Introduction

Why is ethics important in research? People can be harmed and people can be wronged, even if they are not harmed. In addition, groups and populations can be exploited when they are taken advantage of by powerful agents seeking their own ends. While most of the ethical concerns addressed in this chapter can apply to research in any setting, the increase in multinational research conducted in developing countries poses some special concerns, some of which remain unresolved.

Leading historical examples of abuses in research illustrate the ways in which people have been harmed or wronged. Each example violates one or more fundamental ethical principles, which will be elucidated further below.

The Nazi experiments

The most significant cases that revealed the need for establishing guidelines in research ethics were the abuses during World War II. Physicians conducting experiments under the Nazis forced people to drink seawater to find out how long a person could survive without fresh water. In the concentration camp, Dachau, Russian prisoners were immersed in icy waters to see how long a pilot might live when shot down over the English Channel and to find out what kinds of protective gear or warming techniques were most effective. In another experiment, 52 prisoners were exposed to phosgene gas, a biological warfare agent, to test possible antidotes. Also in Dachau, inmates were infected with a broad range of pathogens to test homeopathic preparations. Nazi military authorities were worried about exotic diseases that German troops might contract in Africa or Eastern Europe, and physicians in the camps reasoned that the “human materials” at their disposal could be used to develop remedies. Hundreds of people died in these experiments, and many of those who survived were forced to live with painful physical or psychological scars (Annas and Grodin 1992). The celebrated Nuremberg Code, a consequence of the trial of the doctors who conducted these experiments, broke new ground. Its requirement for informed consent in the first article stated: “The voluntary consent of the human subject is absolutely essential” (Nuremberg Code 1949). A later influential document
that again embodies this requirement is the *Declaration of Helsinki* issued by the World Medical Association.

*The Tuskegee syphilis study*

From the mid-1930s into the early 1970s, the US Public Health Service conducted observations of African American men in a rural setting who were suffering from secondary syphilis. At the time, no efficacious treatment existed. However, after 1945, penicillin became available and was routinely used successfully to treat patients with syphilis. That treatment was withheld from these men, without their knowledge or consent. The Public Health Service officials used the ethically unsound defense, claiming that now that antibiotics could successfully treat syphilis, it would impossible to study its long-term effects.

*Jewish Chronic Disease Hospital*

In 1964, in the Jewish Chronic Disease Hospital in Brooklyn New York, 22 elderly patients were approached by a researcher who wished to study the body’s immune mechanisms. The material actually injected into these patients was tissue consisting of live cancer cells. The subjects were told only that some tissue would be injected, that a lump would form, and would disappear in a few days. The researcher was certain that injecting cancer cells into the subjects would not cause cancer, but he wanted to determine how quickly and in what manner the patients’ immune systems would reject the cancer cells. He defended withholding the information that the tissue consisted of cancer cells, noting that the fear that the word “cancer” strikes in people is very great. Although these elderly patients, some of whom were debilitated or senile, were not physically harmed, they were wronged.

**Fundamental Ethical Principles for Research**

Three principles, respect for persons, beneficence, and justice, are widely accepted as stipulating the requirements of ethics in research involving human beings. Although the principles and their elaboration are derived from sources in Western philosophy, they have become acknowledged as governing research designed and conducted throughout the world, as noted in the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002).

*Respect for persons* is described as incorporating at least two fundamental ethical considerations (CIOMS 2002):

- respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination;
- protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.
The second ethical principle, beneficence, refers to the ethical obligation to maximize benefit and minimize harm; this requires that risks be reasonable in light of expected benefits.

The third principle, justice, can embody several different conceptions. The most common application to research is known as distributive justice. Distributive justice requires a fair distribution of the benefits and burdens of research:

- risks of research should not be borne by groups or populations that will not receive the benefits of the research;
- those who share in the benefits of research should also share in the risks;
- differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions, such as vulnerability. (CIOMS 2002)

Another conception of justice is compensatory justice, which requires that subjects who are injured in the course of their participation deserve appropriate medical treatment and possibly also monetary compensation. A third conception is justice as reciprocity. According to this conception, something is owed to research subjects who may still need treatment when their participation is ended in a trial that results in successful products.

The informed consent requirement of the Nuremberg Code illustrates the need to comply with the first ethical principle, respect for persons. The participation of the concentration camp inmates was coerced; there was no respect for them as autonomous human beings. The episode in the Jewish Chronic Disease Hospital was a clear violation of this same principle, since the elderly subjects were not truthfully informed about the research procedures. The Tuskegee syphilis study violated all three fundamental principles. The men in the study were uninformed, so their autonomy was not respected; they were harmed when they could have been benefited by not being treated once penicillin became available; and, as they were poor and members of a racial minority, selecting them was unjust because they were doubly disadvantaged and, therefore, vulnerable.

The following sections address the three fundamental principles, their application to the research setting, and some of the ethical problems they confront.

Respect for Persons: Informed Consent

Empirical studies and anecdotal evidence make it abundantly clear that a large gap exists between the ideal of informed consent to research and the reality. Prospective research participants must be provided with information sufficient to make an informed choice of whether or not to enroll in a study. The information must be conveyed either in writing (the preferred method) or orally (when it does not make sense to have written documents) in terms that potential subjects can understand: in their mother tongue, obviously; free of medical jargon; at a level of language comprehensible to people whose schooling has not gone beyond the elementary level. Consent must also be voluntary, that is, obtained without pressuring potential subjects and without exerting “undue influence.” Despite the reasonableness of these requirements, informed consent documents remain overly long, filled with technical information, and far from “user friendly.”
The therapeutic misconception

A major problem that exists in industrialized countries as well as in developing countries has come to be known as “the therapeutic misconception” (Appelbaum et al. 1982; King 1995). Empirical studies of informed consent practices have revealed that subjects often do not read the consent documents they are given to sign, because they trust their doctors to act in their best interest (Advisory Committee on Human Radiation Experiments 1996). This illustrates the widespread confusion between participating in research investigating new, unproven therapies, on the one hand, and receiving an established, effective treatment for a health-related condition, on the other. The trust that patients have in their own physicians in the clinical setting relies on the important feature of the physician–patient relationship that physicians should choose the most appropriate treatment for the individual patient. To think that that same obligation applies in the research setting is to fall prey to the confusion between the aims of research and the aim of individualized treatment of patients. The features that characterize the physician–patient relationship should not be assumed to be present in the researcher–subject relationship.

Informed consent in developing countries

A frequent assumption is that the quality of informed consent in clinical research in developing countries is deficient or worse than in developed countries. Part of the rationale has to do with beliefs that may often be true: Participants are illiterate, lack familiarity with biomedical research and informed consent, and have limited access to health-care services (Alvarez Castillo 2002; Levine 1998; Resnick 1998). However, the assumption that the quality of informed consent is worse in developing countries was shown to be unwarranted. As Pace et al. (2003) wrote: “There are indeed warning signs about participants’ comprehension and whether they are acting voluntarily, but in contrast to some claims, these warnings seem to apply to both developed and developing countries.”

Although informed consent requirements have been introduced in the research setting in many developing countries, it is much less common for physicians to obtain consent from patients for medical treatment in those parts of the world. Some of the same problems persist in industrialized countries, despite their long experience with human subjects research. Still, particular problems pertaining to the process and documentation of informed consent appear especially difficult to resolve in countries where cultural features differ considerably from those common to most Western nations.

One example of this problem is a breast cancer study conducted in Vietnam in the 1990s. A researcher from the United States encountered problems surrounding informed consent in a randomized clinical trial of adjuvant treatment for breast cancer conducted in Vietnam: the investigator reported that he “found himself uncertain about the application of American standards of informed consent in the Vietnamese setting.” After consultation with Vietnamese persons and cultural experts, he concluded: “American standards would not be acceptable to Vietnamese physicians, political leaders in Vietnam, or the vast majority of Vietnamese patients” (Love and Fost 1997: 424).
A key reason for this unacceptability is the paternalistic practice of medicine in Vietnam, in which patients do not participate in medical decision-making, but look to their physicians to tell them the appropriate treatment. As a result, the researcher contended that it was necessary to withhold from potential subjects any elements of the consent process that would convey uncertainty by the treating doctor. Specific items that were to be left undisclosed were alternative therapies and an explanation that the subject’s proposed treatment had been determined by randomization. The investigator requested that the research ethics committee in his American medical school that reviewed the proposal “waive the requirement for informed consent, at least with respect to the subject of randomization” (Love and Fost 1997: 429). After many months of deliberation and considerable negotiation, the final version of the consent form did include the key elements of informed consent, “though with somewhat less detail than is typical in a US consent form” (Love and Fost 1997: 430). Yet the authors acknowledge that it is unclear whether the women in the study understood that their treatment was determined by chance.

How to deal with cultural practices that depart from the requirements of informed consent embodied in international ethical guidelines and many national laws and regulations remains a challenge for researchers who conduct clinical trials in developing countries. Ethical relativists have defended at least the following situations that constitute departures from widely accepted ethical standards for informed consent; that is, the perceived need to withhold key information from potential research subjects. Supporters cite three different considerations in defense of such departures.

The first is that the departures are justified by the cultural context in the country or community where the research is carried out. This relies on the widely accepted view that researchers should be culturally sensitive. Second, researchers contend that it would be impossible to conduct research without these deviations from what they call “Western” requirements of informed consent. This is the pragmatic defense. The third consideration follows from the second: requiring adherence would result in a loss of contributions to medical science and lack of consequent benefits to the population in those countries or communities. This is an appeal to justice, citing the consequences of not conducting the research in the developing country.

Cultural differences are challenging for research in the international arena and conducted in multicultural settings because of the tension between the ethical requirements of informed consent and the need to remain culturally sensitive, both of which are stated in international guidelines.

Beneficence

Beneficence is best understood as a variant of the philosophical principle of utility, which stipulates that right actions are those that have a preponderance of good consequences over bad. Beneficence therefore requires that research projects maximize potential benefits and minimize the risk of harm. However, if harms do occur, they are borne by the research participants, whereas the benefits may accrue to the participants themselves, to future patients, or may even constitute contributions to
knowledge. In designing and carrying out their projects, researchers have an obligation to comply with the principle of beneficence. In addition, committees that conduct prior review of research proposals are similarly bound by the obligation of beneficence (see below).

Applying the principle of beneficence to research studies is easier to describe than to implement in practice. For one thing, although it is common to speak of “balancing risks and benefits,” or “assessing the risk–benefit ratio,” no objective methodology exists for doing this. In addition, even experienced researchers may assign different levels of risk to the same procedure used in a research study. Moreover, the benefits may be largely unknown and difficult to anticipate, especially in an early phase of research. Finally, research that provides no direct benefits to subjects (such as baseline physiological measurements in healthy individuals) is permissible, as long as it holds the prospect of benefits to future patients or contributions to scientific knowledge. This makes it all the more difficult to determine that the risks to subjects are reasonable in light of the anticipated benefits.

"Gold standard" methodology and ethics

The requirements of beneficence cannot be met unless research projects are well designed and comply with rigorous methodological standards. Poorly designed research can yield no benefits, either to the participants or to others. One major concern is the long-standing controversy over the appropriate use of placebos, or inert substances, to compare with an active experimental medication in a clinical trial.

There are several methodological reasons why it is sometimes desirable to compare an experimental medication with a placebo. The least problematic, from an ethical point of view, is the situation in which there simply is no known treatment for a medical condition. In that case, the purpose of the trial is to see whether the experimental medication is better than nothing. Since good scientific methodology dictates that neither the researcher nor the participant should know which product is being administered, the placebo is manufactured to resemble the experimental drug. The ethical problem arises, however, when a placebo is proposed to compare with an experimental drug even if there exists a proven treatment for the condition under study. Proponents argue that some illnesses have a fluctuating course, others spontaneously get better, and still others are affected by patients’ beliefs that they are receiving a medication that will make them better (the so-called “placebo effect”). Drug regulatory authorities generally require, or strongly prefer, placebo-controlled design of trials for the above reasons. Drug companies prefer placebo-controlled trials because they can be conducted more quickly and cheaply than a study that compares an experimental medication with a standard treatment.

Critics argue that it is unethical to withhold proven, effective medications from trial participants. The argument is that it is unethical deliberately to make people worse off in research than they would be outside a clinical trial. Withholding from research subjects an existing treatment that they could obtain from their own physicians if they were not in the trial violates the obligation to minimize harm and maximize benefits to research subjects.
Azidothymidine (AZT) trial in developing countries

A clinical trial that came to light in 1997 sparked new, worldwide attention to international research. That episode was a controversy that surrounded a set of studies of mother-to-child HIV transmission carried out in several developing countries, in which some of the women were given a placebo even though a proven, effective treatment was available in industrialized countries.

The international collaborative studies were carried out in Thailand and other developing countries that could not afford the expensive, high-dose AZT regimen routinely used in the US and European countries. These clinical trials were testing a lower dose of AZT, which was much cheaper and therefore presumed to be affordable to the poorer countries that would make it available to pregnant women. The developing country studies also began the cheaper AZT treatment much later in pregnancy, since women in those parts of the world do not routinely receive early prenatal care. And the AZT was administered by mouth rather than through a vein, which was more in line with the medical facilities used in these developing countries. These departures from the proven treatment available in industrialized countries were intended to adapt the treatment to the medical realities in the developing countries where it could be introduced.

Critics of this research argued that women in the trials should have been given the treatment used in industrialized countries and proven to reduce the incidence of HIV infection in their infants, and many lives could have been saved. The rebuttal by defenders of the research included the following main points (not all defenders invoked all of these justifications). The first defense was that the “standard of care” for HIV-positive women in these developing countries is no treatment at all, so they are not being made worse off by being in the study. A second point was that a placebo-controlled trial can be carried out with many fewer subjects and completed in a much shorter time than could a study with a control arm containing an active treatment, so benefits to this population could be available much sooner. A third justification was that the expensive AZT treatment that has become standard in the West is not, and will never be, available to this population, so its use in a research study cannot be justified. A final point was that the actual rate of transmission of HIV from mother to child was not precisely known. That meant there would be no way to tell if the new, experimental treatment would be better than no treatment, or sufficiently better to justify the expense of providing the new treatment.

The chief ethical problem identified by the critics was that these studies used a placebo to compare with the experimental treatment when they could have used the treatment available in the industrialized world. In that case, none of the women in these studies would have been denied a proven or potentially effective treatment. However, this trial raises another ethical concern about research conducted in developing countries. These AZT trials could not have been conducted in the North, since they would have denied participants an effective preventive method available outside the study. Those who defended the study agreed that it could not ethically have been conducted in industrialized countries, yet argued that the situation in developing countries is different. That argument defends the use of “double standards”: one for poor countries and another for wealthier nations. Critics of double standards in research contend that the standards
are not merely different, but lower in the developing country, and therefore violate a principle of global justice.

The above controversy was not limited to a discussion of the AZT trials themselves. The debate gave rise to an examination of the Declaration of Helsinki and a call to revise some of its key provisions. That process was itself fraught with controversy, and ended with the current substantially revised version issued in 2000, which was amended twice since then.

Justice

The original concerns of ensuring justice in research focused on the fair selection of subjects. If the pool of research subjects was mainly a poor population in a country, but those who would receive the eventual benefits were the middle and upper classes, that situation was perceived as unjust. More recently, however, failure to share in the benefits of research when successful products or contributions to knowledge result has been acknowledged as a major shortcoming in research sponsored by industrialized countries or industry and conducted in resource-poor countries. This poses the question, “What, if anything, does justice require when industrialized countries sponsor or conduct research in resource-poor countries?”

Although not universally accepted, current thinking about justice in international collaborative research accepts the following premises:

- research should be responsive to the health needs and priorities of the population where the research is conducted;
- it is unjust for research subjects to be made worse off afterwards than they were during the research – that is, by not providing them with a treatment they still need when their participation ends;
- it is ethically unacceptable for external sponsors to conduct research in developing countries and leave nothing behind when the research is over, that is, failure to provide some post-trial benefits to the community.

Evidence of an evolution of thought in this regard is that earlier versions of the Declaration of Helsinki did not include any statement expressing a general requirement for making successful products available to research subjects or to others. The 2000 revision of Helsinki, however, addresses the point in two separate paragraphs. Paragraph 19 says: “Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.” The brevity of this statement, and the absence of any commentary or explication in the Declaration of Helsinki, leave crucial questions wide open. For example, what are the criteria by which “likelihood of benefit” is to be determined? And what degree of likelihood is necessary?

Helsinki also addresses the question of benefits to the research participants in a strong requirement in paragraph 30: “At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.” Although some commentators
research involving human beings objected to this strong requirement, others argued that failure to provide post-trial benefits would be to exploit the individuals who volunteered to participate, without whom there could be no proven results of clinical trials.

Vulnerability and Exploitation

What makes individuals, groups, or even entire countries vulnerable? And why is vulnerability a concern in research ethics? A simple answer to both questions is that vulnerable individuals and groups are subject to exploitation, and exploitation is morally wrong. Although there is virtually universal agreement that exploitation is wrong, there are sharp disagreements on what constitutes exploitation. The answer is too simple also because not all wrongful actions can properly be considered exploitation. Some situations may be unjust without being exploitative, and some may involve harm inflicted on vulnerable people without having exploited them. Moreover, actions seeking to protect vulnerable individuals or groups might be construed as paternalistic, and therefore questioned by the very groups for whom protection is sought.

An interesting example is the view that women are potentially vulnerable as research participants. What characteristics of women would make them more vulnerable than their male counterparts of the same age and circumstances? Is it that women are less capable of protecting their own interests? That they lack autonomy? Or is it, rather, that women are capable of becoming pregnant so that it is the fetus – not the woman herself – that stands in need of protection? The latter is the likely explanation. However, given that women do not lack capacity to protect their own interests, the question remains whether those who are capable of becoming pregnant are the ones who should determine the best interest of their fetus or future child, and therefore decide whether to be participants in biomedical research. But if not the woman, then who is the most appropriate decision-maker in this context? The woman’s husband? The state? There is no reason to believe that the alleged father of a child or the government cares more or is a more appropriate decision-maker than the woman who will be the mother of the future child.

When it comes to enrolling children in research, the parents are the legally and ethically appropriate decision-makers. The historical and still prevailing view is that research should not be conducted on children for conditions that affect both adults and children. Or at least, that adults should be participants in these studies first. The result is that much research has not been conducted on children, with the result that data is lacking about safety and efficacy for this group. Not only must the appropriate dose for children be tested, but also some medications that are effective in adults are not similarly effective in children.

Moreover, a paradox arises from two opposing perceptions of research. One – the standard view – construes research involving human beings as a risky enterprise, one that can harm or exploit people. At the same time, research can provide direct benefits to participants, giving rise to a positive view of the research enterprise. This may especially be true of individuals who lack adequate medical care outside clinical trials. This shift in the perception of research as beneficial came to light especially at the outset of the HIV/AIDS epidemic, a fatal disease for which there was no treatment or
cure. As a result, HIV-infected individuals were eager to enter the few clinical trials in which new potential treatments were being tested. It is true that participants in clinical trials often receive better care and treatment than they would receive outside a trial. This can be because of the expertise of the research personnel, the diagnostic tests that have to be performed that could reveal an undiscovered medical problem, and the possibility that illnesses other than the one being studied will be treated. Given these opposing perceptions and the reality underlying both, the question arises whether conducting multinational research in resource-poor countries benefits or exploits the population in those countries.

Drug companies are especially eager to conduct their clinical trials in developing countries. The research can be done more cheaply, more quickly, and possibly with less rigorous ethical review. One of the major concerns regarding these forays by the pharmaceutical industry is that the population in developing countries may be exploited. Exploitation occurs when wealthy or powerful individuals or agencies take advantage of the poverty, or powerlessness, or dependency of others by using the latter to serve their own ends (those of the wealthy or powerful), without any compensating benefit for the less advantaged individuals or group. This charge has been leveled at some industry-sponsored research.

One viewpoint considers populations in developing countries to be vulnerable, and therefore inappropriate to involve in research when the same studies could be done in an industrialized country. An opposing view maintains that requiring research to be conducted in industrialized countries before initiating a similar study in a developing country is an unacceptable form of paternalism. It treats developing country decision-makers, researchers, and research subjects like children, incapable of knowing their own interests and protecting those interests in the way the rights and welfare of research subjects are protected in industrialized countries.

A great deal of research is conducted in both industrialized and developing countries when the same health problem exists in both places. Some people from developing countries are among those who encourage this trend, arguing that their countries are capable of protecting their own citizens from harm or exploitation at the hands of local and foreign researchers alike. If the population in these countries has to wait for drug trials to be completed in industrialized countries before the medications can be tested and approved by their own regulatory authorities, the delay can result in untreated diseases and loss of lives. Others remain concerned about exploitation, and point out that in the absence of routinely available medical treatment, the population is likely to accept whatever is offered in the context of research.

Research Ethics Committees

How can human subjects of research be adequately protected against harm or exploitation? What mechanisms exist to protect the rights and welfare of research subjects? The two main safeguards are the requirement of voluntary, informed consent of each individual research subject (discussed earlier), and prior review of proposed research by an independent ethical review committee. Despite the universally
acknowledged need for these two safeguards, ample evidence exists that they are at times flawed, often inadequate, and sometimes even nonexistent.

The two main charges to research ethics committees are to assess the risks and benefits of proposed research, and to review and approve the informed consent documents for the study. Research ethics committees conduct prior review of research proposals to ensure fulfillment of fundamental ethical principles. Multidisciplinary committees may be established within a research institution, on a regional level, or sometimes at the national level. An increasing number of commercial or “for profit” committees have been established. Critics argue, however, that these private boards operate with very limited government oversight and, because they are being paid by the drug company sponsoring the research, they have a direct financial interest in keeping their drug company clients happy (Elliott and Lemmens 2005).

All research ethics committees face many obstacles. A frequent concern is the gap between what laws or regulations stipulate and what actually occurs in practice. Another problem focuses on the constitution of these committees, which are made up mostly of researchers and physicians who can be biased in favor of research.

Many developing countries face these and other problems. One is the poor training of some of the members, as well as the lack of resources for infrastructure (for example, subscriptions to journals, photocopies, and books) and administrative backup, which undermines the efficacy of the committee. Part of the problem lies in the lack of a system that can assess the performance of the ethics committees and the accuracy of their work. In contrast to the strong responsibility and demands implied in approving a research protocol, there is a lack of institutional support (for example, committee members may not be given time off work to sit on the committees; physicians or hospital staff may have to attend patients at the same time; or there may be a lack of secretarial support). This is closely related to the status of these committees, but it also has to do with the scarce resources and revenue to finance some of their tasks. Finally, unlike the model in Northern Europe, which has a high percentage of lay members of the community, many committees in developing countries experience serious difficulties in incorporating representatives of the community.

Conclusion

Research involving human beings is continually evolving in many ways. Despite the existence of settled issues, such as the need for individual, voluntary informed consent, new problems continue to arise. One of the most salient is the increase in international collaborative research, raising, among other problems, the issue of whether double standards are acceptable. Perhaps surprisingly, debates in this connection have challenged the long-standing provision in the Declaration of Helsinki: “In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society” (WMA 2000: para. 5). Research continues to bring new complexities and subtleties, requiring ethical resolutions and when possible, consensus among all stakeholders. Nevertheless, the need exists to maintain universal ethical standards that protect the rights and welfare of all human participants in research.
Acknowledgments

Portions of this chapter are excerpted from the following previously published works:


References


