

3. The Shifting Focus of Ethical Concern: From Thinking About Risks to Thinking About Benefits

Medical research ethics rest on three fundamental principles: first, autonomy and respect for persons; second, beneficence; and third, justice (Box 3).

Formal codification of research ethics dates back only 60 years, when outraged reaction to Nazi medical experimentation on human beings led to the Nuremberg Code of 1947. The Nuremberg Code and subsequent follow-up documents that provide ethical

guidance on medical research have consistently focused on the first of these three principles—respect for persons. As discussed in the following chapter, concern for persons underpins the theory and practice of informed consent, the ethical issue that has received the greatest attention during the past half century. In contrast, the other two ethical principles—beneficence and justice—have received far less consideration. For those involved in rethinking the ethical roadmap for clinical testing of microbicides, particularly in developing countries, application of these latter two principles may pose an even greater challenge for those who wish to put ethical principles into practice.¹

BOX 3: The Three Principles of Ethical Research

1. Respect for Persons

At least two ethical convictions are incorporated in this principle—first, that individuals should be treated as autonomous agents; and second, that those with diminished autonomy are entitled to special protection. The notion of "informed consent" derives from this principle.

2. Beneficence

The principle of beneficence creates the obligation to protect research participants from harm and to maximize possible benefits. It also leads to the notion that risks from the research must be commensurate with expected benefits.

3. Justice

Justice is usually understood to mean that the benefits and burdens of research must be equitably distributed.

The shifting focus: from abuse and risk to beneficence and distributive justice

From early emphasis on the protection of human research subjects, the ethical debate has shifted to focus on the benefits that trial participants receive and the broader implications for distributive justice. This shift began in the 1980s. In response to the growing HIV epidemic, AIDS activists vigorously demanded broader access to potentially life-saving drugs, even those still considered to be experimental. In the 1990s, feminists in the United States increasingly joined in common cause as they protested women's historical exclusion from

¹ IJsselmuiden, C. Some ethical aspects of HIV/AIDS prevention trials: Protecting subjects against research risks and ensuring a fair distribution of potential research benefits. Background paper commissioned for: Practical and Ethical Dilemmas in the Clinical Testing of Microbicides, April 27-30, 1997; Warrenton, Virginia.

clinical trials—a reality that in effect denied women trial benefits. These developments first came to the forefront as political issues in developed countries; but their practical ramifications soon spread, and they have helped to reshape clinical research around the world.

Initially, the priority was to rethink the risks and benefits that could and should be expected by individual participants. Discussions focused on the quality and type of health care the trial provided individuals. Yet research also offers benefits at the collective level—to research institutions, host governments, and communities. Collective benefits might include improved health care services and infrastructure, and access to diagnostic tests, information, and training. Given this second kind of potential, attention has gradually shifted from individual to community-level benefits. This shift has brought the third principle of ethical research, the question of justice, more sharply into focus.

Consideration of distributive justice requires a different set of questions—in particular, who receives (or more to the point, who should receive) the specific goods within a total benefits package. This perspective requires weighing benefits, at both individual and collective levels, against the burden of risk and then finding the balance of short- and long-term benefits for respective stakeholders.

In reframing such questions, the general trend has been to rely far more directly upon consultation with the individuals and the

communities who are directly affected. Typically, clinical researchers now turn to social scientists, nongovernmental organizations, and community-based organizations. They solicit input from both individuals and communities to help prioritize benefits that contribute more broadly to justice. Inevitably, new questions arise on the ethics of the process: Who represents and speaks for the community? What precisely qualifies as “input”? What is meant by “involvement”? And ultimately, who decides when tradeoffs must be made?

Evolving ethical guidance

With this shift in focus, ethical debate has continued to evolve. Several bodies have recently updated their guidance documents on clinical research ethics. As shown in Table 4, these include the Council for International Organizations of Medical Sciences and the World Medical Association (authors of the Declaration of Helsinki). Other entities have issued new guidance, including the Council of the European Union. Still others have issued specialized documents to interpret existing guidance (e.g., the Nuffield Council on Bioethics), to guide their own constituents (e.g., the UK Medical Research Council² and the National Institutes of Health),³ or to offer interpretations in a specific area, such as HIV prevention (e.g., HPTN) or vaccine research (e.g., UNAIDS).

This deepening debate has raised vexing questions on who is to determine the balance of risks versus benefits and on what basis. One response, beginning in the 1980s, has been to require ethics training for



² UK Medical Research Council (MRC). Ethics Guide: Research Involving Human Participants in Developing Societies. London: MRC; 2003.

³ National Institutes of Health (NIH); Guidelines for the Conduct of Research Involving Human Subjects at NIH; 1997. Fifth printing, Washington DC: NIH; August 2004.



TABLE 4: Key Ethical Guidance Documents

Document	Status	Source
<p>World Medical Association (WMA) Since first published in 1964, the Declaration of Helsinki has been generally regarded as the preeminent guidance on the ethics of research related to health care. It has been revised five times by the WMA, most recently in 2000. Paragraphs 29 (Standard of Care) and 30 (After the Research) were discussed and clarified in 2002 and 2004 respectively.</p>	Not legally binding, but frequently referred to in other forms of guidance and regulation	World Medical Association (Declaration of Helsinki), 2000. Ethical Principles for Medical Research Involving Human Subjects. Available at http://www.wma.net/e/policy/b3.htm
<p>The Council for International Organizations of Medical Sciences (CIOMS), in collaboration with World Health Organization In 1982, CIOMS, published <i>International Ethical Guidelines for Biomedical Research Involving Human Subjects</i>, which addressed the special circumstances when applying the Declaration of Helsinki to research in developing countries. The CIOMS guidelines were revised in 1991, 1993, and 2002.</p>	Not legally binding	CIOMS, 2002. International Ethical Guidelines for Biomedical Research involving Human Subjects. Available at http://www.cioms.ch/frame_guidelines_nov_2002.htm
<p>European Parliament and the Council of the European Union Directive 2001/20/EC relates to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, April 2001. Adopted by member states by May 2003; brought into force, May 2004.</p>	Incorporated into national law for EU member states; applies within the EU and for multicenter clinical trials taking place in member states and other countries	Directive 2001/20/EC of the European Parliament and of the Council. See http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf
<p>Steering Committee on Bioethics of the Council of Europe Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, adopted by the Committee of Ministers, June 2004.</p>	Legally binding if signed and ratified	Protocol to the Convention on Human Rights and Biomedicine. Available at http://conventions.coe.int/Treaty/EN/Projets/Protocol-Biomedical%20research.htm#
<p>The European Group on Ethics in Science and New Technologies (EGE) Opinion No. 17 on the ethical aspects of clinical research in developing countries, published on February 4, 2003.</p>	Advisory	Opinion No. 17. Available at http://europa.eu.int/comm/european_group_ethics/docs/avis17_en.pdf

Document	Status	Source
<p>Office of Human Research Protection (US Health and Human Services Department) 45 CFR 46. Provides ethical regulations for all research involving human subjects conducted or supported by the US government, including research outside of the United States.</p>	Legally binding on US-sponsored research	Code of Federal Regulations/ Part 46: Protection of Human Subjects. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
<p>Nuffield Council on Bioethics In April 2002, the Nuffield Council issued <i>The Ethics of Research Related to Healthcare in Developing Countries</i>. This document does not provide specific guidelines; but it attempts to establish an ethical framework for those conducting such research, and it provides recommendations. An updated paper was issued March 17, 2005.</p>	Advisory	Nuffield Council on Bioethics: The Ethics of Research Related to Healthcare in Developing Countries, April 2002; updated March 2005. Available at http://www.nuffieldbioethics.org/go/ourwork/developingcountries/page_246.html
<p>UNAIDS After extensive consultation on four continents, UNAIDS published <i>Ethical Considerations in HIV Preventive Vaccine Research</i> in 2000.</p>	Advisory	UNAIDS, 2000. Ethical Considerations in HIV Preventive Vaccine Research. Available at http://www.unaids.org/html/pub/publications/irc-pub01/jc072-ethicalcons_en_pdf.htm
<p>HIV Prevention Trials Network (HPTN) <i>Ethics Guidance for Research</i>, issued April 15, 2003.</p>	Advisory	HPTN, 2003. HIV Prevention Trials Network Ethics Guidance for Research. See http://www.hptn.org/HPTNResearchEthics.htm

researchers in order to internalize ethical reasoning into research design. In addition, formal ethics review boards are used increasingly to review and approve biomedical research involving human beings. In recent years, both ethical review boards and capacity building in ethics has come to be more commonplace in the Global South, where more and more clinical research on human populations is now taking place.

Ethicists from the US NIH recently set new benchmarks for ethical research in developing countries, highlighting the need for collaborative partnership, social value, scientific validity, fair selection of study

populations, favorable risk-benefit ratio, independent review, informed consent, and respect for recruited participants and study communities.⁴ This framework provides an important new articulation of research ethics, though many pressing questions remain unanswered: Who determines social value and scientific validity? And most importantly, who is seated at the table when such judgments are made?

Most current conceptualizations of research ethics derive from Western traditions in religion and philosophy. Recently, developing country ethicists have begun to articulate their own notions of research ethics,



⁴ Emanuel E, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases*. 2004;189:930–937.



sometimes challenging and sometimes endorsing prevailing constructions. The capacity of less-developed countries to articulate and argue their own perspectives is increasingly threatened by efforts of drug regulators and the pharmaceutical industry to harmonize testing and approval procedures for new pharmaceutical drugs. This effort is being spearheaded by the International Conference on Harmonization of Technical Requirements. Driven largely by the needs of the US, European, and Japanese drug industry, it seeks a single standard to which all drug testing would conform. To challenge such trends, the voices of a broader range of stakeholders will need to be heard in upcoming global dialogue on research practice and ethics.

Ethical deliberation

During the 2003 International Consultation, considerable intellectual tension surfaced on whether ethical standards should or could be moderated in the interest of science for the public good. Should scientific standards sometimes be compromised in order to preserve the highest standards of ethical integrity? Some Consultation participants justified selective infringement on ethical ideals where not doing so might compromise socially beneficial scientific research or undermine the overall credibility and usefulness of a scientific study. Some pointed out that research that is *not* scientifically sound is itself unethical, because it exposes individuals to burdens or risk without providing clear answers to the question under study. Others argued that scientific progress must occasionally be set back in order to maintain ethical standards, especially since scientific priorities are seldom purely objective, much less democratically determined.

Participants recognized that not every

ethical argument carries the same weight. The real work of ethics is to make reasoned judgments by balancing the principles. Consultation participants agreed that measures to reduce harm and maximize good must always be taken as the starting point. Yet rigidity is no friend to ethics. The capacity to balance wisely among competing claims and potential opportunities is by far the harder part of the thinking and doing process. The problem is not whether “to do good,” but how to allocate limited resources for the greatest overall social benefit in particular situations.

Consultation participants strongly reiterated the continuing need to protect individuals from potential risks in trials. Yet for those involved in clinical microbicide trials, the distribution of benefits—as expressions of beneficence and justice—is perhaps an even harder challenge. To act responsibly, the field of research ethics must first embrace a wider spectrum of actors and perspectives.

Finally, several participants suggested that adopting a human rights perspective might provide a useful complementary framework for thinking about the conduct of ethical research. In addition to the three mainstay ethical principles—respect for persons, beneficence, and justice—the practice of human rights focuses attention on rights to health, information, and bodily integrity. More work should be done to explore the utility of human rights norms and mechanisms to improve medical research practice.⁵

⁵ Faunce TA. Will international human rights subsume medical ethics? Intersections in the UNESCO Universal Bioethics Declaration. *Journal of Medical Ethics*. 2005;31:173–178.