of a given research protocol. When randomization and blinding are deemed useful and appropriate for a particular protocol, there are two main ethical concerns: (1) Preferences for an intervention and information about which intervention a subject is receiving may be relevant to autonomous decisions, and (2) information about which intervention the subject is receiving may be important in managing an adverse event or a medical emergency. With respect to the first concern, when consenting to an RCT subjects are informed about the purpose of the research and asked to consent to random assignment and to a temporary suspension of knowledge about which intervention they are receiving. To balance the need for scientific objectivity with respect for a research subject's need for information to make autonomous decisions, investigators should provide subjects with adequate information about the purpose and methods of randomization and blinding, and investigators should assess their understanding of these methods. Subjects are asked to consent to a suspension of knowledge about their treatment assignment until the completion of the protocol or some other predetermined time point, at which time they are informed about which intervention they received in the clinical trial.

Knowledge of which medications a subject is receiving may in some cases also be important to the treatment of adverse events or other medical emergencies, consistent with a concern about the safety and welfare of subjects. To balance the need for scientific objectivity with concern for subject safety, investigators should consider in advance the conditions under which a blind may be broken to treat an adverse event. Specifically, the protocol should specify where the code will be located, the circumstances (if any) under which the code will be broken, who will break it, how the information will be handled (i.e., will the investigator, the subject, the IRB, and the treating physician be informed), and how breaking of a blind will influence the analysis of data. A research subject should always have information about who to notify in the event of an emergency. The IRB should be satisfied that these plans provide adequate protection of patient safety.

A concern that has received recent attention especially in the international research context is how to ensure that when the trial is over, a subject can continue to access an investigational intervention that is providing benefit.[38] Some argue that those who volunteer for RCTs deserve assurance that they will receive the intervention proven to be superior in the RCT. That is, those subjects randomized to an intervention proven to be superior will continue to receive that intervention, and those randomized to the inferior intervention will be given an opportunity to receive the better one. Considerable disagreement exists regarding the extent of the obligation of the researchers or sponsors to ensure access. Additional dialogue regarding the practicalities and resources needed to ensure continued access to treatment would be very useful.

Consent to randomization may be more difficult for the subject if one of the potential treatment assignments is placebo. Some people perceive randomization to placebo in clinical trials as problematic

because it potentially deprives the individual of treatment that he or she may need. On the other hand, if there is clinical equipoise and therefore no proof of the superiority of the experimental treatment, it is just as possible that those randomized to placebo are simply deprived of potentially toxic side effects or of a useless substance.[39] Scientifically, comparing an experimental drug or treatment to placebo allows the investigator to establish efficacy in an efficient and rigorous manner. Alternatively, an RCT involving comparison to another already established therapy, if one exists, may allow the investigator to establish superiority or equivalence (i.e., no difference between the experimental drug and the standard therapy control). Placebo controls in research are justified when there is no standard treatment for a given condition, when new evidence has raised doubts about the net therapeutic advantage of a standard treatment, or when investigating therapies for groups of people who are refractory to or reject standard treatments.[40] In studies that meet these criteria, subjects are not harmed and their rights are not violated by participation in placebo-controlled research. What remains controversial is the use of placebo controls in studies when available alternative therapies do exist. Some authors have argued that the use of placebo controls in these cases is ipso facto wrong and contrary to principles enunciated in the Declaration of Helsinki.[41] Others have argued that the most appropriate choice of a control in an RCT depends on the goals of the study, with considerations of the expected consequences to subjects of randomization to one arm or another, the quality of evidence regarding the effect of existing therapies, the expected variability of spontaneous changes in measured outcomes, and the extent to which a placebo effect may play a role.[42] Some authors have suggested a "middle ground" that considers both scientific design and possible risk to subjects as determinative of the acceptability of placebo.[43] It is widely agreed, however, that if the outcome for the patient of no treatment or placebo treatment is death, disability, or serious morbidity, a placebo control should not be used.[44]

7. CONCLUSION

Ethical principles and guidance for the conduct of human subjects research help to minimize the possibility of exploitation and promote respect and protection of the rights and welfare of individuals who serve as human subjects of research. This chapter reviewed an ethical framework for the conduct of clinical research, some of the historical evolution of research ethics, and ethical considerations of some of the unique features of randomized clinical trials. In addition to adherence to principles, codes of ethics, and regulations, the ethical conduct of human subjects research depends on the integrity and sagacity of all involved.

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