

Ethics in the Design and Conduct of Clinical Trials

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The history of medicine reveals the need for clinical research. All too frequently, interventions thought to be safe and effective by clinicians prove to be otherwise. The current emphasis on “evidence-based medicine” enunciates the need for carefully obtained data from carefully conducted clinical research; yet the history of medical research in general, and clinical research in particular, has been an unfortunate and littered one in which some physician-scientists have undermined the rights and interests of the participants. While some of the most frequently cited examples of unethical research are clearly egregious, such as the dangerous experimentation on unwilling concentration camp prisoners by Nazi physicians, others are more subtle and involve the misuse of commonly employed, rigorous methods of study design such as randomization and use of placebos. While underrecognition of these issues may be the norm, recent headlines demonstrate that ethical issues associated with certain types of study designs can animate substantial debate. Witness, for example, the controversy over the use of placebo controls in trials aimed at decreasing vertical transmission of human immunodeficiency virus infection (1). Regardless of whether such ethical issues are overt or subtle, it is critical that persons designing, sponsoring, overseeing, conducting, reviewing, and reading the results of clinical research understand these issues so as to ensure that all persons who agree to participate in research are adequately protected.

In this article, I outline some of the important ethical issues in the design and conduct of clinical research. To set the appropriate context, I first sketch some of the most notorious examples of unethical research and explain how the ethics of research came to be recognized and articulated, especially in public declarations. Next I describe the basic ethical principles that can be of assistance in understanding the relevant ethical issues encountered in clinical research. I then outline the ethical implications associated with selected issues in research design: randomization, use of placebos, confidentiality, and selection of participants. Finally, I discuss some of the ethical considerations

involved in the research process: obtaining valid informed consent, dealing with interim results, and the responsible conduct of research. Although the scope of this article does not permit a detailed analysis of any of these particular issues, I have attempted to provide a sense of the relevant concerns and to point the reader towards literature appropriate for further discussion of them.

RECOGNIZING ETHICAL OBLIGATIONS IN RESEARCH

Medical scientists have a long tradition of paying close attention to the physical well-being of participants in research (2). When research was risky, it was common for investigators themselves to undergo experimental interventions, especially for the first use of a substance in a human being (3). By the turn of the 20th century, some investigators had also recognized the need to obtain explicit consent from subjects. A prominent example is Walter Reed's experiments on yellow fever that were conducted in Cuba following the Spanish-American War. Reed obtained witnessed consent from volunteers, using consent forms written in both Spanish and English (2). Despite this early example of obtaining consent from healthy volunteers, consent was not typically obtained for research involving patients (4). Rather, physicians accustomed to making most medical decisions for patients did the same with regard to medical research. Nevertheless, minimizing risk remained a central concern.

Over the course of the 20th century, a variety of hazards were identified relating to the use and testing of drugs. Prior to the promulgation of the current regulatory approach, which was enacted in 1962, drugs were being marketed without sound evidence of their efficacy and safety. Furthermore, experimentation with new drugs frequently involved haphazard testing in physicians' offices. In response to such problems and in reaction to the devastating birth defects caused by the use of thalidomide in pregnant women, a complicated set of processes was put into place to test new drugs for safety and efficacy (5, 6). Of course, such an approach was only possible once the now-familiar techniques of conducting and analyzing clinical trials had been developed.

While these approaches to drug testing and evaluation were being developed, other types of human experimentation attracted considerable attention. Arguably, the most notable among these were the experiments conducted by Nazi physicians using concentration camp prisoners as unwilling subjects. Although a complete description of these

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experiments is beyond the scope of this paper, many of the Nazi experimenters posed needless risk, pain, suffering, and death to their victims. Following the revelation of these experiments at the end of World War II, many of the Nazi physicians were tried in Nuremberg; some were condemned to death and others to life imprisonment. The Nuremberg Code, a list of 10 obligations for persons conducting medical research, was announced near the conclusion of this court case (7). These obligations include obtaining consent, minimizing risk, and permitting subjects to stop their participation in the research at any time.

Although the Nuremberg Code laid out an important set of obligations, clinical researchers thought that a more nuanced set of standards would be more appropriate to most research with human participants. For example, the Nuremberg Code's requirement for consent would seem to obviate conducting research with children or with persons who would otherwise be incapable of giving consent. Consequently, to be responsive to such situations, the World Medical Association adopted the Declaration of Helsinki (8). By the 1960s, there seemed to be broad recognition of the need to have explicit standards for the ethical conduct of research.

Despite these standards, there gradually came to be a recognition that the research practices being employed did not really meet the obligations of investigators to protect the interests of participants. In a landmark article published in the *New England Journal of Medicine* in 1966, Henry Beecher, a prominent researcher and physician, described several research projects in which this was indeed the case (9). One of the research projects involved injecting or inoculating institutionalized retarded children with hepatitis to follow the natural course of the disease and to develop treatments. Another experiment that received attention involved injecting live cancer cells into elderly cancer patients without their permission. Discussions of experiments like these that involved research practices that were familiar at the time raised ethical questions—for example, the obligation to protect the least well-off members of society and the need to obtain consent from patients as well as from volunteers.

Further scrutiny of the ethics of research occurred when the Tuskegee Syphilis Study was brought to popular attention through newspaper accounts in 1972. In this 40-year study of the natural history of the disease in 399 African-American men with syphilis and 201 controls, initiated in 1932, several ethical violations occurred. These included the selection of a poor farming community as the study site, even though syphilis was prevalent at many other sites; the belief among research subjects that the procedures being applied had therapeutic value; the use of funeral benefits as an incentive; and failure to provide effective treatment, namely penicillin, once it was discovered and found to be effective (6).

Following an evaluation of the Tuskegee Syphilis Study by a federal panel, the National Research Act (Pub. L. 93-348) was passed in the United States in 1974. This law outlined a regulatory approach for ethical research involving human participants and mandated the formation of the National Commission for the Protection of Human Subjects

in Biomedical and Behavioral Research. A central component of this regulatory approach involves the prospective and continuing review of research by an Institutional Review Board. Federal regulations outline the composition of Institutional Review Boards and the procedures and criteria they should use in conducting oversight (10, 11).

The National Commission's Belmont Report outlines three important ethical principles in research: respect for persons, beneficence, and justice (12). Respect for persons is based on the political principle of liberty, or the right to be left alone. Applied to research, it underscores the obligation to obtain informed consent. Beneficence is the ethical obligation to benefit others and to avoid harming them. It implies that in the course of research, benefits should be maximized and risks should be minimized. Appropriate research design is inherent to meeting this obligation, because alternative interventions and designs can present the possibility of markedly different benefits and risks. Justice is the ethical requirement of fairness, which at its most basic level demands that people be treated as equals. Justice is relevant when considering the fair selection of participants, both as groups and as individuals. This has many implications for research, including the implication that those who bear the burdens of research should stand to benefit from it.

ETHICS IN RESEARCH DESIGN

In meeting the ethical obligations inherent in research, it is critical to address the ethical aspects of commonly used methods of clinical research. For example, even when robust methods such as randomization or use of placebos seem to be ideal from a strictly scientific perspective, the ethical implications of employing these methods can suggest the need to use alternative designs. In designing research studies, it is also important to consider the mechanisms that will be used to protect confidentiality and to select participants.

Randomization

Random assignment to different treatment groups is a powerful means of eliminating bias in research. Eliminating bias is an important obligation in designing and conducting research, since it would be inappropriate to expose participants to research that is unlikely to yield valid information (13). However, the use of randomization or any other method of assigning treatment arms can be inappropriate if participants are unnecessarily harmed as a result, such as being deprived of a therapy known to be effective. Accordingly, the use of randomization needs to be justified. While different proposals work to justify the use of randomization, one that has gained much currency involves the notion of "clinical equipoise." Clinical equipoise is the situation in which experts are uncertain as to whether any of the proposed arms of a trial is superior to another (14). For example, clinical equipoise exists if there is uncertainty in the expert community as to whether treatment A is better than treatment B, or whether treatment A is better than placebo. It is argued that it is acceptable to consider the use

of randomization when clinical equipoise exists but unacceptable to do so if it does not.

Even if clinical equipoise exists, it is important to realize that there are lingering ethical challenges associated with randomization in clinical research due to the usual tight relation of research to clinical care (15). First, obtaining valid informed consent can be difficult in many circumstances. Patients who are asked to participate in research may not recognize the distinction between clinical care and research, failing to understand that their medical care has been selected by randomization rather than by their physicians. In fact, empirical work has demonstrated that such a “therapeutic misconception” exists in clinical research (16). Second, as Royall (17) cogently argued, the obligation of clinicians to provide personalized care is central to medical practice. Randomization may simply interfere with personalized care. Third, individual patients may prefer one treatment to another, even in the setting of clinical equipoise, and there may be strong reasons to honor these choices. A powerful historical example is an early trial comparing radical mastectomy with wide excision for treatment of early-stage breast cancer (11). Even though there was clinical equipoise regarding important outcomes such as mortality, the procedures had different effects on other outcomes, such as the degree of disfigurement of women, whose preferences for extensive surgery versus breast conservation are understandably personal.

Given the practical issues faced in obtaining adequate enrollment and informed consent in some clinical studies involving randomization, alternative methods have been proposed that are collectively termed “pre-randomization” or “randomized consent” or “Zelen randomization” (18). These methods involve assigning potential participants to a treatment arm prior to obtaining informed consent. Although such methods might solve some of the design problems at hand, it has been argued that they are either unnecessary or unethical (19, 20). Finally, in certain cultural settings, the concept of randomization may be unworkable because of local norms that do not accept uncertainty as appropriate for clinicians (21).

Placebos

Much like the case with randomization, there are strong arguments suggesting that it is desirable to use placebo control groups instead of “active” control groups in clinical research. Placebo controls are sometimes believed to facilitate the demonstration of efficacy in comparison with historical or active controls; and use of a placebo group, as compared with an active control group, is typically associated with a smaller sample size, resulting in a less expensive and more rapid trial. Although Freedman et al. (22, 23) have suggested that the need for placebos is exaggerated, even if it is accepted that placebos are desirable from a design standpoint, it can be inappropriate to use a placebo control group when a known effective therapy exists (24). In fact, the most recent version of the Declaration of Helsinki makes this point clearly: “The benefits, risks, burdens and effectiveness of a new method should be tested against those of

the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists” (8). Nevertheless, using placebos in some settings, such as those that do not pose a substantial risk to subjects, may be appropriate (25–28). Regardless, given the controversy associated with the use of placebos, it is arguably critical to justify their use in proposed research and to outline the measures that will be employed to monitor participants closely for any adverse consequences (29).

Protecting confidentiality

In research requiring the collection of information that might pose a legal or social risk to participants, it is important to be able to ensure that this information will be kept confidential. It is generally assumed that by ensuring confidentiality, investigators will increase the likelihood of obtaining good participation rates and reliable data. At the same time, by incorporating measures to protect confidentiality, investigators can minimize the likelihood of harm to participants.

Multiple techniques can be used to protect confidentiality, and consideration should be given to using the optimal combination of methods. For instance, in situations where unauthorized access to information might pose a legal risk to subjects, such as research involving illegal drug use, it is possible to obtain a Certificate of Confidentiality from the federal government. These certificates are designed to protect research records from subpoena for criminal or civil prosecution (30). Overall, in situations where information obtained in research might be embarrassing or stigmatizing, it is important not to rely simply on the integrity of persons with access to the data. In research involving complicated sets of medical information that require continuous updating, a mechanism of transferring data in a secure fashion should also be considered (31).

Selection of participants

Multiple considerations related to justice come into play when making decisions about who to include in research. Following revelation of the cases of unethical research described above, many of which involved the enrollment of some of the most disadvantaged members of society (e.g., the institutionalized, the poor, the mentally retarded), federal resolutions took a protective stance towards the selection of research participants. While this was true for virtually all research, additional protections were put in place for research involving children, pregnant women and fetuses, and prisoners. These measures probably contributed to what many (6, 32), but not all (33), believe to be a tendency to conduct most medical research among men. Because it is important for scientific reasons to conduct research with participants who are similar to persons to whom the results are to be applied, such a pattern has led to an inability to use the results of important scientific studies in many populations. For example, only a small proportion

of drugs used in children have actually been tested in children. Similarly, only a few of the drugs used in the treatment of pregnant women have undergone rigorous testing in pregnant women (6). In the aggregate, the desire to protect the “vulnerable” in research has led to an inability to treat such persons in an informed way.

To make matters more complicated, the protective measures put into place in the 1970s met with considerable resistance among persons with devastating illnesses who had no available treatment options. In particular, in the 1980s, acquired immunodeficiency syndrome activists led the way towards changing policies regarding the cumbersome drug approval processes that had been put into place, and cancer activists soon followed suit (34). These too are claims related to justice; however, they are about access to research rather than protection from it (6). New policies requiring the inclusion of multiple different groups in clinical research have now been adopted with this approach in mind.

ETHICS IN THE RESEARCH PROCESS

Just as elements of research design raise ethical questions, so too does the conduct of research. These ethical questions relate to obtaining valid informed consent, dealing with interim results, and the responsible conduct of research.

Informed consent

From an ethical point of view, informed consent is a process, rather than the simple completion of a consent form. The process can be categorized as having three steps: threshold, information, and consent (35). The threshold step requires that the persons being asked to give informed consent have adequate decision-making capacity, or competency, to do so and that they are positioned to make a voluntary choice about participation. If these conditions are met, the potential participants must be given relevant information about the proposed research in a manner that is understandable to them. Finally, those agreeing to participate must explicitly express this decision, and they typically do so by signing an informed consent document. Under this ethical model of informed consent, a variety of obligations arise, such as the need to verify adequate decision-making capacity when it may be questionable and the need to ensure that potential research participants have a level of understanding adequate to make a choice. In meeting these tasks, it may be useful to review evaluations of the efficacy of alternative approaches (36, 37).

Interim results

The knowledge and experience that is generated during the process of research can raise important practical, scientific, and ethical issues. Emerging data can affect the acceptability of continuing a trial, either because one arm is shown to be superior to another or because an arm is causing unanticipated harm. On the other hand, isolated experiences, whether good or bad, within trials can be misleading to

those involved with the research and if acted upon can undermine the integrity of the trial. To address some of these issues and to consider the relevance of results obtained from other research, many trials use an independent data safety and monitoring committee to evaluate emerging data from clinical trials (38). Nonetheless, the current approach for dealing with adverse events from clinical trials is cumbersome and confusing and would benefit from streamlining so that this potentially important information can be used appropriately (39).

Responsible conduct of research

It is critical to ensure that research is conducted responsibly throughout the entire study cycle, from the way participants are selected to the way data are entered, analyzed, and reported. Attention to each aspect of research conduct is necessary to the success of the scientific enterprise and to the protection of study participants and others from unnecessary harm. Because many of the norms and practices associated with science are implicit and difficult to discern, it is becoming clear that everyone involved in research may require education on these matters so that they understand the implications of their actions (40).

CONCLUDING COMMENTS

While the process of designing and conducting medical research obviously raises numerous scientific, statistical, and practical questions, it also raises ethical questions, as the history of such research makes clear. To meet the ethical obligations inherent in clinical research, it is necessary to address this range of questions in tandem. Given the nature of clinical research, these considerations must be addressed not only by persons designing the research but also by those reviewing, funding, overseeing, conducting, publishing, and reading it.

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