Chapter 21
Ethical Considerations in Clinical Trials

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Clinical trials are crucial to answering important questions in surgery, but they do raise ethical issues. After the historical atrocities of the experiments conducted by Nazi physician researchers on prisoners in concentration camps during World War II, the current standards of ethical conduct are based on protecting human subjects. Several key issues arise when determining the ethicality of human experimentation. When does medical practice cross the line to biomedical research? When do risks outweigh the benefits? What constitutes informed consent in clinical research?

The Nuremberg Code, Declaration of Helsinki, Belmont Report, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects form the present basis for ethical conduct of clinical research. The Nuremberg Code of 1947, considered to be the first time it was outlined that human experimentation should be rooted in informed consent, emphasized the need for consent and favorable risk–benefit ratio [1]. The Declaration of Helsinki highlighted the necessity of independent review, distinguishing between therapeutic and nontherapeutic research [2]. The Belmont Report was written to protect vulnerable populations after the Tuskegee and Willowbrook scandals [3–6]. Beauchamp and Childress proposed four classic principles of biomedical ethics: autonomy, nonmaleficence, beneficence, and justice [7]. Nonmaleficence is defined as inflicting the least harm possible to reach a beneficial result. Beneficence requires researchers keep the welfare of the human participant as the ultimate overall goal of the

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experimentation. In his research, David Resnik proposed four slightly different "standards" or ethical principles for biomedical research [8]. The four ideals include truth telling or veracity, dialogue or free exchange, caution or prudence, and social responsibility or civic duty.

Truth telling is vital in research as scientists have a moral obligation to report accurate results and avoid all fabrication, falsification, and plagiarism of data [9]. Fabrication is the creation of data in the absence of experimental results. One of the more notorious cases of research fabrication was William T. Summerlin's misrepresentation of results relating to immunological rejection of transplanted tissues in a mouse model in 1974. This scandal highlighted some of the pressures clinical researchers face to publicize positive results [10]. Falsification relates to the manipulation or misrepresentation of experimental results and can occur during data collection, statistical analysis, or with omission of contradictory findings [9]. Plagiarism is defined as taking credit for another researcher's work. This includes taking ideas, methods, and techniques or not attributing appropriate credit for previous work. Dishonesty erodes confidence in research findings among the scientific community and the public at large. Unfortunately, scientific dishonesty can be ambiguous and difficult to prove.

Ideally, the scientific community promotes free exchange of ideas through the peer review process. However, researchers often compete for the same funding resources, academic promotions, and prestige that may lead to secrecy of ideas and techniques. Open dialogue promotes sharing of information, methods and data allowing for more efficient use of resources and potentially faster achievement of research objectives [9].

Caution or prudence is crucial to minimize errors. Errors can be categorized as practical errors (mistakes made by people using instruments, performing calculations, or recording data) or theoretical errors (bias in analysis). Resnik proposed informal rules of scientific methodology, including use of controlled experiments, repeating experiments to confirm findings, use of reliable instrumentation, necessity of using instrumentation correctly and reliably, careful recording and duplication of data records and regular engagement in informal peer review of experimental design and data interpretation [8]. Clinical researchers have a social responsibility to behave humanely and utilize scarce resources in a judicious manner when designing and performing experiments. In addition, they should strive to minimize harm and ensure the social utility and benefit of their research [9].

Building on Resnik's work, Emanuel et al. subsequently defined seven ethical requirements for clinical research. These requirements include social or scientific value, scientific validity, fair subject selection, favorable risk–benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects. These requirements draw from the ethical principles of scarce resources and nonexploitation, justice, nonmaleficence, public accountability, and respect for subject autonomy (Table 21.1) [11].

In designing clinical trials, evaluating operative and nonoperative procedures, certain ethical issues arise. There is an ongoing ethical debate regarding "sham surgery." Beecher published the first paper on surgery as placebo in 1961 [12]. Since

Table 21.1 Seven requirements for determining whether a research trial is ethical

Requirement	Explanation	Justifying ethical values	Expertise for evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect of potential and enrolled subjects	Respect for subjects by 1. Permitting withdrawal form the research 2. Protecting privacy through confidentiality 3. Informing subjects of newly discovered risks/benefits 4. Informing subjects of results of clinical research 5. Maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

Based on data from Ref. [11]

Table 21.2 Placebo-controlled trials

The research design addresses a valuable, clinically relevant question
The placebo control is methodologically necessary
The risk of placebo is minimized, does not exceed acceptable research risk and is justified by clinical knowledge to be gained
Deception used to blind the placebo arm is disclosed to and authorized by participants
There is an ability to cross over to the active intervention arm

Based on data from Refs. [16, 17]

that time, patients have infrequently been placed under anesthesia and had surgical incisions created for the placebo arms of surgical trials [13, 14]. Opponents argue that unlike a placebo medication (or sugar pill) that has no risk associated with it, research participants are necessarily put at some risk in a sham surgery trial, violating the principle of nonmaleficence. Conversely, those in favor of placebo-controlled surgical trials cite the existence of the placebo effect and thus the necessity of these trials to determine the true efficacy of treatment [15]. Proponents argue that in the realm of clinical research, there is no requirement to offer participants direct benefit. Participants in the placebo arm may actually be exposed to less risk, as they would not encounter the potentially adverse effects of the intervention.

Sham surgery mandates thorough informed consent. Researchers should be cautious of enrolling patients who do not have decision-making capacity. Placebo-controlled trials should optimally minimize risk, be justified in forwarding clinical knowledge, and fully disclose the deception used to blind the placebo arm (Table 21.2) [16, 17]. The research must be peer-reviewed to determine that the question being asked is important to clinical medicine and that the knowledge gained justifies a placebo arm to determine the true benefit of the intervention. The placebo arm should be disclosed to offer no direct therapeutic benefit and its risks should be minimized and not be considered unduly excessive. There may be a role for pre-research consultation with patient groups in potentially controversial clinical trials to ameliorate concerns and optimize patient educational materials. If possible, agreement should be sought in advance for the participation of non-surgeon clinicians (i.e., anesthesiologists) and support staff who will necessarily be participating in the research [15, 18, 19].

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