The Ethical Approval Process

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9.1 Important Documents in Biomedical Ethics

Prior to the Nuremberg Code, issued by the Nuremberg Military Tribunal during the Nuremberg trials in 1947 (also known as the "Doctors' trial"), there was no generally accepted code of ethics for human research. The Nuremberg Code is a ten-point statement of ethics to prevent abuse of human research subjects and establishes that participation in research must be voluntary (Fact Box 9.1). While the Nuremberg Code were never formally adopted by any state or international agency, it is considered one of the most influential documents in human medical research and served as the basis for documents that later followed [5].

Fact Box 9.1: Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

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3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.
10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Reference: reproduced from "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181–182. Washington, D.C.: U.S. Government Printing Office, 1949.

The Declaration of Helsinki was originally developed by the World Medical Association (WMA) in 1964 in order to establish a set of ethical principles regarding research involving human subjects. This document is widely regarded as the cornerstone for medical research involving human subjects, including identifiable human material and data [19]. The declaration is primarily written for physicians, though it is intended as a guideline for the broader research community. The fundamental principles of the Declaration of Helsinki include respect for the individual, right to self-determination, protection of privacy, and the right to make informed decisions [19]. The document proclaims that the physician's duty is solely to the participant; the participant's welfare supersedes the interest and benefit of science and society [19]. This document has undergone multiple revisions, most recently in 2013, addressing issues more relevant to countries with limited resources, such as post-trial access to interventions, compensation and treatment for individuals harmed during participation in research, access to clinical trial for underrepresented groups, and need for dissemination of research results [12, 19].

9.2 History of Biomedical Human Research in the United States

In the United States, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created by the

National Research Act of 1974 to identify ethical principles and guidelines for conducting human research in response to the Tuskegee syphilis experiment [5]. The Tuskegee syphilis experiment was a prospective clinical study conducted between 1932 and 1972 by US Public Health Service to study the natural history of untreated syphilis in rural African-American males in Alabama. The men were never told of their diagnosis, and although penicillin was found to be an effective cure for the disease, treatment was withheld [16]. A whistle-blower by the name of Peter Buxtun revealed the story to the press, leading to public outrage and major changes in US law and regulation on how human research is conducted [2, 16]. Other controversial research projects in the United States during this era include the Stanford prison experiment (1971), where the participants were unable to withdraw from the study [20], and Project MKUltra (1950s–1973) where subjects were not informed of their participation in the studies [14].

In 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the Belmont Report, which established three core principles (Fact Box 9.2) for research involving human studies: respect for persons, beneficence, and justice [18]. The applications of these principles led to the consideration of the following requirements: informed consent, risk/benefit analysis, and patient selection [17].

Fact Box 9.2: Belmont Report, Three Core Principles for Research Involving Human Studies [18]

1. Respect for persons
2. Beneficence
3. Justice

9.3 Common Rule (Part 46, Protection of Human Subjects, of Title 45, Public Welfare, in Code of Federal Regulations)

The National Research Act of 1974 established a set of guidelines for research involving human subjects, introducing the concept of the Institutional Review Board (IRB). The basic provisions of the IRB are outlined by the Federal Policy for the Protection of Human Subjects, or "Common Rule" was published and codified by 15 federal department and agencies [3]. The Common Rule also outlines the basic provisions for IRB, informed consent, and assurances of compliance [3]. Any research that is conducted by or for these federal agencies must abide by the "basic policy for protection of human research subjects" (also known as Subpart A, Part 46, Protection of Human Subjects, of Title 45, Public Welfare, in Code of Federal Regulations (46 CFR 45)).

The IRB is an independent, administrative group tasked with the responsibility of reviewing and approving research on human subjects, with the purpose of protecting the rights and welfare of human subjects. IRBs, and human subject research in general, are regulated by the Office for Human Research Protections (OHRP), an organization within the Department of Health and Human Services (HHS). The goal of the IRB is to insure that proper informed consent is obtained and documented, risks to subjects are minimized, research design is sound and do not unnecessarily expose subjects to risk, patient selection is equitable, appropriate data monitoring provisions are in place, and privacy and confidentiality of the subjects are maintained [3]. The IRB also has the power to terminate or suspend any research that is not in accordance with the policy [3]. The IRB is comprised of scientists, lay community members, physicians, and lawyers [3]. The average size of the IRB is 14 members. One study found internal medicine to be most commonly represented and orthopedic surgery to be the least represented, among physician members of IRBs [10].

The Common Rule also includes regulations for addressing vulnerable populations, such as pregnant women, fetuses, in vitro fertilization, prisoners, and children. Subpart B of 46 CFR 45 affords special protections to pregnant women, fetuses, and neonates of uncertain viability or nonviable neonates. Research must directly benefit the mother and/or the fetus; if not, risks to the fetus must be minimal, and the purpose of the study must be "the development of important

biomedical knowledge that cannot be obtained by any other means." Subpart C of 46 CFR 45 affords special protections to prisoners, to ensure that they are not exploited, but at the same time given equal opportunity to participate in research studies.

9.4 Research in Children and Adolescents

Children and adolescents comprise an important group of study participants in orthopedics. Importantly, this is a vulnerable population that warrants additional protections. The risks and benefits must be carefully evaluated, to prioritize the welfare of the patient, while recognizing the positive potential benefits of research. This risk/benefit evaluation often impacts participant inclusion/exclusion criteria and consideration for how the standard of care may be affected by research activities [8].

One of the major differences in terms of research in children is that, by definition, they are unable to provide informed consent [5]. Instead, children can provide assent, which is defined in the policy as "a child's affirmative agreement to participate in research" (§46. 402 [b]), and parents or legal guardians can grant permission for their child to participate (§46. 402 [c]). The process of obtaining assent should address the developmental stage of the child and provide opportunities for the child to discuss their willingness or unwillingness to participate, the degree to which the child has control over the participation decision, and whether certain information will or will not be shared with the parents [8]. Typically, local IRBs will provide guidelines for the age and conditions where a child's assent is required.

If the research involves acute illnesses or injuries, the investigators and IRB should provide for "ongoing process for permission and assent" to accommodate for the evolving understanding in the changes of the child's medical and mental condition [8]. Waivers of parental permission for adolescent participation should be considered by the IRB when the "research is important to the health and well-being of adolescents and cannot reasonably or practically be carried out without the wavier" or if the research involves treatments that adolescents can receive without parental permission (may differ by state law) [3, 8]. Additionally, the investigators also need to present evidence that the adolescents have the ability to understand the research and their rights as participants and the research protocol must contain safeguards to protect the interests of the adolescent, consistent with the risk presented to them [8].

9.5 IRB Submission and Approval Process

The definition of research involving human subjects set forth by the common law [45 CFR 46.102 (d)] states that it is "[a] systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" [3]. A majority of research involving human subjects adheres to this definition and, subsequently, requires IRB approval, but there is a subset of research that appears to adhere to this definition that does not require IRB oversight. This includes certain quality improvement and quality assurance initiatives, case reports, and case reviews [13]. The Food and Drug Administration (FDA) provides two general guidelines indicating that a quality improvement or quality assurance initiatives constitute human research if the investigators will seek publication in a scientific/national journal or presentation at a national meeting or if the results will be applicable in a wider setting [13]. With regard to case series or case reports, there is no regulatory guidance on this particular issue [13]. If there are any questions of whether IRB approval is required for a particular study, it is advisable to consult with the IRB prior to starting the study.

The IRB submission process can be an arduous and time-consuming task that may involve multiple modifications and revisions. It can especially be cumbersome in multicenter trials involving multiple IRBs, and the variability between institutions can hinder multi-institutional

research [4]. One study in the United Kingdom found that only 24% of studies submitted were approved without modifications [11]. Common reasons for proposal rejection were improperly designed consent form, poor study design, unacceptable risk to subjects, and ethical and legal reasons (Fact Box 9.3) [10]. Some suggestions to the young investigator navigating the IRB include collaborating with an experienced mentor, familiarizing oneself with the IRB guidelines and procedures of the research site(s), and discussing the protocol with the IRB prior to submission [10].

Fact Box 9.3: Common Reasons for Proposal Rejection [10]

1. Improperly designed consent form
2. Poor study design
3. Unacceptable risk to subjects
4. Ethical and legal reasons

There are three levels of review that are identified by federal regulation: expedited review, full or convened review, and exemption from review. If the study poses only "minimal risk" to the subject, the study may be suitable for expedited review. "Minimal risk" is defined as such "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests" [45 CFR 46.102(i)]. Studies that may be suitable for expedited review based on aforementioned definition are shown in Table 9.1. For minimal risk studies, there is considerable variability in the IRB process [7]. These studies are not reviewed by the full IRB and typically reviewed by a subcommittee or administratively within the office [13].

A study may be exempt from review if it meets one of six of the federally defined exempt categories. Examples include research conducted in established or commonly accepted educational settings, retrospective review of existing data, documents, specimens, and taste and food quality evaluation (for full list, see 45 CFR 46.101 (b)). However, an exemption of a study must be made by the IRB, and no further notification is required from the IRB if that status is granted. A study requires full review if it poses "greater than minimal risk." Examples include Phase I, II, and III clinical trials, studies involving vulnerable populations, and studies including investigational devices.

Table 9.1 OHRP expedited review categories [3]

1. Clinical studies of drugs and medical devices only if one of the following conditions are met:
(a) Research on drugs for which an investigational new drug application is not required
(b) Research on medical devices for which an investigational device exemption application is not required or the medical device is cleared and approved for marketing and is being used for which it has been cleared and approved for
2. Collection of blood samples (finger stick, heel stick, ear stick, venipuncture)
3. Prospective collection of biological samples for research purposes by noninvasive means
4. Collection of data through noninvasive measures (excluding X-rays and microwaves)
5. Research involving materials that have been collected or will be collected for non-research purposes
6. Collection of voice, video, digital, or image recordings for research
7. Research on individual or group characteristics or behavior or research involving interviews, surveys, etc.
8. Continuing review of research previously approved by IRB if:
(a) Enrollment of new subjects is closed or if all subjects have completed the research-related interventions or if the research remains active only for long-term follow-ups
(b) No subjects have been enrolled and no additional risks have been identified
(c) Remaining research activities are limited to data analysis
9. Continuing review of research (not conducted under an investigational new drug application or investigational device exemption that does not fit under items 2 through 8) for which the IRB has determined that the research involves no greater than minimal risk and no additional risks have been identified

* This concise summary is modified and abbreviated from the OHRP Expedited Review Categories [3]. Refer to the OHRP for complete information

9.6 Informed Consent

The Common Rule sets forth the components of informed consent in 45 CFR 46.116 [3]:

- A statement that the study involves research, its purpose, its duration, description of procedures, and identification if the research is experimental
- Description of any "reasonably foreseeable" risks and discomforts
- Description of any possible benefits to the participant or others that may be reasonably expected from the study
- Disclosure of appropriate alternative interventions (if any) that may be advantageous to the participant
- Statement describing the extent (if any) to which confidentiality of subject data is maintained
- If the research involves more than minimal risk and explanation of any compensation or if medical treatments are available if an injury occurs
- Information of the contact person regarding questions about the research, participants' rights, and the contact person when an injury occurs

Additionally, the IRB may request for additional elements when appropriate:

- Risks that may be "unforeseeable" (e.g., to the embryo or fetus if the participant becomes pregnant)
- Anticipated circumstances where the investigator will terminate the participant's involvement in the study without their consent
- Additional costs that the participant may incur
- Consequences if a participant decides to withdraw from the study and procedures for "orderly termination"
- A statement that "significant new findings" which may affect the participant's willingness to continue during the course of the study will be provided to the participants
- An approximate number of participants in the study

The informed consent process may be expedited or waived if the research is considered "minimal risk," if the waiver or alteration of the consent does not adversely affect the participant's rights and welfare, if the research cannot be practically achieved without the waiver/alteration, and if pertinent information will be given to the patients after the study if appropriate.

Studies have demonstrated that participants' understanding of the informed consent is oftentimes inaccurate or incomplete [1, 9]. Additionally, one of the most requested changes required for study approval by the IRB are modifications to the consent form [10]. A systematic review found use of multimedia and enhanced consent forms had limited success in improving participants' understanding, but having a study team member or a neutral educator spending one-on-one time with the participant was found to be the most effective way of improving their understanding [6]. It is important to keep in mind that the investigator's obligations regarding the consent process does not end once the participant signs the form; if the investigator believes this to be true, they may be committing a "serious disservice to the participant by not observing the ethical standards" [13]. For example, the investigator or a member of the research team should be available to answer questions regarding the study at any point in the study.

Take-Home Messages

- Institutional regulations and laws exist to protect human subjects in research.
- The IRB process may be difficult, oftentimes with several modifications, but working with the IRB prior to submission is helpful and recommended.
- Obtain proper informed consent (following the requirements set forth by 45 CFR 46.116), and keep in mind that the investigator's obligations do not end as soon as the participant provides their signature on the form.

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