The Council for International Organizations and Medical Sciences (CIOMS) Guidelines on Ethics of Clinical Trials

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Numerous bodies from many countries, including governments, government regulatory departments, research organizations, medical professional bodies, and health care providers, have issued guidance or legislation on the ethical conduct of clinical trials. It is possible to trace the development of current guidelines back to the post–World War II Nuremburg war crimes trials, more specifically the "Doctors' Trial." From that trial emerged the Nuremburg Code, which set out basic principles to be observed when conducting research involving human subjects and which subsequently formed the basis for comprehensive international guidelines on medical research, such as the Declaration of Helsinki. Most recently, the Council for International Organizations and Medical Sciences (CIOMS) produced detailed guidelines (originally published in 1993 and updated in 2002) on the implementation of the principles outlined in the Declaration of Helsinki. The CIOMS guidelines set in an appropriate context the challenges of present-day clinical research, by addressing complex issues including HIV/AIDS research, availability of study treatments after a study ends, women as research subjects, safeguarding confidentiality, compensation for adverse events, as well guidelines on consent.

Keywords: ethics; health policy; clinical trial; guidelines

HISTORICAL CONTEXT FOR CLINICAL STUDY ETHICS

Even a cursory review of the literature will reveal a vast array of guidance on the ethical conduct of clinical trials (1). Government legislators, health departments, government regulatory departments, research organizations, and medical professional bodies and patient's advocacy organizations from many countries have weighed in on this issue, resulting in a complex web of occasionally incomplete or conflicting advice. The website for the U.S. Food and Drug Administration publishes a list of the laws, regulations, and guidelines that govern human subject research in many countries around the world, "The International Compilation of Human Subject Research Protections" (http://www.hhs.gov/ohrp/international/).

From a historical perspective (Table 1), most of our current views on research ethics emerge from the post–World War II Nuremburg trials of Nazi war criminals, specifically, the "Doctors' Trial," in which 23 German physicians and administrators were tried. Of these, 16 were found guilty and 7 were executed. During the trial, evidence put forth by the defense indicated that there was no national or international law or statement that differentiated between legal and illegal human experimentation. As a result, Dr. Leo Alexander, one of the medical experts informing the court, created a 6-point code defining legitimate human research (which was ultimately expanded to a 10-point code by the court), which came to be known as the Nuremburg Code (Table 2) (2).

The code includes many of our current requirements for ethical clinical research, such as avoiding unnecessary suffering, assessing risk versus benefit, provision of ongoing health care, ensuring scientific qualification of the research, and ensuring the ability of subjects to withdraw from the study at any time (Table 2). Importantly, a central tenet of the Nuremburg Code, which has formed the basis of current international guidelines for ethical research in humans, is the concept of voluntary consent (2). The code states specifically that the duty and responsibility for ascertaining the quality of consent rest with the individual who initiates, engages in, or directs the experiment (i.e., the investigator). It is a personal duty from which the investigator cannot be removed (e.g., "I was told to do it") (2).

Despite the potency of the Nuremburg Code, abuses of medical research in the 1950s and 1960s occurred (e.g., the Tuskegee syphilis experiment). Thus, in 1964, the World Medical Association met in Helsinki, Finland, and produced guidelines for physicians in biomedical research involving human subjects, which became known as the Helsinki Declaration. In fact, this document is continuously being updated, with the most recent revision in 2000. The Helsinki Declaration addressed deficiencies in the Nuremburg Code, specifically with regard to research in the legally incompetent (e.g., mentally ill, temporarily incapacitated, children) and introduced the concept of therapeutic versus nontherapeutic research. Although the Nuremburg Code focused on voluntary consent, the Helsinki Declaration was founded on the following premise: "It is the mission of the physician to safeguard the health of the people" (3).

INTERNATIONAL ETHICAL GUIDELINES

In the United States, guidelines and regulations on ethics in clinical trials emerged from the Belmont Report, published in 1979, and the Code of Federal Regulations, Titles 21 and 45 (as reviewed by June Smith-Tyler, elsewhere in this symposium). Although these guidelines are recognized by many countries outside the United States, especially those wishing to collaborate with U.S. investigators on studies funded by the U.S. National Institutes of Health, there was a need for a more international perspective. In 1997, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use published the "Good Clinical Practice: Consolidated Guideline," to "provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guidance was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO)." (4)

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TABLE 1. LANDMARKS IN THE EVOLUTION OF RESEARCH ETHICS GUIDANCE

1946–1947	The Nuremburg "Doctors' Trial"
1947	The Nuremburg Code
1948	UN Universal Declaration of Human Rights
1964	World Medical Association: Declaration of Helsinki
1979	The Belmont Report
1993	CIOMS International Ethical Guidelines for Biomedical Research (updated 2002)
1996	US CFR, available online*
1997	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use†

Definition of abbreviations: CFR = Code of Federal Regulations; CIOMS = Council for International Organizations and Medical Sciences; UN = United Nations.

* The U.S. CFR was available before 1996, but previous versions can be viewed online back to 1996. Titles 21 and 45 are updated annually on April 1 and October 1, respectively (http://www.gpoaccess.gov/cfr/about.html).

† See Reference 4 for publication details.

The Council for International Organizations and Medical Sciences (CIOMS) was formed in 1949 jointly by the WHO and the United Nations Scientific and Cultural Organization (UNESCO). The goals of CIOMS are to facilitate and promote international activities in the field of biomedical sciences, in collaboration with the United Nations and WHO. To these ends, CIOMS has undertaken important work in the areas of bioethics, international health policy (including consideration of social justice and individual dignity in relation to health policy), and drug development (safety, pharmacogenetics, reporting of adverse reactions, ethics of drug promotion). In the 1970s, CIOMS undertook research on bioethics in cooperation with the WHO, which resulted in "Proposed Ethical Guidelines" published in 1982. The "International Ethical Guidelines for Biomedical Research Involving Human Subjects" (which were developed in conjunction with the WHO and superseded the Proposed Ethical Guidelines) were published in 1993, and were updated in 2002. This latest document consists of 21 guidelines (outlined in Table 3) and is available in print or via the CIOMS website (http://www.cioms.ch/; CIOMS 2002 guidelines: http://www.cioms.ch/frame_guidelines_nov_2002.htm). The guidelines acknowledge their historical foundations in the Declaration of Helsinki and set out how these principles might be applied in current practice. The CIOMS guidelines address mainly ethical justification and scientific validity of research; requirements for ethical review and informed consent; consideration of vulnerability of individuals, groups, communities, and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health care services.

TABLE 2. A SUMMARY OF THE NUREMBURG CODE

1. The *voluntary consent* of the human subject is absolutely essential*
2. Scientific rigor
3. Good design
4. Avoid unnecessary suffering
5. Death or serious injury should not be an expected outcome
6. Risks weighed against importance of the problem
7. Preparation/facilities to protect subject
8. Scientific qualification of researcher
9. Subject must be free to withdraw at any time
10. Be able to stop study at any time

* This means that the person involved should have legal capacity to give consent; should be able to exercise free power of choice, without any form of constraint or coercion; and should have sufficient knowledge and understanding of the elements of the proposed research and their associated risks, such that the subject can make an informed decision. Although not specified in the Nuremburg Code, it is widely acknowledged that research is at times necessary and may be permissible in groups of human subjects who cannot decide for themselves—for example, children and adults who are temporarily or permanently incapacitated. Very strict safeguards must be applied in such situations.

TABLE 3. SUMMARY OF CIOMS GUIDELINES: INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

1. Ethical justification and scientific validity of biomedical research involving human beings
2. Ethical review committees
3. Ethical review of externally sponsored research
4. Individual informed consent
5. Obtaining informed consent: essential information for prospective research subjects
6. Obtaining informed consent: obligations of sponsors and investigators
7. Inducement to participate
8. Benefits and risks of study participation
9. Special limitations on risk when research involves individuals who are not capable of giving informed consent
10. Research in populations and communities with limited resources
11. Choice of control in clinical trials
12. Equitable distribution of burdens and benefits in the selection of groups of subjects in research
13. Research involving vulnerable persons
14. Research involving children
15. Research involving individuals who by reason of mental or behavioral disorders are not capable of giving adequately informed consent
16. Women as research subjects
17. Pregnant women as research participants
18. Safeguarding confidentiality
19. Right of injured subjects to treatment and compensation
20. Strengthening capacity for ethical and scientific review and biomedical research
21. Ethical obligation of external sponsors to provide health care services

Definition of abbreviation: CIOMS = Council for International Organizations and Medical Sciences.

CONSENT

The CIOMS guidelines state that informed or valid consent must address three questions: (*1*) does the patient have the capacity to consent requiring consideration of such issues as age, maturity, cognitive ability; (*2*) is the consent voluntary (i.e., is the decision made free from coercion, inducement, or intimidation including pressure from a family member); and (*3*) has the patient received sufficient information on which to base his/her decision?

The CIOMS guidelines also stress that consent is a process, not an event. Patients need to have time to study information and ask additional questions before being asked to make a decision. Information should be available in appropriate languages and written in a style that is understandable by patients, taking into consideration relevant factors, including cultural differences.

In addition, the CIOMS guidelines stipulate that the consent process must be documented, and the use of biologic materials, including their possible storage and future use and whether the material will be anonymized, needs to be frankly discussed (5). Finally, the CIOMS guidelines recommend the use of a checklist to guide the consenting process (Table 4) (5).

WHY STUDY VULNERABLE GROUPS?

Definitions of vulnerable groups vary. Vulnerable groups are defined by CIOMS as adults without the capacity (relative, absolute, or temporary) to give voluntary consent and children, who are generally considered to lack capacity to decide for

TABLE 4. CHECKLIST FOR CONSENT PROCESS: THE CIOMS GUIDELINES

- □ Inform the subject why they are being approached.
- □ Ensure that consent in voluntary.
- □ Explain freedom to withdraw.
- □ Explain the purpose of the research.
- □ Describe the trial design in lay terms.
- □ Explain duration of participation required.
- □ Discuss any remuneration.
- □ Discuss mechanisms to inform participants of study results.
- □ Notify participant of confidentiality arrangements and safeguards about access to individual data.
- □ Confirm ethical review has been obtained.
- □ Discuss foreseeable risks.
- □ Discuss possible benefits to the individual or community.
- □ Will the treatment be available after study completion?
- □ What are the alternative treatments to study medication or therapy?
- □ Are any secondary studies proposed?
- □ Is there a distinction between the role of the investigator and the patient's physician?
- □ Are medical services provided for the subject during the study?
- □ Explain what arrangements have been made to deal with research-related injury.
- □ How will the subject be compensated in the event of research-related injury?

Definition of abbreviation: CIOMS = Council for International Organizations and Medical Sciences.

themselves. More specifically (as reviewed by June Smith-Tyler herein), they include the following groups: those who are economically disadvantaged or educationally disadvantaged/illiterate, employees, those who are physically impaired, those with life-threatening conditions or seriously debilitating illnesses, those who are mentally disabled/cognitively impaired, non–native language-speaking subjects, nursing home residents, pregnant women, prisoners, university students, and wards of the state. Because of the inherent complexities of informed consent with these populations, one might ask, "Why study vulnerable groups?" Clinical research in vulnerable groups is critical to medical advances being available to the entire population. For example, excluding children from drug-related research will prevent children from benefiting from new drugs and possibly risk their exposure to medications of unproven efficacy and unknown safety through off-label administration. One can therefore argue that clinical research in vulnerable groups is not only ethical but also may be required in the interests of equity, if the research cannot be conducted in a nonvulnerable population.

It is generally held that research should not be performed in a vulnerable group if the research can be reasonably performed in a nonvulnerable group. CIOMS offers several specific guidelines on research in vulnerable populations. For example, the research should be intended to benefit the group to which the vulnerable patient belongs. Also, the research should be therapeutic or, if nontherapeutic, it should pose minimal risk. In other words, the risks of nontherapeutic research should not be more than those of standard care. As a guide, nontherapeutic low-risk research procedures (e.g., venipuncture) may considered be ethical in children, whereas higher risk procedures would be considered unethical. The risks of therapeutic research in children should be weighed against the potential benefits (5).

The parent or guardian must be asked to give permission according to the same standards that pertain to obtaining valid consent. Children should participate in decisions to the extent that their capacity allows; unwillingness to participate by the child should be noted and usually respected. The caveat "usually" is used because of cases in which the child may simply be afraid of a drug that could be lifesaving (e.g., a cancer study), whereby a parent may choose to overrule a child's view. However, if the research proposed is nontherapeutic, a child's objection should always be respected. In cases in which the child is afraid, the investigators may wish to work with the parents or family to persuade the child of the study's value, but this would vary based on the nature of the study and the treatment in question (4). The situation pertaining to consent for research by "mature minors," who can, in many jurisdictions, consent to medical treatment without parental involvement, is unclear. It is wise therefore to always seek parental involvement in decision making in such cases, or if a child objects to this, to not include that child as a research subject.

CONCLUSIONS

Developing from the Nuremburg Code, CIOMS offers comprehensive guidelines with an international perspective for the ethical conduct of clinical research. The interface between international ethical guidance and legal or administrative direction is complex and may be very inflexible. In some countries, such as the United States and increasingly in Europe, the trend is toward a more uniform approach to research ethics. International pharmaceutical companies based in Western countries are under considerable legislative pressures to adhere to international standards of good clinical practice in the design and ethical conduct of clinical research, not only in those countries but in any location where research is conducted.

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References

1. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701–2711.
2. National Institutes of Health, Office of Human Subjects Research. Regulations and ethical guidelines: the Nuremburg directives. Available from: http://ohsr.od.nih.gov/guidelines/nuremberg.html (accessed September 2006).
3. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. Available from: www.wma.net/e/policy/b3.htm (accessed September 2006).
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). E6(R1). Good clinical practice: consolidated guideline. Available from: http://www.fda.gov/cder/guidance/959fnl.pdf. (Accessed January 2007.) Also published in *Fed Reg* 1997;62:25691–25709E7.
5. Council for International Organizations and Medical Sciences; World Health Organization. International ethical guidelines for biomedical research involving human subjects. Geneva, Switzerland: World Health Organization; 2002. Available from: www.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=84&codcch=201 (accessed September 2006).

DISCUSSION HIGHLIGHTS

Consistency across Guidelines

DR. MACRAE: A lot of the guidelines have emerged from the same lineage: the Nuremburg Code, the Declaration of Helsinki, and

then CIOMS. The CIOMS criteria are quite detailed and most likely have all of the important information. The basic principles are neutral and widely applicable, and I don't really see that there's a need for a completely international approach that is different from the one that is in that document. The difficulty comes when the legal and administrative systems become intertwined with what is purely an ethical view. That is hugely difficult.

Dr. Henry Silverman (*University of Maryland School of Medicine, Baltimore, MD*): If you look at all of the guidelines, including guidelines of individual countries, there are some differences, such as the level of acceptable risk in vulnerable subjects and the use of a waiver of consent in the emergency setting. There's been a lot of research involving waiver of consent in Australia and Canada and a little in the United States, due to the existence of more rigorous guidelines in the United States. Even CIOMS was developed without participation by some members from the developing world, and experts from the developing world need to specify those guidelines to their local, cultural, and socioeconomic context. One example would be the requirement or the documentation of informed consent. In the United States, except for rare exceptions, you need to have a written signature, but many individuals in the developing world can't sign their own name, or only desire to sign their name to documents that involve marriage or real estate transactions. So, they wonder why they have to now sign their name to get "treatment" from their doctor when they never had to before.

Dr. Macrae: That's right, and in the most recent edition of CIOMS, there was some attempt to broaden the input into the document.

Dr. Robert R. Fenichel (*Independent Consultant, Washington, DC*): Differences in the guidelines can also be found within the United States. You don't need to look internationally. As of 5 years ago, there were differences in the emergency therapy restrictions imposed by the Department of Health and Human Services and the FDA, which caused at least one trial to be deferred for about 18 months while that was being sorted out.

Dr. Macrae: There are efforts underway to increase homogeneity, at least in Europe, among the academies and specialties. For instance, later this year will be the first meeting of the European Academy of Pediatrics. That's one of the areas where, as a profession, we can lead. On the regulatory side, the EMEA [European Medicines Evaluation Agency], through its educational role, is another way that a more cohesive approach can be achieved in Europe. I think local differences are good in some ways. They're incredibly frustrating if you're doing a large, randomized, controlled trial, particularly if it involves several countries. But I think local differences are good because they hopefully will reflect the views of the population that the research ethics committee is serving. We shouldn't assume that one country or one region has a uniform ethical perspective.

Clinical Research in Developing Countries

Dr. Gerald J. Criner (*Temple Lung Center, Philadelphia, PA*): What role do the guidelines play in one's ability to conduct a clinical trial in an economically disadvantaged country, in which the patient population may not be able to afford the therapy if it is found to be effective?

Dr. Macrae: In terms of equity or justice, that certainly is discussed in several of the guidelines. I have found that it is considered unethical to do research in a group of patients if, at the end of the day, they will not benefit in their future treatment, assuming it's a chronic disease, that is, that therapy will not be available to them. If you decide to continue giving the drug only to those who participated in the clinical study, what about those in the control group—do they get the drug as well when the study is over? Or, what do you do about the other patients in that hospital's clinic who aren't enrolled in the study, and therefore will not get benefit from the drug?

It's a huge ethical issue, and I don't have an instant answer. Some countries and some pharmaceutical companies have made the study drugs (e.g., HIV drugs) available at study end at a fraction of the cost in Western countries. That seems to be an equitable way forward. One can price drugs, certainly in the developing world, according to that country's assets, and contribute on some sort of pro rata basis.

Dr. Silverman: The guideline says somebody owes something to somebody, but it doesn't define who, it doesn't define what, and it doesn't define to whom. Are the "who" the investigators or the sponsors? Is the "what" the medicine itself, or is it something more than the medicine (e.g., money to support the local health care system)? And regarding "to whom," are we talking about just the people in the trial, all the people in the community, or everybody in the country? I think you need that level of specificity in the guidelines.

Dr. Macrae: You also raise the political element to all of this. If we agree to send Country X a 1-year's supply of HIV medicines, for example, that won't work because as soon as it arrives in Country X, it will be in somebody else's truck, and it will be sold at a huge cost. It is out of our hands. So, it isn't just simply providing the drug. It's actually helping the health care system and infrastructure to develop, to then be able to go on and use the drug in the long term.