Chapter 2
A Review and Critique of International Ethical Principles

Nuria Homedes and Antonio Ugalde

History shows that health professionals who conduct biomedical research continually confront the tension between the advancement of scientific knowledge and the protection of human subjects. There have been spectacular advances in the science of medicine during the past 150 years, but the associated disregard and active malfeasance towards the participants in some experimental situations have led to many attempts to protect study volunteers. Unfortunately, ethical violations continue in clinical research, possibly more so in developing countries where regulations to protect human subjects are not fully in place. This chapter reviews the internationally accepted Codes of Ethics, their relevance and potential for low- and middle-income countries, and the issues that continue to be discussed by bioethicists when they try to agree on standards for clinical research in the developing world.

2.1 The Nüremberg Code and Its Predecessors

The Nüremberg Code (1947) is frequently identified as the first document to discuss ethical rules for human beings. The Code was written in response to the behavior of some researchers in the mid twentieth century and the lack of ethical guidelines. Vollmann and Winau (1996) note that the first attempts to protect study participants date to the end of the nineteenth century. At that time, most research was directed towards understanding the pathophysiology of disease and the response of the individual, with research into disease prevention and treatment following at a later date. Most of these studies took place with hospitalized patients, frequently without their

N. Homedes (✉)
School of Public Health, Division of Management Policy and Community Health, University of Texas Houston Health Science Center, El Paso, TX, USA
e-mail: nhomedes@utep.edu

A. Ugalde
Department of Sociology, University of Texas, Austin, TX, USA

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consent. Research was also sometimes conducted on prisoners. In 1891, the Prussian Minister of the Interior sent an official letter to all prisons forbidding the use of tuberculin as a treatment for tuberculosis without previously obtaining informed consent from all prisoners.

A study by Dr. Albert Neisser was one of the most controversial cases of that time. In 1898, without obtaining informed consent, he injected serum from patients with syphilis into prostitutes who had been hospitalized for other reasons. This case was investigated by the Prussian public prosecutor, and was discussed for some time in the Prussian Parliament and among prominent scientists, many agreeing with Dr. Neisser. Later, a report was requested from the Scientific Medical Office of Health. The legal argument against Dr. Neisser was not about questionable science, but that consent had not been obtained from his study participants. He was found guilty by the Royal Disciplinary Tribunal, and fined. Discussion continued about issues of autonomy (the right of an individual to make a personal decision without any type of coercion) and beneficence (do only good), and that there was a need for studies to be first conducted with animals, then with the researchers themselves, and only then with other human beings who had freely given their informed consent.

In 1900, the Prussian Minister for Religious, Educational, and Medical Affairs issued the first ethical standards to govern "non-therapeutic" research in hospitalized humans. The standards included: (1) obtaining informed consent, and forbidding research on children and persons who, for whatever reason, did not have the capacity to understand the risks of the proposed experiment and give their full consent to participate; (2) that the research would take place with the authorization of the director of the center, who would be held responsible for any ill effects on the patient, and (3) that compliance with these requirements and other circumstances related to the study would be documented in the medical record. In 1902, Albert Moll, a German psychiatrist, developed a contract to guide the physician-patient relationship, incorporating areas of beneficence, autonomy, and informed consent (Vollmann and Winau 1996).

In 1931, the German government issued detailed ethical guidelines for research with human subjects that distinguished between therapeutic and non-therapeutic research. At that time, Germany had the most advanced regulations for research with humans, but they did not prevent the criminal experiments on concentration camp prisoners, for which Germany was condemned during the Nüremberg Trials. Several of these guidelines were strengthened and included in greater detail in the Code of Nüremberg and in the Declaration of Helsinki.

2.1.1 The Nüremberg Code

During the second world war, both Japan and Nazi Germany conducted cruel experiments on human beings, causing death for many and permanent injury to others. At the end of the war, the United States Government granted immunity from prosecution to the Japanese in exchange for information about the results of the studies. German scientists, however, were judged at trials for war crimes. With the intention of avoiding similar situations in the future, the Nüremberg Military

Box 2.1: Summary of the Nüremberg Code

1. Informed consent: given voluntarily, without pressure, based on access to and understanding of the information about the study. The principal investigator is solely responsible for the quality of the informed consent process
2. The research will provide benefits to society, which would otherwise not be available
3. The research will be designed based on animal studies and on knowledge of the natural history of the disease
4. All possible efforts will be made to reduce any physical or mental suffering of the volunteers
5. No experiments will take place if it is known in advance that they may cause death or disability
6. Risks taken must not exceed the scale of the problem to be solved
7. Precautions must be taken to protect volunteers from any possible danger, disability, or death
8. Only trained personnel may conduct research
9. The volunteer must be able to withdraw from the study at any time
10. The researcher must be willing to end the study at any time if the welfare of a volunteer is in jeopardy

Source: Nüremberg Code (see Appendix 1)

Tribunal issued a 10 point document, known as the Code of Nüremberg (see Box 2.1). The Code had little resonance among researchers at first, as they considered it was written in response to situations of extreme brutality, far removed from customary medical research. The Code became more important as ethical violations increased, but many researchers felt that it was too rigid and that it was almost impossible to meet the conditions (Faden et al. 1996).

The Code of Nüremberg, although never formally adopted by any country, has since been very influential in the development of ethical principles for research with human subjects.

2.2 The Declaration of Helsinki

The World Medical Association (WMA), established in London in 1946, condemned the actions of the Nazi physicians and published the International Code of Medical Ethics in 1949, based on the Declaration of Geneva. The document was vague and subject to different interpretations. It was amended in 1968, 1983, and 2006. It is short, and specifically addresses the duties of physicians in general, to patients, and to colleagues (WMA no date).

In 1953, stimulated by the war horrors revealed during the Nüremberg Trials, WMA members asked the Medical Ethics Committee for recommendations to guide physicians who were – or would be – conducting biomedical research involving human subjects. After several years of discussion and study, a draft declaration was prepared, revised, and adopted in 1964 at the 18th General Assembly of the WMA in Helsinki, Finland (WMA no date). The first Declaration of Helsinki had 11 basic principles, but it has since been revised and expanded several times – in 1975, 1983, 1989, 1996, 2000, and 2008. In addition, the WMA issued clarifications to Article 29 in 2002, and Article 30 in 2004. The most recently amended 2008 version has 35 paragraphs.

Both the Code of Nüremberg and the 1964 Declaration of Helsinki established that the welfare of the individual was more important than scientific advancement. The 1964 Declaration of Helsinki is weaker than the Nüremberg Code in the area of informed consent, because the researcher may be exempted from the obligation to obtain informed consent, but the responsibility of the physician as a protector of the patient's health and well-being is increased. Research is permitted on persons who are not able to give informed consent themselves (children, captives, and people with mental disabilities) if and when consent is given for them by their legal representative (Leaning 1996). The Declaration of Helsinki distinguishes between therapeutic and non-therapeutic research, and clearly states the obligation to respect ethical principles when conducting therapeutic experimentation.

Violations of ethical principles continued, including in projects financed by government agencies (Beecher 1966; Brandt 1978; Katz et al. 2003). In response to these abuses, the Declaration of Helsinki of 1975 (approved in Tokyo) is more specific and almost twice the length of the original version, stating explicitly that the protection of the individual is above any community interest (paragraph III. 4. 1975), and conditions the publication of the study results to the prior approval of the research protocol by an ethics committee and adherence to the Declaration of Helsinki. The revisions of 1983 (Venice) and 1989 (Hong Kong) focused on the consent of minors (I. 11. 1983), and the independence of ethics committees and their conformity with national laws (I. 2. 1989), respectively. The 1996 revision (South Africa) introduced a controversy, which has increased over time and is still far from being resolved – the use of placebo. The 1996 amendment limited the use of a placebo to cases where no approved procedure is available, allowing placebo control groups in studies of pathologies where a diagnostic method or therapy currently doesn't exist (II. 3.1996) (de Abajo 2001). The Food and Drug Administration (FDA), USA, was concerned about the limitation on the use of placebos, and has still not accepted either the 1996 revision or any of the subsequent revisions. The FDA continues to operate from the 1989 Declaration of Helsinki (FDA 2001; Temple 2003).

The 1996 and 2000 revisions were in response to a situation arising in the mid1990s. Studies on the prevention of the transmission of HIV/AIDS in Africa were designed with a placebo arm, but in industrialized countries the control group was given an approved treatment. In 1997, Lurie and Wolfe (1997) published an article condemning the use of placebo in 15 of 18 clinical trials on the perinatal

transmission of HIV, which had been – or were being conducted – since 1994. All 15 trials were taking place in low- and middle-income countries and received financing from the National Institutes of Health (NIH), an agency of the USA federal government, while control groups for trials in the USA and in Thailand received treatment with ACTG076.[1] ACTG076 is a regime for the administration of zidovudine, a standard treatment adopted in industrialized countries in 1994, which reduced the perinatal transmission of HIV by two thirds.

Lurie and Wolfe (1997) criticized the use of placebo for both scientific and ethical reasons. In their opinion, clinical trials with placebo controls did not contribute to the advancement of science as much as other study designs would have contributed; they considered this to be an ethical problem. Of greater importance, however, was the establishment of two ethical standards: one for the industrialized world, and another for low- and middle-income countries. Study sponsors justified placebo use in low- and middle-income countries because in general these patients had no access to treatment and probably would not have access to treatment in the near future. In other words, study participation did not imply any additional risk. The counter argument was that the lack of access to treatment was a purely economic issue which, when applied to clinical research, only encouraged the exploitation of vulnerable residents of low- and middle-income countries who, regardless of the result of the clinical trial, would contribute to the advance of science. However, if the procedure studied had positive results, the only participants likely to benefit would be residents of high-income countries, since for the rest the new product would be unaffordable. The unequal distribution of risks and benefits is a violation of the principle of justice, discussed in the Belmont report (see below). Accepting the double standard may be interpreted as an admission that people in low socio-economic circumstances do not have a right to treatment. Placebo control is a subject which has been intensively discussed and which continues to be controversial. Some scientists, including members of the NIH, the FDA, and the European Medicines Agency (EMA, formerly EMEA) (EMEA 2002), defend the need for placebo controlled studies for methodological reasons related to: (1) the sensitivity of clinical trials; (2) efficiency – they require smaller sample sizes, less study time and therefore lead to faster commercialization of the new drug; and (3) the fact that, in many studies, in the long term, the use of placebo does not have negative consequences for participants in the placebo group – for example, studies of treatments for allergies, insomnia, anxiety, etc. (Temple and Ellenberg 2000). At the other extreme are those who ask the FDA to revise its policies for placebo-controlled clinical trials when there are other effective treatments (Ramsay 2000), and who say that even if scientific advances require the use of placebos, this causes a direct confrontation between science and ethics (Rothman et al. 2000), and also creates a clash between the benefits to society *vs.* the rights of the individual.

[1] The National Institutes of Health (NIH), USA, pressured Harvard University researchers to use a placebo for the control group in the Thailand study.

The American Medical Association (AMA), which did not support the 1996 revision of the Declaration of Helsinki, in 1997, suggested another revision of the Declaration and, once the proposal was accepted during the General WMA Meeting in Hamburg, formed a working group, organized several meetings for discussion, and published various editorials and articles -both for and against- the proposed changes (Brennan 1999; Loff and Black 2000; Rothman et al. 2000; Stockhausen 2000; Zion et al. 2000). At the WMA meeting in Edinburgh in the year 2000, a new version of the Declaration of Helsinki was approved without the consensus of all participants (Nicholson 2000). The new version included the following points: (1) reference to the concept of social justice was included for the first time, establishing that "[m]edical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stands to benefit from the results" (paragraph 19); (2) research must not take place in any person who is "...legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor...unless the research is necessary to promote the health of the population represented, and this research cannot instead be performed on legally competent persons" (paragraph 24); (3) "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." (paragraph 29); (4) "At the conclusion of the study, every patient entered into the study should be assured access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." (paragraph 30); (5) "The researcher should also submit to the ethics committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects." (paragraph 13); (6) "...each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal..." (paragraph 22); and (7) the Declaration addresses "medical research", eliminating any distinction between therapeutic and non-therapeutic research (Klimovsky et al. 2002). Predictably, the most contentious changes were the limitations on the use of placebo (paragraph 29); that the study population should have the possibility to benefit from the study results (paragraph 19); and that there is an obligation to provide access to the best procedure at the end of the study (paragraph 30).

The adoption of this revision did not resolve anything; it actually deepened the differences in perspective between high and low- and middle-income countries while the USA was accused of moral imperialism (Angell 1988; Benatar 1998; Rothman et al. 2000; Dawson and Garrard 2006; Tealdi 2006; Garrafa and Lorenzo 2008). Eventually, in response primarily to pressure from the United States and the pharmaceutical industry (Wolinsky 2006), a clarification to paragraph 29 was added in 2002, to specify circumstances when a placebo could be used when other therapies were available. Another clarification, this time to paragraph 30, was added in 2004, stating that study protocols were to include a section describing the conditions for the

provision of the best methods of prevention, diagnosis and treatment. This section would be included in the protocol and would be evaluated by the ethics committees. As predicted (O'Neil 2008), these clarifications were not well received by the low- and middle-income countries, especially in Latin America, because the experts (Tealdi 2006; Garrafa and Lorenzo 2008) saw them as facilitating placebo use, and allowing ethics committees to decide the circumstances when communities would have access to the study procedure if it were shown to be the best available.

In this atmosphere, in May 2007, a working group was formed to once more revise the Declaration of Helsinki. Revision proposals were circulated and three workshops organized: one in Helsinki in March, 2008, and the others in Cairo and São Paulo in August, 2008. After evaluating the proposed revisions, the Brazilian Ministry of Health rejected the revision on the use of placebos, and the Medical Confederation of Latin America and the Caribbean (CONFEMEL) rejected the proposed changes to the Declaration because the clarifications to paragraphs 29 and 30 were now in the text of the Declaration (paragraphs 32 and 33 in the Declaration of Helsinki, 2008), and in their view they violated human rights. However, in Seoul in 2008, the new version of the Declaration of Helsinki was approved, with Brazil and 23 other countries voting against it.

Even with these changes, the FDA did not accept the new version of the Declaration of Helsinki. In 2008, as discussed below, the FDA announced that it was not necessary for clinical trials conducted outside the United States to comply with the 1989 Declaration of Helsinki, only with Good Clinical Practice guidelines of the International Conference on Harmonisation (ICH GCP 1996). During a scientific congress organized by the Bioethics Network for Latin America and the Caribbean (coordinated by UNESCO), ten Latin American countries signed the Declaration of Cordoba, rejecting the 2008 Declaration of Helsinki and proposing to adopt the ethical standards of the UNESCO Universal Declaration of Bioethics and Human Rights, approved by 191 countries in 2005 (Redbioética-UNESCO 2008). In addition, the Brazilian Federal Council of Medicine (Conselho Federal de Medicina 2008) issued a prohibition for physicians conducting medical research with human subjects to use placebos when an effective treatment was available for the health problem under investigation.

There is concern that the controversy over the use of placebo and post-study access to the best procedure might erode the influence of the Declaration of Helsinki as a worldwide reference document for research involving humans (Garrafa and Lorenzo 2008; Kimmelman et al. 2009; Rid and Schmidt 2010). In most countries of the world, the laws and regulations related to biomedical research include the need to implement the Declaration of Helsinki, but over time this could change. Some members of the WMA have spoken against governments mandating compliance with the Declaration of Helsinki for two reasons: (1) the Declaration included higher standards than those required by the laws and regulations of some countries; and (2) nations could not change their legal framework in response to the frequent revisions of the Declaration of Helsinki (Wolinsky 2006).

Less frequently discussed clauses in the 2008 Declaration are two clauses that will lead to improved transparency of clinical trials: requiring the registration of

the protocol in a public data base before the recruitment of study participants (paragraph 19) and the publication of the results (paragraph 30) (Krleza-Jeric and Lemmens 2009). The pharmaceutical industries do not welcome the registration requirement because they claim it threatens their intellectual property rights and could delay the start of clinical trials (Normile 2008).

2.3 International Covenants on Civil and Political Rights, and on Economic, Social and Cultural Rights

In 1966, the General Assembly of the United Nations adopted the International Covenant on Civil and Political Rights, which states in Article 7: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation" (United Nations 1966a). This clearly establishes the relationship between research ethics and human rights (Tealdi 2006). Article 2.1 of the International Covenant on Economic, Social, and Cultural Rights asks countries "individually and through international assistance and co-operation, especially economic and technical," to protect the human rights of their population, especially for the most vulnerable and marginalized groups (United Nations 1996b). And the Declaration of Human Rights, Article 27(1), states that "Everyone has the right … to share in scientific advancement and its benefits." (United Nations 1948; Toebes 1999).

2.4 The Belmont Report, 1979

Concerned about the ethical violations that occurred in the USA between 1963 and 1972, the federal government established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission operated between 1974 and 1978, and issued the Belmont Report on the basic principles for research involving human subjects (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). The report was based on three basic principles: respect for the individual (informed consent and voluntary participation); beneficence (do not harm, maximize possible benefits and minimize possible risks), and justice (equitable distribution of risks and benefits in a population). Many of the proposals made by the Commission have been incorporated into the laws and regulations which govern research in the USA, especially in the areas of informed consent, the composition and operation of ethics committees, and the system to protect vulnerable populations (infants and young children, pregnant women and their fetus, prisoners, institutionalized people, and people with mental disorders).

Part of the Belmont Report was incorporated into the 1991 Federal Policy for the Protection of Human Subjects, known as the Common Rule, which was accepted by all the agencies of the federal government that could be affected by the policy. The

FDA requirements for the approval of new medications are consistent with this policy, especially in regard to obtaining informed consent and prior review by an ethics committee (Emanuel et al. 2003:27).

2.5 The CIOMS/WHO Guidelines

After the approval of the 1964 Declaration of Helsinki, the World Health Organization (WHO) asked the Council for International Organizations of Medical Sciences (CIOMS), a non-governmental organization founded in 1949 to collaborate with the United Nations, to transform the Declaration of Helsinki into a guide for WHO member countries, primarily for low- and middle-income countries. In 1982, CIOMS published the Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects, and, in 1993, the International Ethical Guidelines for Biomedical Research Involving Human Subjects, containing 15 points with commentaries. In 2002, in response to the crisis generated by AIDS-related research studies (see above), CIOMS published a revision of the ethical guidelines containing 21 points with commentary (CIOMS 2002; Fischer 2006).

The CIOMS guidelines were the first to address the socio-economic and political environments of emerging and newly independent countries, and taking into consideration that research is necessary, proposed the use of the guidelines to protect both the participants and the research itself. The first three guidelines relate to the scientific justification of the study and the review by ethics committees, establishing that studies conducted in various countries must be approved in the country of origin (Fischer 2006).

Guidelines 4–7 discuss the parameters to be observed when obtaining informed consent (voluntary; the right to withdraw from the study; an explanation that it is a research study and may not benefit the participant; confidentiality; an explanation of the research design, including issues of randomization and double-blind studies; a description of the risks and benefits; the sources of funding; any compensation for study participants; the right to know the results; the availability of the product after the conclusion of the study; and the obligation of sponsors and researchers to avoid unjustified deception, undue influence, or intimidation, etc.). CIOMS clarifies that informed consent is a process, and that patients should have time to study the information provided by the researchers and to question anything before they grant their consent to participate in the study. The list of requirements considered sufficient by CIOMS guidelines is shown in Box 2.2.

Guideline 8 discusses the risks and benefits that may be considered acceptable, and Guideline 9, how to protect vulnerable populations, including people living in low socio-economic conditions, those with low educational levels, employees, the disabled, people with chronic or debilitating illnesses, indigent groups, residents in homes for aged persons, pregnant women, prisoners, university students, and inmates in state facilities (Macrae 2007).

Guideline 10 establishes that the sponsor or investigator must do everything possible to ensure that the studied procedure, within reason, is accessible and

Box 2.2: Summary of the Rules for Informed Consent, Council for International Organizations of Medical Sciences (CIOMS)

- Discuss the study objective and the reason why the individual is asked to participate
- Assure that participation is voluntary
- Explain that a study participant may withdraw from the study at any time
- Explain the objective of the study in greater detail
- Describe the study design in a way that the participant can understand it
- Discuss the length of time necessary for study participation
- Discuss any compensation provided to participants
- Describe how participants can learn about the study results
- Explain that personal information is confidential, with safeguards to prevent access to information on individuals
- Confirm that an ethics committee has approved the study
- Give information about possible risks
- Discuss the potential benefits for the individual and the community
- Discuss the possibility of access to treatment after the conclusion of the clinical trial
- Present alternative treatment or medication options to the study material
- Explain any possible future use of information or samples obtained in this study
- Explain the role differences between a personal physician and a physician conducting research
- Describe the medical treatment to be provided during the study
- Explain the measures to be taken if the participant suffers any adverse effects as a result of study participation
- Explain the compensation to be offered to the participant if he or she suffers an adverse event attributable to his/her participation in the study

Source: Adapted from Macrae (2007).

benefits the population or community in which it has been studied.[2] Guideline 11 states that the use of placebo is justified only in the following circumstances: (1) when an effective intervention does not exist; (2) when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; and (3) when it is necessary to establish

[2] Levine's argument justifies the use of the best treatment for control groups that is available in developing countries. According to Levine, comparing new treatments with the best available in industrialized countries would not help to answer the questions of poorer countries (Klimovsky et al. 24).

the efficacy of a treatment and the placebo would not add any risk of serious or irreversible harm to the study participants (Emanuel et al. 2003:27). Guideline 12 requires the risks and the benefits of the study to be equitably distributed among the community and at the global level (Fischer 2006).

Guidelines 13–17 discuss the participation of vulnerable groups and establish that these populations may participate only under certain circumstances. These circumstances include the participants' benefiting from the results of the studies, and the studies should be relevant only to people with their own medical conditions; therefore the studies can only be conducted in these population groups. Guideline 18 addresses information confidentiality; 19 establishes the need to offer compensation in case of adverse effects, and the final two guidelines strengthen the quality of the ethical review in low- and middle-income countries and place the responsibility for complying with the guidelines on the sponsors and the host countries.

2.6 Good Clinical Practice Guidelines

Until recently, the regulatory agencies of the different industrialized countries used a variety of processes to determine if a product should be marketed within their jurisdiction. In 1990, the European Federation of Pharmaceutical Industries and Associations (EFPIA) convened a meeting in Brussels to discuss the possible collaboration of the USA, Japan and Europe to develop joint standards for the approval of medications. The regulatory agencies agreed, and established the International Conference for the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), with an office in Geneva, Switzerland.

The ICH published several documents related to the evaluation of the safety, quality, and efficacy of medications, among them one, which addressed clinical trials: The Guide to Good Clinical Practices (GCP), published in 1996 (Mercosur 2012; Williams 2005). During the same year, Mercosur[3] published resolution number 126/96, which is a technical document on how to verify compliance with good clinical practices. This document offers guidance to Mercosur member countries, which decide how to incorporate it in their legislations. Compliance with good clinical practices has also been discussed at the regional level. The regulatory agencies, under the leadership of the Pan American Health Organization, established the Pan American Network for Drug Regulatory Harmonization (PANDRH) and one of its working groups revolves around issues of Good Clinical Practices. In March 2005, during the IV Pan American Conference on Drug Regulatory Harmonization, the document Good Clinical Practices: Document of the Americas was officially adopted (Red PARF 2005).

On October 27, 2008, the FDA announced that it was no longer necessary for clinical trials conducted outside the United States to comply with the Declaration of

[3] Mercosur or the Southern Common Market is an economic and political agreement between Argentina, Brasil, Paraguay, Uruguay and Venezuela that was founded in 1991.

Helsinki, that compliance with the GCP would be sufficient (Department of Health and Human Services 2008). According to the GCP, vulnerable patients are those whose willingness to participate may be affected by the perception of the benefits to be obtained as a result of participation, or by the threat of reprisals from their superiors, which may include the following groups of people: students in the health professions, employees in the health sector, members of the military, prisoners, people with chronic or terminal illnesses, residents of homes for the aged, people of low economic resources, ethnic minorities, people needing emergency care, infants and children, and those who cannot give informed consent (Fischer 2006).

According to the FDA, the decision to eliminate the need to comply with the Declaration of Helsinki and to adhere to GCP was due to a need to assure the quality of the information received from low- and middle-income countries, to avoid the confusion caused by the frequent revisions to the Declaration of Helsinki, and to the concern that future revisions may conflict with USA laws and regulations. This justification does not explain why the change affected only studies carried out in low- and middle-income countries, especially since most of these countries have adopted laws and regulations which include the principles of the Declaration of Helsinki. In the opinion of critics, the FDA action is consistent with its interest in conducting placebo-controlled studies in low- and middle-income countries. It seems that this was an independent decision in isolation from the other authors of GCP, and is curious because the GCP document states that clinical trials must be in accordance with the ethical criteria presented in the Declaration of Helsinki.

Kimmelman et al. (2009) compared the GCP with the Declaration of Helsinki and voiced concern because the GCP had neither the breadth nor the depth of the Declaration, and could leave participants in biomedical research unprotected. The major objective of the GCP is to harmonize the registration of medications. It is not a guide of ethical principles for clinical trial sponsors and researchers. Box 2.3 presents clauses of the Declaration of Helsinki, which are not included in GCP. Another problem is that the GCP was developed only by the regulatory agencies and representatives of the pharmaceutical industry in the USA, Europe, and Japan, while the Declaration of Helsinki is endorsed by the WMA, which at that time represented the medical associations of 85 countries from all around the world.

Box 2.3: The Declaration of Helsinki *vs.* Good Clinical Practice (ICH GCP[4])

In a comparison between the Declaration of Helsinki, 2008, and Good Clinical Practice (GCP), it was found that the following items are not included in the GCP:

- Requirement for researchers to give information about study financing, sponsors, and conflicts of interest to ethics committee members and to the study participants

(continued)

[4] ICH GCP: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Good Clinical Practice.

Box 2.3: (continued)

- Publication of the study design (for example, through public records)
- Assurance that the study objectives are relevant for the study population
- Limitations on the use of placebo
- Assurance that there will be access to procedures or therapies after the conclusion of the clinical trial
- Accurate reports of results, with negative results available to the public

Source: Kimmelman et al. (2009).

2.7 The Universal Declaration on Bioethics and Human Rights (UNESCO)

The Universal Declaration on Bioethics and Human Rights is the first bioethics document ranked as a non-binding international agreement, and was approved by the 191 countries participating in the UNESCO 33rd. session of the General Conference, on October 2005. It is a succinct document of 28 Articles covering many topics while omitting detailed definitions or clarifications. It was prepared by an intergovernmental commission, and to some extent reflects what is feasible from a political point of view. Andorno (2007) says that the status of a non-binding agreement enabled many countries to sign the document since this type of document carries significant moral and political rather than legal weight. Several authors agree that the most important value of this document is that is has been supported by 191 governments (Andorno 2009; Gunson 2009).

Andorno (2002, 2007, 2009) suggests that from the point of view of bioethics, an agreement on basic values is the foundation for future laws that will provide a structure for implementation. From his perspective, respect for human dignity is closely tied to the enjoyment of human rights. Others have criticized the use of a human rights framework because of its ideological base, which does not have universal acceptance and is rarely used by bioethicists (Landman and Schüklenk 2005). Faunce and Nasu (2009) agree with Andorno that the principles underlying the bioethics and human rights frameworks are not irreconcilable, although bioethics is not a set of rules, but rather a gathering of ideas, debates, and ways of thinking, while "rights" implies systems to make sure certain principles are met. These authors continue by saying that in order to reconcile both perspectives, documents need to clearly explain the intersection between bioethics and international law, and must include more detail than in the UNESCO Declaration. Gunson (2009) thinks that the most prominent values in the UNESCO Declaration are human dignity, human rights, and solidarity, although "solidarity" is not defined, but rather is implied. Box 2.4 shows that a high proportion of the Articles in this Declaration include clauses reflecting the need to respect and the wish to understand different perspectives, which, for Gunson, is a form of solidarity and respect for human dignity.

Box 2.4: Summary of the Universal Declaration on Bioethics and Human Rights

- Respect for human dignity and human rights (section II, article 3.1)
- Priority to individual interests and well-being over the interests of science and society (section II, article 3.2)
- Beneficence, not maleficence (section II, article 4)
- Autonomy (section II, article 5)
- Informed consent (section II, article 6)
- Protection of persons who cannot give informed consent (section II, article 7)
- Special attention to vulnerable people (section II, article 8)
- Privacy and confidentiality (section II, article 9)
- Equality, justice, and equity (section II, article 10)
- No discrimination or stigmatization (section II, article 11)
- Respect for cultural diversity and pluralism (section II, article 12)
- Solidarity and cooperation (section II, article 13)
- Access to health services and to essential medications (section II, article 14)
- Sharing benefits (section II, article 15)
- Protection of future generations (section II, article 16)
- Protection of the environment, the biosphere, and biodiversity (section II, article 17)
- The need for professionalism, honesty, integrity, and transparency in decision-making related to bioethical issues (section III, article 18)
- The need for ethics committees to be independent, multidisciplinary, and pluralist (section III, article 19)
- Appropriate use of measurement systems and risk management in the biomedical area (section III, article 20)
- The need for justice in transnational research (section III, article 21)

Source: Modified by the authors from Adorno (2007), p 151.

The UNESCO Declaration has been criticized many times, both for the process of its development and for its content. UNESCO has been criticized also for impinging upon the territory of another United Nations agency, The World Health Organization, which could have undertaken this effort (Landman and Schüklenk 2005; Williams 2005; Trotter 2009). In reply to the last criticism, Andorno (2007) said that it is not unusual to have some overlap between the different United Nation's agencies. UNESCO has been working with bioethics issues since 1993, when it established the International Bioethics Committee (IBC) with 36 members appointed by the UNESCO Director General. In 1998, the Intergovernmental Bioethics Committee (IGBC) was added with representatives from 36 member states elected by the UNESCO General Assembly; IGBC's role was to advise the IBC and review documents before publication, although IBC is not obligated to

incorporate the IGBC suggestions (Snead 2009). UNESCO's work has produced two Declarations and 14 reports on bioethical topics. WHO focuses more on technical matters, using its scarce resources to respond to international health challenges, but it lacks experience in developing regulations and in discussing philosophy and bioethics from a multidisciplinary perspective.

Development of the UNESCO Declaration began in 2001 when the Director General asked the International Bioethics Committee (IBC) to prepare a report on bioethical issues, which, in 2003, became the basis for a larger project. The IBC was asked to develop a document that would set a worldwide standard for bioethics, based on human dignity, rights and freedoms in a multicultural context.

In January, 2004, the IBC sent questionnaires to 190 countries, receiving only 67 replies (including 31 from North America and Europe, 11 from Africa, and 6 from Latin America). The questionnaires were criticized for not providing a context and for being too superficial (Snead 2009), but the responses resulted in a meeting to decide the process for the preparation of a draft document. Representatives from many international agencies participated, including the World Health Organization, NGOs, and national ethics commissions. In April, 2004, at the end of the meeting, a committee was formed to develop the Declaration. The committee was given a tight work schedule, with seven meetings prior to the first draft of the document due in January, 2005.

The IBC issued the first outline of the proposed document in June, 2004, and shared it with the Intergovernmental Bioethics Committee (IGBC). IGBC members, especially Brazil, fiercely criticized the document for not being sufficiently ambitious and for not including a section on piracy of traditional medicine and the pharmaceutical knowledge of indigenous people. Other IGBC members (USA, Canada and Germany) criticized the binding character proposed for the Declaration. Between July, 2004, and January, 2005, the IBC met four times and asked for more input from the different countries, but received only 27 responses. The IBC and the IGBC met from January 24–28, 2005, to discuss the fourth draft. The IGBC members expressed similar objections to those of the previous June, and found important discrepancies in some subjects; for example, Holland had wanted to eliminate explicit phrases such as "respect for human life" which could be used against stem cell research or abortions, and the USA objected to phrases such as "access to health care services, including sexual and reproductive health", because of their possible interpretation as a defense of abortion rights. Two weeks after the meeting, the IBC issued the final draft, which ignored most of the suggestions of the IGBC (Snead 2009).

Two months later, negotiations began with the country representatives, who considered the draft to be inadequate and in need of important modifications. There were criticisms about the secrecy of the IBC, the questionnaire that had been distributed, and the composition of the IBC itself – for not having sufficient regional diversity, and for having too many human rights lawyers and too few bioethics experts. National differences surfaced during these discussions. The low- and middle-income countries, led by Brazil, asked to include issues of biopiracy, access to quality health services and essential medications, and protection of the biosphere. Germany, Japan, Canada, and the United States objected to the binding nature of the

Declaration, the breadth of the issues (which included many social problems), and threats to intellectual property rights. Other countries (United Kingdom, South Korea, Japan, and Holland) wanted to eliminate everything that could impede research with embryos and even proposed the use of the term person rather than human being, while the Vatican, United States, and Costa Rica insisted on respect for human dignity and the right to life. France, for its part, wanted the Declaration to be binding, and to be the first of a series of documents on bioethical issues.

In subsequent meetings, all references to "binding" clauses and virtually everything that had been written by the IBC were eliminated, and the differences between the viewpoints of high and low- and middle-income countries persisted. The United States shared with low- and middle-income countries – especially in Africa and Latin America – an interest in upholding respect for life and human dignity, while disagreeing about including social, political, and economic issues, such as an emphasis on illiteracy and a right to medications, within the concept of bioethics. The different positions were well defined, and appeared irreconcilable until the United States offered the possibility of including low- and middle-income country concerns in the language of the World Health Organization, without mentioning "bioethics", and changing the reference to sexual and reproductive health to "access to quality health services and essential medications, especially for the health of women and children." With this suggestion, the tone of the negotiations changed, and the Universal Declaration of Bioethics and Human Rights was adopted by acclamation at the UNESCO 33rd. General Conference, October 19, 2005 (Snead 2009).

While some defended the Declaration (Andorno 2007, 2009; Macklin 2005), others criticized it for being too vague and abstract (Faunce and Nasu 2009; Snead 2009; Trotter 2009), having internal contradictions (Selgelid 2005; Williams 2005), repeating what was already included in other documents (Macklin 2005; Bennett and Murray 2009), and for not having credibility among bioethicists (Williams 2005). Benatar (2005) pointed out that Declarations approved by consensus generally were vague and minimal, that is, they could be interpreted in many ways and ignored points where there was disagreement. Many felt it would have been preferable to utilize UNESCO's resources to study the principles on which to base a universal declaration of bioethics, take the necessary time to consult with member countries, reflect seriously on the information gathered, and improve implementation possibilities (Macpherson 2007). Others said that cultural differences had received too little attention, and that there had not been sufficient emphasis on the great inequality of access to power and the resources available to different countries, with the need to reduce these differences before the Declaration could be implemented (Rawlison and Dochin 2005). While recognizing that the document contains theoretical inconsistencies and practical limitations, Asai and Oe (2005) and Häyry and Takala (2005) think that the Declaration is useful because it promotes taking into account ethical ideas when discussing issues concerning human beings. It is certain that the Declaration has been the topic of much discussion between bioethicists and promoters of human rights.

2.8 The Declaration of Buenos Aires

The Declaration of Buenos Aires was approved during the General Assembly of the First Latin-American Workshop on Ethics and Clinical Trials, attended by 22 professionals from five countries (Argentina, Brazil, Costa Rica, Mexico, and Peru) held in Buenos Aires, Argentina, on May 13–15, 2008. One objective of the Workshop was to develop a research agenda, which would produce useful information to put pressure on, and eliminate ethical violations in clinical research conducted in Latin America. Workshop participants included social scientists, clinicians, community organizations, and bioethics specialists. A 20-point Declaration emerged from the workshop discussions, with the wording of each item based on the knowledge and observations of the workshop participants on how clinical trials are being implemented in Latin America. The Declaration of Buenos Aires is not a Code of Ethics, but a preliminary and incomplete assembly of ideas, to bring the ethical violations routinely occurring in Latin America to the attention of clinical trials sponsors, researchers, governmental authorities and the Courts. It is supported by 17 Latin American institutions (Ugalde and Homedes 2009).

2.9 Discussion

Of all the codes and/or declarations of ethics, not one is perfect. Several contain internal contraindications, and a comparison between the different documents reveals even more (Lie et al. 2004; Fischer 2006; Goodyear et al. 2007; Rid and Schmidt 2010; Gunson 2009). All have been compiled in response to ethical violations taking place during research with human subjects up to the present day. Some are very general, and can be interpreted in many ways; the most specific cannot be adopted by consensus, because they represent the opinions of the groups which were able to dominate the discussions at that time, as has occurred with the recent versions of the Declaration of Helsinki (Benatar 2005; Rid and Schmidt 2010).

Ethical problems during clinical trials are present in all parts of the world,[5] but tend to be greater in low- and middle-income countries where the regulatory agencies are weaker, where there is less ability to conduct a scientific-ethical evaluation of research projects, where there are fewer opportunities to carry out research independently from pharmaceutical industry financing, and where there are fewer groups able to monitor the implementation of clinical trials. The concerns and disagreements generated around the Declaration of Helsinki (1996 and 2000) led to the development of standards to govern clinical trials in low- and middle-income countries by the pharmaceutical industry (Bennett and Murray 2009), bioethicists (Benatar and Singer

[5] *The American Journal of Bioethics* published a series of articles on the weaknesses of the United States system in November, 2008 (Vol. 8, No. 11). Also Burris and Moss (2006), and Federman et al. (2002).

2000; Hutton 2000; Shapiro and Meslin 2001; Benatar 2002; David 2002; Participants 2002; Emanuel et al. 2004; Hyder et al. 2004; Wendler et al. 2004; Skene 2007), and various countries themselves. The report by the National Bioethics Advisory Commission (USA) (2001), the report by Nuffield Council on Bioethics (United Kingdom) (2002), and the 2003 report by the European Group on Ethics and Science and New Technologies (European Council and European Parliament 2001) brought into force by the Member states in 2004 offer their opinions on the ethical aspects of clinical research in low- and middle-income countries. In 2004, the Nuffield Council on Bioethics and the Medical Research Council of South Africa organized a conference, which produced another discussion document (Nuffield Council of Bioethics 2005). Not all these initiatives have been well received (see below).

When talking about ethical guidelines to govern clinical research in low- and middle-income countries, various issues should be part of the discussion, including: (1) imperialism, and moral universalism or relativism; (2) standard treatment in low- and middle-income countries and the concept of vulnerability; (3) risk-benefit balance; and (4) the ability to appropriately conduct clinical trials and ethical and scientific reviews.

2.9.1 Imperialism, and Moral Universalism or Relativism

Are the ethical principles, which govern research with humans the same everywhere in the world, or should they be adapted to the conditions in the country where the research takes place? If we look for the answer to this question in the ethical codes, they all clearly put the welfare of the individual before any scientific advances that may result from the study. From this, we can deduce that all human beings have the same rights, and that nobody should be exposed to risks for the benefit of science. However, when ethicists have to embed these principles in the specific reality of each project, the answer is not so clear. Some say that ethical principles are absolute, and therefore universal, although perhaps the way respect for those principles is expressed may vary according to local culture (Angell 1988; Shapiro and Meslin 2001; Kopelman 2005). For example, in many Latin American contexts, respecting the autonomy of the patient may require the involvement of his/her nuclear family when obtaining informed consent, especially if the patient is unaware of the diagnosis, which, for different reasons, is common when faced with cancer or another terminal illness. Love and Fost (1997) give a similar example when obtaining consent from mothers with breast cancer in Vietnam. At the other extreme are those who consider that ethical principles depend on the environment (Christakis et al. 1991). Their viewpoint is that studies with placebo control in low- and middle-income countries are justified, because none of the study participants would receive treatment if they were not enrolled in the clinical trial.

Another contemporary viewpoint is that northern countries, especially the USA, should not try to impose their ethical values on the rest of the world (Macklin 2001; Tealdi 2006; Garrafa and Lorenzo 2008). This view has been strengthened during

the last decade as a result of the controversy surrounding the revisions to the Declaration of Helsinki regarding the use of placebos and the need to provide access to the most effective treatment, at least to the study participants, and possibly (CIOMS and the Nuffield Council on Bioethics) to the whole community (Wolinsky 2006). The conflicts surrounding the Declaration of Helsinki have been seen as breaking the universal character of ethics in the declarations, codes, and ethical standards written before 1990. Obviously, when the FDA announced that studies conducted in other countries had to comply only with Good Clinical Practice, the debate became more antagonistic (Kimmelman et al. 2009).

Latin American bioethicists (Tealdi 2006; Garrafa and Lorenzo 2008) defend the need to develop a bioethics framework responsive to Latin American values, with an emphasis on increasing solidarity to decrease social inequity, one of the most serious problems of the region. Following the same line of thought, these authors say that the provision of courses in research bioethics by the Fogarty 6 International Center (NIH), USA, in response to a 2001 report from the National Bioethics Advisory Committee (2001) is one way to gain influence among Latin American ethicists, a form of moral imperialism which is not imposed by force, but rather by changing the culture.

Macklin (2001) recognized the frequent limitations of ethics committees in low- and middle-income countries, but also questioned the supposed superiority of the United States to dictate the application of ethical criteria in less developed nations. Approval of clinical trials through an ethics committee based in the USA – or another part of the world – does not guarantee that the clinical trial would be ethical. As a consultant to the UNAIDS program, she revised several protocols which had been approved by ethics committees in the USA for studies to be conducted in low- and middle-income countries, and verified that some ethics committees were not aware of the psychological risks of clinical trials, ignored issues of confidentiality, and/or approved informed consent materials with major shortcomings.

2.9.2 Standard Treatment in Low- and Middle-Income Countries, and the Concept of Vulnerability

In the world population, 13 % consume 87 % of medications, which, leads us to safely say that most residents of low- and middle-income countries lack access to needed medicines. Several ethicists have no objection to placebo controlled studies in these countries, because patients have no access to treatment anyway and the trials offer the possibility to advance science (Levine 1998, 1999). Others (Lurie and Wolfe 1997) argue that lack of access is an economic issue, which cannot justify studies in these populations that would not be permitted in industrialized countries. Some think that people who have limited access to medications qualify as vulnerable because participation in a study may be their only opportunity to receive treatment (see Chap. 3). It is at least probable that this population, with probably low levels of education and income, has more difficulty in understanding

that they are participating in a study, and will assume risks without any guarantee of therapeutic benefit. If the person offering the possibility of participating in a clinical trial is the patient's public sector physician, patient autonomy is further limited. Low income residents in Latin America respect physicians and accept medical recommendations without question. Consent to participate may be given because people feel pressured and fear reprisals, such as problems with access to future care. In these circumstances it is important to do whatever possible to respect the autonomy of patients (and/or their families or legal representatives), and to ensure that potential study participants understand what the study will, and will not, accomplish, together with its related risks and benefits.

Other ethicists express a distinct opinion, saying that the treatment offered to study participants in low- and middle-income countries does not always have to be the best available worldwide, because the provision of treatment not normally available could delay the advancement of therapeutics in the countries where the study takes place (London 2000; Koski and Nightingale 2001; Killen et al. 2002; Zumla and Costello 2002; Wendler et al. 2004). Lie et al. (2004) studied the various ethical guidelines for low- and middle-income countries, and concluded that they all allow the implementation of clinical trials in low- and middle-income countries that do not offer participants in the control group the best available treatment in the world for the pathology studied. Although each document had a slightly different emphasis, all used basically the same criteria to justify the use of a lesser treatment than that available on an international level: (1) there is a valid scientific reason to offer that particular treatment to the control group; (2) the clinical trial must provide sufficient benefits to the population involved in the study, and (3) there must be an acceptable risk/benefit balance for each one of the study participants (see Table 2.1). According to this perspective, all these documents, which with the exceptions of CIOMS (2002) and UNAIDS (2000) for the most part had been written by various groups of experts in industrialized countries during the decade between 2000 and 2009, did not include as a moral absolute the provision of the best internationally available treatment for the control group.

2.9.3 The Balance of Risks and Benefits

All ethical guidelines say that no treatment or intervention can be withheld from clinical trial participants who can benefit from them and they would receive if they were not participating in biomedical research (Lie et al. 2004). Controversial issues are: (1) whether clinical trials conducted in low- and middle-income countries should respond to the health priorities of the country; and (2) what are the "reasonable" benefits to be provided to clinical trial participants and their communities if the study intervention is shown to be effective, and at what price and for how long should treatment be provided (Fair benefits 2002).

Some think that clinical trials could take place in low- and middle-income countries whenever some residents are affected by the disease studied, even if it

Table 2.1 Ethical Guidelines for Human Research in Low- and middle-income Countries and Acceptable Therapies for the Control Group

Organization	Scientific validity	Social benefits for the country	Risk//benefit ratio for the volunteer
UNAIDS	Acceptable scientific protocol	Plans to ensure availability must be defined during the initial phases of vaccine development	As a minimum, there must be guarantees of the best health service available in the country
National Bioethics Advisory Committee (2001)	There must be justification of the choice of study design	Explanation of how an effective study medication will be made available to the residents of the country where the study took place	The ethics committee must assess the risk to participants
CIOMS (2002)	The study would not yield reliable scientific information if the available treatment was to be provided	The clinical trial should relate to the needs of the participating population, and assure "reasonable" access to the treatment which has been shown to be effective	There is a balance between risks and potential benefits, with a minimization of risks for participants in clinical trials
European Group on Ethics etc. (2001)	The method meets the objectives of the study, and there is no other alternative methodology	One possible justification is to simplify or reduce the cost of treatment in the country where research is conducted	Special attention must be paid to the risk/benefit balance at the individual level
Nuffield Council (2002, 2005)	The research design must meet the research objective	Consideration must be given to the sustainability and affordability of the treatment selected	As a minimum, the selected treatment should be available at the national level

Source: Lie et al. (2004)

is not a government priority, and they say that if the study complies with both ethical principles and the regulations of the host country, the researchers have no further obligation to the study participants (Macklin 2001). Others feel that if there is no intent to improve access to a proven treatment for study participants and their communities, there is a violation of the principle of distributive justice, and the study should be rejected (Page 2000; Crouch and Arras 1998; Glantz et al. 1998). Benatar and Singer (2000) go to the root of the problem, asserting that the need to eliminate social injustice and inequality between nations requires clinical trials to benefit the places where they are carried out, and that ways must be found to turn new discoveries into accessible therapies for the study community.

2.9.4 *The Ability to Conduct Clinical Trials and Ethical Reviews*

There is some concern about the ability of low- and middle-income countries to conduct scientific and ethical evaluations of clinical trials. There have been suggestions that research should not take place in countries that do not have the capacity to protect their residents, but other experts think that this is an extreme position and have suggested ways to overcome the problem. The CIOMS document (2002) and the article by Hyder et al. (2004) are interesting because they recognize the weaknesses of low- and middle-income countries and ask for protocols to be approved also by an ethics committee in the country of the sponsor. The National Bioethics Advisory Committee (2001) and the Nuffield (2002) reports support the exportation of the ethical review model to low- and middle-income countries and promote the development of resources in countries where research is conducted. Some authors see this as moral imperialism (Tealdi 2006; Garrafa and Lorenzo 2008; Lescano et al. 2008; McIntosh et al. 2008). One initiative has been to establish agreements between universities in high income countries and those in low- and middle-income countries to improve the skills needed to conduct clinical trials (Sidle et al. 2006).

From our perspective, and as can be seen throughout this book, there is little doubt that the systems for ethical and scientific review of studies with human subjects must be improved, especially in low- and middle-income countries.

2.10 Conclusion

The improvement of ethical codes governing clinical trials is a constant concern for bioethicists, but, even if the codes achieve perfection, their application is a different matter. In most cases, the problems are basic violations of human rights. Latin America needs to establish monitoring systems for each stage of clinical trial implementation; the reviews currently conducted by some regulatory agencies during the process of deciding whether or not to market a product are not enough.

But however sophisticated the monitoring systems may be, real change will occur only when the culture of those who sponsor and conduct research with human subjects will have internalized ethical and scientific principles, and will express increasing respect for both the research process and the rights of the study participants. Governments, universities, and professional associations could take the lead in this by developing legislation and systems supportive of the principles of the desired culture.

Finally, if clinical trials in low- and middle-income countries continue, ways must be found so that all residents in these countries can access necessary medications. Without this provision, we condone the violation of the principle of justice, exploiting the vulnerability of those who cannot receive treatment unless they participate in clinical trials.

Appendix A: A Review and Critique of International Ethical Principles: Annexes

THE NÜREMBURG CODE. (Nüremberg International Tribunal) 1947

Reprinted from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181–182*. Washington, DC: U. S. Government Printing Office, 1949. (http://ohsr.od.nih.gov/guidelines/nuremberg.html)

Directives for Human Experimentation

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility, which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. Introduction

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. Principles for All Medical Research

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study

when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

http://www.wma.net/en/30publications/10policies/b3/17c.pdf

Universal Declaration on Bioethics and Human Rights

Adopted by acclamation on 19 October 2005 by the 33rd session of the General Conference of UNESCO.

The General Conference

Conscious of the unique capacity of human beings to reflect upon their own existence and on their environment, to perceive injustice, to avoid danger, to assume responsibility, to seek cooperation and to exhibit the moral sense that gives expression to ethical principles,

Reflecting on the rapid developments in science and technology, which increasingly affect our understanding of life and life itself, resulting in a strong demand for a global response to the ethical implications of such developments,

Recognizing that ethical issues raised by the rapid advances in science and their technological applications should be examined with due respect to the dignity of the human person and universal respect for, and observance of, human rights and fundamental freedoms,

Resolving that it is necessary and timely for the international community to state universal principles that will provide a foundation for humanity's response to the ever-increasing dilemmas and controversies that science and technology present for humankind and for the environment,

Recalling the Universal Declaration of Human Rights of 10 December 1948, the Universal Declaration on the Human Genome and Human Rights adopted by the General Conference of UNESCO on 11 November 1997 and the International Declaration on Human Genetic Data adopted by the General Conference of UNESCO on 16 October 2003,

Noting the United Nations International Covenant on Economic, Social and Cultural Rights and the International Covenant on Civil and Political Rights of 16 December 1966, the United Nations International Convention on the Elimination of All Forms of Racial Discrimination of 21 December 1965, the United Nations Convention on the Elimination of All Forms of Discrimination against Women of 18 December 1979, the United Nations Convention on the Rights of the Child of 20 November 1989, the United Nations Convention on Biological Diversity of 5 June 1992, the Standard Rules on the Equalization of Opportunities for Persons with Disabilities adopted by the General Assembly of the United Nations in 1993, the UNESCO Recommendation on the Status of Scientific Researchers of 20 November 1974, the UNESCO Declaration on Race and Racial Prejudice of 27 November 1978, the UNESCO Declaration on the Responsibilities of the Present Generations Towards Future Generations of 12 November 1997, the UNESCO Universal Declaration on Cultural Diversity of 2 November 2001, the ILO Convention 169 concerning Indigenous and Tribal Peoples in Independent Countries of 27 June 1989, the International Treaty on Plant Genetic Resources for Food and Agriculture which was adopted by the FAO Conference on 3 November 2001 and entered into force on 29 June 2004, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) annexed to the Marrakech Agreement establishing the World Trade Organization, which entered into force on 1 January 1995, the Doha Declaration on the TRIPS Agreement and Public Health of 14 November 2001 and other relevant international instruments adopted by the United Nations and the specialized agencies of the United Nations system, in particular the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO),

Also noting international and regional instruments in the field of bioethics, including the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine of the Council of Europe, which was adopted in 1997 and entered into force in 1999, together with its Additional Protocols, as well as national legislation and regulations in the field of bioethics and the international and regional codes of conduct and guidelines and other texts in the field of bioethics, such as the Declaration of Helsinki of the World Medical Association on Ethical Principles for Medical Research Involving Human Subjects, adopted in 1964 and amended in 1975, 1983, 1989, 1996 and 2000 and the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences, adopted in 1982 and amended in 1993 and 2002,

Recognizing that this Declaration is to be understood in a manner consistent with domestic and international law in conformity with human rights law,

Recalling the Constitution of UNESCO adopted on 16 November 1945,

Considering UNESCO's role in identifying universal principles based on shared ethical values to guide scientific and technological development and social transformation in order to identify emerging challenges in science

and technology taking into account the responsibility of the present generations towards future generations, and that questions of bioethics, which necessarily have an international dimension, should be treated as a whole, drawing on the principles already stated in the Universal Declaration on the Human Genome and Human Rights and the International Declaration on Human Genetic Data and taking account not only of the current scientific context but also of future developments,

Aware that human beings are an integral part of the biosphere, with an important role in protecting one another and other forms of life, in particular animals,

Recognizing that, based on the freedom of science and research, scientific and technological developments have been, and can be, of great benefit to humankind in increasing, *inter alia*, life expectancy and improving the quality of life, and *emphasizing* that such developments should always seek to promote the welfare of individuals, families, groups or communities and humankind as a whole in the recognition of the dignity of the human person and universal respect for, and observance of, human rights and fundamental freedoms,

Recognizing that health does not depend solely on scientific and technological research developments but also on psychosocial and cultural factors,

Also recognizing that decisions regarding ethical issues in medicine, life sciences and associated technologies may have an impact on individuals, families, groups or communities and humankind as a whole,

Bearing in mind that cultural diversity, as a source of exchange, innovation and creativity, is necessary to humankind and, in this sense, is the common heritage of humanity, but *emphasizing* that it may not be invoked at the expense of human rights and fundamental freedoms,

Also bearing in mind that a person's identity includes biological, psychological, social, cultural and spiritual dimensions,

Recognizing that unethical scientific and technological conduct has had a particular impact on indigenous and local communities,

Convinced that moral sensitivity and ethical reflection should be an integral part of the process of scientific and technological developments and that bioethics should play a predominant role in the choices that need to be made concerning issues arising from such developments,

Considering the desirability of developing new approaches to social responsibility to ensure that progress in science and technology contributes to justice, equity and to the interest of humanity,

Recognizing that an important way to evaluate social realities and achieve equity is to pay attention to the position of women,

Stressing the need to reinforce international cooperation in the field of bioethics, taking into account, in particular, the special needs of developing countries, indigenous communities and vulnerable populations,

Considering that all human beings, without distinction, should benefit from the same high ethical standards in medicine and life science research,

Proclaims the principles that follow and *adopts* the present Declaration.

General Provisions

Article 1 – Scope

1. This Declaration addresses ethical issues related to medicine, life sciences and associated technologies as applied to human beings, taking into account their social, legal and environmental dimensions.
2. This Declaration is addressed to States. As appropriate and relevant, it also provides guidance to decisions or practices of individuals, groups, communities, institutions and corporations, public and private.

Article 2 – Aims
The aims of this Declaration are:

(a) to provide a universal framework of principles and procedures to guide States in the formulation of their legislation, policies or other instruments in the field of bioethics;
(b) to guide the actions of individuals, groups, communities, institutions and corporations, public and private;
(c) to promote respect for human dignity and protect human rights, by ensuring respect for the life of human beings, and fundamental freedoms, consistent with international human rights law;
(d) to recognize the importance of freedom of scientific research and the benefits derived from scientific and technological developments, while stressing the need for such research and developments to occur within the framework of ethical principles set out in this Declaration and to respect human dignity, human rights and fundamental freedoms;
(e) to foster multidisciplinary and pluralistic dialogue about bioethical issues between all stakeholders and within society as a whole;
(f) to promote equitable access to medical, scientific and technological developments as well as the greatest possible flow and the rapid sharing of knowledge concerning those developments and the sharing of benefits, with particular attention to the needs of developing countries;
(g) to safeguard and promote the interests of the present and future generations;
(h) to underline the importance of biodiversity and its conservation as a common concern of humankind.

Principles

Within the scope of this Declaration, in decisions or practices taken or carried out by those to whom it is addressed, the following principles are to be respected.

Article 3 – human dignity and human rights

1. Human dignity, human rights and fundamental freedoms are to be fully respected.

2. The interests and welfare of the individual should have priority over the sole interest of science or society.

Article 4 – Benefit and harm
In applying and advancing scientific knowledge, medical practice and associated technologies, direct and indirect benefits to patients, research participants and other affected individuals should be maximized and any possible harm to such individuals should be minimized.

Article 5 – Autonomy and individual responsibility
The autonomy of persons to make decisions, while taking responsibility for those decisions and respecting the autonomy of others, is to be respected. For persons who are not capable of exercising autonomy, special measures are to be taken to protect their rights and interests.

Article 6 – Consent

1. Any preventive, diagnostic and therapeutic medical intervention is only to be carried out with the prior, free and informed consent of the person concerned, based on adequate information. The consent should, where appropriate, be express and may be withdrawn by the person concerned at any time and for any reason without disadvantage or prejudice.
2. Scientific research should only be carried out with the prior, free, express and informed consent of the person concerned. The information should be adequate, provided in a comprehensible form and should include modalities for withdrawal of consent. Consent may be withdrawn by the person concerned at any time and for any reason without any disadvantage or prejudice. Exceptions to this principle should be made only in accordance with ethical and legal standards adopted by States, consistent with the principles and provisions set out in this Declaration, in particular in Article 27, and international human rights law.
3. In appropriate cases of research carried out on a group of persons or a community, additional agreement of the legal representatives of the group or community concerned may be sought. In no case should a collective community agreement or the consent of a community leader or other authority substitute for an individual's informed consent.

Article 7 – Persons without the capacity to consent
In accordance with domestic law, special protection is to be given to persons who do not have the capacity to consent:

(a) authorization for research and medical practice should be obtained in accordance with the best interest of the person concerned and in accordance with domestic law. However, the person concerned should be involved to the greatest extent possible in the decision-making process of consent, as well as that of withdrawing consent;

(b) research should only be carried out for his or her direct health benefit, subject to the authorization and the protective conditions prescribed by law, and if there is no research alternative of comparable effectiveness with research participants able to consent. Research which does not have potential direct health benefit should only be undertaken by way of exception, with the utmost restraint, exposing the person only to a minimal risk and minimal burden and if the research is expected to contribute to the health benefit of other persons in the same category, subject to the conditions prescribed by law and compatible with the protection of the individual's human rights. Refusal of such persons to take part in research should be respected.

Article 8 – Respect for human vulnerability and personal integrity
In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected and the personal integrity of such individuals respected.

Article 9 – Privacy and confidentiality
The privacy of the persons concerned and the confidentiality of their personal information should be respected. To the greatest extent possible, such information should not be used or disclosed for purposes other than those for which it was collected or consented to, consistent with international law, in particular international human rights law.

Article 10 – Equality, justice and equity
The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably.

Article 11 – Non-discrimination and non-stigmatization
No individual or group should be discriminated against or stigmatized on any grounds, in violation of human dignity, human rights and fundamental freedoms.

Article 12 – Respect for cultural diversity and pluralism
The importance of cultural diversity and pluralism should be given due regard. However, such considerations are not to be invoked to infringe upon human dignity, human rights and fundamental freedoms, nor upon the principles set out in this Declaration, nor to limit their scope.

Article 13 – Solidarity and cooperation
Solidarity among human beings and international cooperation towards that end are to be encouraged.

Article 14 – Social responsibility and health

1. The promotion of health and social development for their people is a central purpose of governments that all sectors of society share.

2. Taking into account that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition, progress in science and technology should advance:

   (a) access to quality health care and essential medicines, especially for the health of women and children, because health is essential to life itself and must be considered to be a social and human good;
   (b) access to adequate nutrition and water;
   (c) improvement of living conditions and the environment;
   (d) elimination of the marginalization and the exclusion of persons on the basis of any grounds;
   (e) reduction of poverty and illiteracy.

Article 15 – Sharing of benefits

1. Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries. In giving effect to this principle, benefits may take any of the following forms:

   (a) special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research;
   (b) access to quality health care;
   (c) provision of new diagnostic and therapeutic modalities or products stemming from research;
   (d) support for health services;
   (e) access to scientific and technological knowledge;
   (f) capacity-building facilities for research purposes;
   (g) other forms of benefit consistent with the principles set out in this Declaration.

2. Benefits should not constitute improper inducements to participate in research.

Article 16 – Protecting future generations
The impact of life sciences on future generations, including on their genetic constitution, should be given due regard.

Article 17 – Protection of the environment, the biosphere and biodiversity
Due regard is to be given to the interconnection between human beings and other forms of life, to the importance of appropriate access and utilization of biological and genetic resources, to respect for traditional knowledge and to the role of human beings in the protection of the environment, the biosphere and biodiversity.

Application of the Principles

Article 18 – Decision-making and addressing bioethical issues

1. Professionalism, honesty, integrity and transparency in decision-making should be promoted, in particular declarations of all conflicts of interest and appropriate sharing of knowledge. Every endeavour should be made to use the best available scientific knowledge and methodology in addressing and periodically reviewing bioethical issues.
2. Persons and professionals concerned and society as a whole should be engaged in dialogue on a regular basis.
3. Opportunities for informed pluralistic public debate, seeking the expression of all relevant opinions, should be promoted.

Article 19 – Ethics committees

Independent, multidisciplinary and pluralist ethics committees should be established, promoted and supported at the appropriate level in order to:

(a) assess the relevant ethical, legal, scientific and social issues related to research projects involving human beings;
(b) provide advice on ethical problems in clinical settings;
(c) assess scientific and technological developments, formulate recommendations and contribute to the preparation of guidelines on issues within the scope of this Declaration;
(d) foster debate, education and public awareness of, and engagement in, bioethics.

Article 20 – Risk assessment and management

Appropriate assessment and adequate management of risk related to medicine, life sciences and associated technologies should be promoted.

Article 21 – Transnational practices

1. States, public and private institutions, and professionals associated with transnational activities should endeavour to ensure that any activity within the scope of this Declaration, undertaken, funded or otherwise pursued in whole or in part in different States, is consistent with the principles set out in this Declaration.
2. When research is undertaken or otherwise pursued in one or more States (the host State(s)) and funded by a source in another State, such research should be the object of an appropriate level of ethical review in the host State(s) and the State in which the funder is located. This review should be based on ethical and legal standards that are consistent with the principles set out in this Declaration.
3. Transnational health research should be responsive to the needs of host countries, and the importance of research contributing to the alleviation of urgent global health problems should be recognized.

4. When negotiating a research agreement, terms for collaboration and agreement on the benefits of research should be established with equal participation by those party to the negotiation.
5. States should take appropriate measures, both at the national and international levels, to combat bioterrorism and illicit traffic in organs, tissues, samples, genetic resources and genetic related materials.

Promotion of the Declaration

Article 22 – Role of states

1. States should take all appropriate measures, whether of a legislative, administrative or other character, to give effect to the principles set out in this Declaration in accordance with international human rights law. Such measures should be supported by action in the spheres of education, training and public information.
2. States should encourage the establishment of independent, multidisciplinary and pluralist ethics committees, as set out in Article 19.

Article 23 – Bioethics education, training and information

1. In order to promote the principles set out in this Declaration and to achieve a better understanding of the ethical implications of scientific and technological developments, in particular for young people, States should endeavour to foster bioethics education and training at all levels as well as to encourage information and knowledge dissemination programmes about bioethics.
2. States should encourage the participation of international and regional intergovernmental organizations and international, regional and national non-governmental organizations in this endeavour.

Article 24 – International cooperation

1. States should foster international dissemination of scientific information and encourage the free flow and sharing of scientific and technological knowledge.
2. Within the framework of international cooperation, States should promote cultural and scientific cooperation and enter into bilateral and multilateral agreements enabling developing countries to build up their capacity to participate in generating and sharing scientific knowledge, the related know-how and the benefits thereof.
3. States should respect and promote solidarity between and among States, as well as individuals, families, groups and communities, with special regard for those rendered vulnerable by disease or disability or other personal, societal or environmental conditions and those with the most limited resources.

Article 25 – Follow-up action by UNESCO

1. UNESCO shall promote and disseminate the principles set out in this Declaration. In doing so, UNESCO should seek the help and assistance of the

Intergovernmental Bioethics Committee (IGBC) and the International Bioethics Committee (IBC).
2. UNESCO shall reaffirm its commitment to dealing with bioethics and to promoting collaboration between IGBC and IBC.

Final Provisions

Article 26 – Interrelation and complementarity of the principles
This Declaration is to be understood as a whole and the principles are to be understood as complementary and interrelated. Each principle is to be considered in the context of the other principles, as appropriate and relevant in the circumstances.

Article 27 – Limitations on the application of the principles
If the application of the principles of this Declaration is to be limited, it should be by law, including laws in the interests of public safety, for the investigation, detection and prosecution of criminal offences, for the protection of public health or for the protection of the rights and freedoms of others. Any such law needs to be consistent with international human rights law.

Article 28 – Denial of acts contrary to human rights, fundamental freedoms and human dignity
Nothing in this Declaration may be interpreted as implying for any State, group or person any claim to engage in any activity or to perform any act contrary to human rights, fundamental freedoms and human dignity.

http://www.bioethics.gov.cy/Law/cnbc/cnbc.nsf/All/20367BA1ED3D0F34C2257292002AEF74/$file/Universal%20Declaration%20on%20Bioethics%20and%20Human%20Rights_EN.pdf

The Buenos Aires Declaration on Ethics and Clinical Trials

"The Buenos Aires Declaration on Ethics and Clinical Trials" was unanimously approved at the First Latin American Workshop on Ethics and Clinical Trials and endorsed by the Latin American organizations that are listed at the end of the Declaration.

Both the Workshop and the Declaration were a response to the rapidly increasing number of clinical trials that are taking place in the region and to the questions being raised as a result of the many alleged violations of ethics during the approval and implementation of the trials.

The Workshop was organized by the non-profit organization Salud y Fármacos (http://www.boletinfarmacos.org), incorporated both in the USA and Argentina, which also publishes the free-access electronic bulletin Boletín Fármacos. The Dutch Foundation WEMOS, the Health Science Center of the University of Texas and the Pan American Health Organization-Argentine also provided financial assistance for the workshop.

Salud y Fármacos and WEMOS perceive serious ethical flaws in the conditions surrounding clinical trials in Latin America and believe that the international health community should be aware of the situation.

The Declaration

At the General Assembly of the First Latin-American Workshop on Ethics and Clinical Trials (Buenos Aires, May 12 and 13, 2008) participants unanimously approved the following declaration:

1. Clinical trials can only be carried out if the population where the trials take place can benefit from their results.
2. Authorities of countries where clinical trials take place should require studies to strictly adhere to the "Universal Declaration of Bioethics and Human Rights" (UNESCO 2005).
3. All clinical trials that take place in Latin America must be registered with the national drug agency of the country where the trials take place or with the appropriate authority created for this purpose. The key information of the protocols should be made electronically available to the public.
4. In Latin America, protocols originating from outside the region must be translated by regionally-competent, expert translators for presentation to local authorities (the regulatory agencies, ethics committees, etc.) into the language of the country where the clinical trial takes place (Spanish, Portuguese, or French).
5. The informed consent should fulfill the following requirements:
   (a) Informed consent forms originating from outside the region must be translated by regionally-competent, expert translators.
   (b) Persons, totally independent from the clinical trial participants from all social and ethnic strata clearly understand the content of the informed consent form.
   (c) When indigenous populations participate in the trial, the informed consent form should be presented to them in their native language.
6. The ethics committees that approve the implementation of a clinical trial must be active in the supervision and monitoring of all critical steps, including recruiting of participants, data gathering and publication of results. The tasks should be specified in writing at the time the ethics committee approves the trial.
7. National health authorities should create a national registry of approved ethical committees, of research centers that have proven to have the technical competence to carry out clinical trials, and of researchers of known qualifications and honesty.
8. New drugs to be tested in clinical trials should be tested against the best available preventive, diagnostic and therapeutic methods. Placebos can be

used only when no other therapeutic procedure exists, or under exceptional, qualified circumstances, when this method is indispensable.

9. The results and findings of all the clinical trials should be communicated within a reasonable time to those who participated in the trials, and should be made available electronically to the public through the national drug agencies of the countries where the trials took place.
10. We condemn those clinical trials whose main objectives include the promotion of the commercialization of the tested drug.
11. In order to obtain authorization for a clinical trial, the pharmaceutical industry must commit itself to make the product economically accessible to those who need it in the country where the clinical trial took place if the drug tested is useful for the treatment of a disease.
12. It is necessary to initiate as soon as possible multi-centric studies of Contract Research Organizations (CROs) are operating in Latin America. The research should document the financial benefits obtained from the trials, their business history, and any complaints raised against them. Regulatory agencies should publish electronically the results of these studies to allow other countries to know the qualifications of the firms.
13. Following the initiative of the leading professional health journals in United States and the European Union, Latin American medical journals should not publish any results of clinical trials unless their protocols have been electronically posted before the initiation of the trial. Similarly, articles should not be published unless the authors declare possible conflicts of interest.
14. All benefits that clinical trial researchers obtain from trials should be made public. The information must be specific regarding the amount that researchers receive per participant recruited, and per participant that completes the trial. This information should be shared with trial participants as part of the informed consent. Other fringe benefits that the investigator receives from the industry should also be specified.
15. All persons who participate in clinical trials should be insured for potential risks they may suffer during the course of, or as a result of, the trial. The insurance policy should be paid by the pharmaceutical firm, CRO or organization that carries out the trial. The policies should be issued by reputable national or foreign insurance companies, and the damage payment should be equivalent to the amount that a person suffering a similar injury would receive in the country where the pharmaceutical firm responsible for the trial is headquartered.
16. As soon as it is discovered that a person appears as the author of an article on the results of a clinical trial that in fact was written by somebody else paid by a pharmaceutical industry or that his/her participation was minimal, the academic center to which the author is affiliated should start proceedings leading to an adequate sanction. If the author is a member of a CRO, the firm should be sanctioned and not be allowed to carry out additional clinical trials in the country.
17. We believe that clinical trials should be carried out by nonprofit organizations such as universities on their own or in collaboration with the ministry of health. The participation of nonprofit organizations should be promoted.

18. Every effort should be made to insure that those in the lowest income group and other vulnerable groups do not participate in clinical trials, unless they directly benefit from their findings.
19. The goal of a clinical trial is not to create wealth for an enterprise, organization or individual. Clinical trials can only take place to improve or augment the available therapeutic arsenal for the benefit of mankind.
20. There is a need to establish procedures to protect the blood and tissue samples obtained from clinical trial participants in order to preclude future abuses related to patent protection and the for-profit commercialization of derivatives of such samples.

Buenos Aires, May 13, 2008

The Declaration of Buenos Aires was written by the following: Dr. Jose Rubén Alcântara Bofim, Dr Patricia Andreotti, Dr. Corina Bontempo Duca de Freitas, Dr. Martín Cañas, Dr. Hernán Collado, Dr. Elisa Dibarbora, Ms. Susie Dutra, Dr. José Miguel Esquivel, Dr. Duilio Fuentes, Dr. Carmen Lidia Guerrero, Dr Núria Homedes, Dr. Gabriela Minaya, Ms. Susy Olave, Ms. Jimena Orchuela, Dr. Agustin Páez, Dr Analia Perez, Dr. Mario Salinas, Mr. Jacob Sijtsma, Dr. Juan Carlos Tealdi, Dr. Antonio Ugalde, Dra. Edith Valdez, Dra. Emma Verastegui, Dr. Susana Vidal.

The Declaration has been endorsed by the following organizations:

Acción Internacional para la Salud-Coordination Center for Latin America (AIS-LAC)

Roberto López Linares – Coordinator

Acción Internacional para la Salud-Bolivia (AIS-Bolivia)

Óscar Lanza MD – Coordinator

Acción Internacional para la Salud-Nicaragua (AIS-Nicaragua)

Leonel Arguello, MD -President

Asociacion Mexicana para el Uso Racional de los Medicamentos,

A.C. Rogelio Fernández MD – President

Cátedra de Derechos Humanos de la Facultad de Medicina de la Universidad de Buenos Aires

Claudio Capuano MD – Director

Cátedra Unesco de Bioética de la Universidad Nacional de Brasilia

Prof. Volnei Garrafa -Coordinator

Centro de Información de Medicamentos de la Universidad de Colombia (CIMUN)

José, Julián López QF – Coordinator General

Centro Universitario de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata (CUFAR) (Argentina) – Centro Colaborador OPS/OMS

Perla Mordujovich de Buschiazzo MD – Director

Comité de Defensa de los Derechos del Consumidor- Bolivia (CODECO)

Rodrigo Urquieta Arias – Coordinador

Drug Utilization Research Group, Latinoamérica (DURG-LA)

Claudia Vacca QF – President

Fundación Instituto para la Investigación del Medicamento en los Sistemas de Salud, Colombia (IFARMA)

Francisco Rossi MD- Director

Grupo Argentino para el Uso Racional del Medicamento (GAPURMED)

Luis Castiglioni MD – President

International Health Central American Institute Foundation (IHCAI FOUNDATION)

Dr. Mario Tristan, Director-General

Red Latinoamericana de Ética y Medicamentos RELEM (The Latin American Network of Ethics and Medicines)

Núria Homedes MD, DrPH – Coordinator

Red Latinoamericana y del Caribe de Bioética de UNESCO-Redbioética

Volnei Garrafa, DDS, PHD – President of Council of Directors

Salud y Fármacos

Antonio Ugalde, PhD – President, USA
Martín Cañás MD – President, Argentina

Sociedade Brasileira de Vigilancia de Medicamentos (Sobravime)

Jose Rubén Alcántara Bofim MD – President

http://www.saludyfarmacos.org/wp-content/files/Buenos_Aires_Declaration_on_Ethics_and_clinical_Trialsfinal.pdf

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