The 2008 Declaration of Helsinki — First among Equals in Research Ethics?

Annette Rid and Harald Schmidt

Introduction

The World Medical Association's (WMA) Declaration of Helsinki is one of the most important and influential international research ethics documents. Launched in 1964, when ethical guidance for research was scarce, the Declaration comprised eleven basic principles and provisions on clinical research. The document has since evolved to a complex set of principles, norms, and directions for action of varying degrees of specificity, ranging from specific rules to broad aspirational statements. It has been revised six times in an effort to maintain its influence.[1] While all revisions were the result of vigorous debate, the 2000 revision and two subsequent notes of clarification spurred particular controversy surrounding the use of placebo in clinical research and the standard of care and post-trial obligations in research in developing countries.[2] Several institutions opted to cite earlier versions of the Declaration,[3] and the U.S. Food and Drug Administration (FDA) recently removed all reference to the Declaration in its approval requirements for drugs and biological products that are studied outside the United States.[4]

These developments suggest a significant weakening of the Declaration,[5] which is concerning because strong international guidance on the ethics of medical research is sorely needed. However, the recent 2008 revision[6] makes a problematic attempt to strengthen the Declaration. By asserting that "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" (§10), the Declaration seems to position itself as "first among equals" in research ethics and regulation (table 1 summarizes other relevant changes in the 2008 revision of the document). This raises important questions about the Declaration's appropriate normative status. The present paper argues that the new claim of ethical primacy is problematic and makes the Declaration unnecessarily vulnerable to criticism.

The Declaration's New Claim of Universal Ethical Primacy

Part of §10 helpfully clarifies the relationship between ethics and the law. The Declaration rightly emphasizes that legal and regulatory requirements should not contradict ethical principles for the conduct of research, and that researchers' ethical obligations can go beyond what is legally required. For this to be true, however, a given set of ethical principles must be fully justified, and this is what §10 appears to claim for the Declaration. By requiring that no national or international ethical requirements should contradict its principles, the Declaration appears to promulgate a universal baseline of minimal ethical standards that mandates strict adherence from everyone involved in research. However, suggesting this understanding of the Declaration unnecessarily gives rise to significant problems.

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What Is Problematic about the Claim of Ethical Primacy?

Problem 1: Some of the Declaration's Principles Allow of Too Few Exceptions

Many of the Declaration's provisions are very general. This is no fault of the Declaration because guidance documents, unlike legal provisions or regulatory codes, usually omit specifics. However, sometimes there are justified exceptions to general principles. Mandating strict adherence to principles that allow few exceptions can therefore lead to ethically dubious requirements.

For example, the Declaration requires that competent research subjects[7] freely provide informed consent (§24). This general principle is appropriate for the vast majority of research with subjects who have the capacity to consent to study participation (provisions regarding research with subjects who do not have the capacity to consent are set out in §27, §28, and §29). However, some exceptions from consent seem justified even when subjects are competent. The Declaration itself acknowledges an exception in research using identifiable human material or data (§25). But there are further plausible exceptions which the Declaration does not include. For example, it is widely accepted that research involving no more than minimal risk — such as a simple survey of behavioral health risks — does not necessarily require fully informed consent. Further, research involving deception, such as studies investigating the effectiveness of placebo treatment against pain, might be acceptable if the deception is necessary for scientific validity, if the research has important social value and involves no more than minimal risk to subjects, if subjects are debriefed about the study's deceptive nature after its completion, and if subjects are given the opportunity to withdraw their data in the debriefing process. Waivers or modifications of informed consent in these circumstances are recognized by other international guidance.[8] Although appropriate in most research involving competent subjects, the requirements of informed consent as set out in §24 and §25 of the Declaration are, if strictly interpreted, misguided and risk complicating or forestalling valuable research.

The present paper argues that the new claim of ethical primacy is problematic and makes the Declaration unnecessarily vulnerable to criticism.

Problem 2: Some of the Declaration's Principles Are Too Vague

The Declaration aims to provide general ethical guidance. This sets unavoidable limits to the precision and detail of its principles. However, some of the Declaration's provisions are so vague that they fail to provide meaningful directions. In these cases, the Declaration's "ethical minimum" runs the risk of being empty.

For example, the provisions on benefit-sharing and post-trial obligations in international collaborative research are very vague. The Declaration's §33 now states that "patients entered into the study are entitled to (…) share any benefits that result from it, for example, access to interventions identified as beneficial or to other appropriate care or benefits." §14 requires researchers to "describe arrangements for post-study access" in study protocols. However, these provisions leave open what types and what level of benefits subjects are entitled to over a particular time span and, importantly, who is responsible for their provision. Ensuring post-trials access to beneficial interventions, for example, appears to be optional because it is listed only as a *possible*, but not a necessary benefit. However, in a study investigating adherence to antiretroviral treatment in resource-poor settings, is it really optional to ensure continued access to anti-retrovirals after the study is over? §14 requires a statement on post-trial arrangements in the study protocol, but this requirement does not necessarily guarantee continued access for subjects. For instance, if the arrangement is that study medications will be made available for purchase after the trial, then most subjects in resource-poor settings will be unable to continue treatment. While it may not always be feasible to provide post-trial access to treatment, §14/§33 should have provided clearer guidance by stipulating a strong default for sustainable post-trial access arrangements, in particular when the interventions in question have significant impact on subjects' health and/or well-being, and by clarifying the roles and responsibilities of the different actors involved in the process. As they stand, these paragraphs convey no firm requirement for researchers, sponsors, and health officials to ensure post-trial access. It is questionable that such non-committal wording should be accepted as the universal ethical minimum.

Problem 3: Some of the Declaration's Principles Are Internally Inconsistent

The Declaration now notes explicitly that the document "is intended to be read as a whole, and each of its constituent paragraphs should not be applied with-

Table 1

Selected Changes in the 2008 Declaration of Helsinki (DoH)

For better orientation, the changes have been organized according to four major themes. However, there is significant overlap between categories.

Changes related to …	Topic	DoH 2004[1]	DoH 2008
1) Scope and status of DoH	Audience	Physicians and other participants in medical research (§1)	Primarily physicians (§2)
	Authority	Primacy over national ethical, legal or regulatory requirements (§9)	Primacy over national and international ethical, legal or regulatory requirements (§10/15)
2) Access to research and results	Access to research	–	Ensure appropriate access of underrepresented populations (§5)
	Dissemination of research results	–	Publicize research results (§30)
	Information about study outcomes	–	Inform participants about study outcomes (§33)
3) Subject protection	Balance of individual and societal interests	Well-being of individual participant overrides scientific and societal interests (§5)	Well-being of individual participant overrides "all other interests" (§6)
	Vulnerable populations	Special protection for participants who are economically or medically disadvantaged, unable to consent, consent under duress, will not benefit from research, engage in research combined with medical care (§8)	Special protection for participants who are unable to consent or vulnerable to coercion or undue influence (§9)
	Compensation for research injuries	–	Make provisions for treating/compensating for research injuries (§14)
	Review of protocol changes	–	Ethical review of all protocol changes (§15)
	Trial registration	Publicize study design (§16)	Register trial (§19)
	Exemptions from consent (competent subjects)	–	Only if (1) consent is impossible/impractical to obtain or undermines scientific validity and (2) ethical review has occurred (§25; *research with identifiable human material/data*)
	Research with incompetent subjects	Only if (1) necessary to promote health of the population and (2) research cannot be done with competent persons (§24; *all research with incompetent subjects*)	Only if (1) necessary to promote health of the population and (2) research cannot be done with competent persons and (3) no more than minimal risk and burden (§27; *research with incompetent subjects that offers no prospect of direct benefit*)
	Research with incompetent subjects	Obtain assent and surrogate consent (§25)	Obtain assent, respect dissent and obtain surrogate consent (§28)
	Research combined with medical care	Only if research is justified by its potential prophylactic, diagnostic or therapeutic value for subject (§28)	Only if (1) research is justified by its potential preventive, diagnostic or therapeutic value for subject and (2) participation will not adversely affect subject's health (§31)
	Study withdrawal	–	Must never interfere with patient-physician relationship (§34)
4) International research collaborations	Research and benefit for the population	Research only if population benefits from research results (§19; *all research*)	Research only if (1) responsive to health needs and priorities of the population and (2) reasonable likelihood that population will benefit from research results (§17; *research involving disadvantaged or vulnerable populations*)
	Family/community consent	–	Where appropriate, family/community consent can be obtained, but does not substitute or override individual consent (§22)
	Placebo-controlled trials	Only if (1) no proven prophylactic, diagnostic or therapeutic method or (2) compelling scientific reasons or (3) no additional risk of serious or irreversible harm (§30 with note of clarification)	Only if (1) no proven prophylactic, diagnostic or therapeutic method or (2) compelling scientific reasons and no additional risk of serious or irreversible harm (§32)
	Benefit sharing/ post-trial access	Obligation to ensure subjects access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study (§30)	Entitlement to share any benefits resulting from research, for example, access to interventions identified as beneficial in the study or other appropriate care or benefits (§33)

[1] *The DOH 2004 column refers to the 2000 version of the Declaration, including the 2002 and 2004 notes of clarification.*

out consideration of all other relevant paragraphs" (§1). However, this provision does not by itself solve the Declaration's problems of internal consistency. A mandate of strict adherence to the Declaration can therefore generate contradictions.

For example, the Declaration requires that research should be combined with medical care only if the "... research is justified by its potential preventive, diagnostic or therapeutic value [for subjects] and (...) participation in the research study will not adversely affect the health of the patients who serve as research subjects" (§31). By categorically prohibiting adverse effects to the health of subjects, this provision appears to bar any risk of harm to subjects — or, maybe more plausibly, any risk of serious harm. However, this would prohibit almost all clinical research, which typically involves clinical care while posing some risk of serious harm to subjects. For example, a physician-investigator might invite one of his patients to participate in a study after standard therapy has failed. Imagine the study investigates a very promising new drug for brain cancer and requires a lumbar puncture, involving a <1 in 100,000 risk of meningitis. Meningitis arguably is a serious harm, hence it cannot be excluded that participation in the study will not adversely affect his or her patient's health. According to §31, then, this study is not acceptable. But it seems that the <1 in 100,000 risk of meningitis should be considered acceptable because the likelihood of contracting meningitis is very low and the study offers significant potential benefit for both individual subjects and for society. By barring *any* risk of serious harm, §31 therefore forestalls acceptable clinical research. This outcome is inconsistent with the Declaration's emphasis on the importance of research for medical progress (§5).

Problem 4: Some of the Declaration's Principles Take Positions amidst Reasonable Disagreement

The foundations of research ethics remain controversial among reasonable people committed to promoting ethical research. The Declaration takes a particular stance on key issues of controversy, and thereby makes an important contribution to ongoing debates. However, it is one thing to take a stance in the face of reasonable disagreement, and quite another to declare one's position as the universal ethical minimum. Such assertions are inappropriate in cases where reasonable disagreement exists.

For example, consider the long-standing controversy surrounding the standard of care in research in developing countries. Should research interventions be tested against the local standard of care, even if that can be "nothing," or should interventions be tested against the best interventions available worldwide? Prominent commentators disagree about this question. Some argue that testing against the local standard of care would create unethical double standards.[9] Others share the concern that local standards of care can be unacceptably low, but worry that a strict requirement to test against the worldwide best interventions would block important research specifically designed to improve health care under local conditions. These commentators defend deviations from the best available intervention under some restrictive circumstances,[10] similar to ethical guidance documents other than the Declaration.[11] Reasonable people seem to disagree about the appropriate standard of care in research in developing countries.

Future revisions of the Declaration should clarify the document's normative status as a set of strong default recommendations and improve its substance through further specification, precision, and argument.

Clearly, it does not follow from this situation that the Declaration should refrain from taking a stance on controversial issues. In fact, if the standard was that the Declaration could only include provisions that are accepted by all reasonable commentators, it would be a rather short document. It is therefore perfectly acceptable for the Declaration to stipulate that new interventions "must be tested against ... the best current proven intervention[s]" (§32), if this is the WMA's carefully considered position. However, given that reasonable people disagree about the appropriate standard of care in research in developing countries, it is inappropriate for the Declaration to claim that this position must be accepted as the universal ethical minimum.

Problem 5: A Mandate of Strict Adherence Can Convey an Inaccurate Picture of Ethics

The overarching goal of the Declaration is to advance ethical conduct of medical research. Several of its

provisions, when followed, clearly promote this goal. However, requiring strict adherence to the norms set out by a single piece of guidance can convey an inaccurate picture of ethics and may risk alienating researchers.

Researchers should certainly not deviate from sound ethical guidance without good reason, and involvement of an independent ethics body might be important if they intend to do so. But by mandating strict adherence to a single set of rules, the Declaration fails to respect and promote the moral agency of researchers. Moreover, such a mandate could have unintended consequences. Some researchers might be led to believe that ethics is simply a matter of following one set of ethical rules, rather than providing explicit justification for their actions in light of the particulars of a given situation. There is a risk that these researchers will not be encouraged to fully develop their ability to critically reflect upon and evaluate rapid developments in science and technology, or the particular circumstances they are facing. By contrast, researchers with advanced knowledge and experience might simply discount the Declaration as insufficiently compatible with their own ethical judgement. These researchers might take the document less seriously than they should, or ignore it altogether.

Demonstrating Instead of Proclaiming Authority

Given the ongoing controversy about the Declaration, it is understandable that the recent revision aims to bolster the importance of the document. However, the above analysis shows that the Declaration's new claim of ethical primacy is problematic. Moreover, because ethical guidance should demonstrate rather than proclaim authority, this claim makes the Declaration unnecessarily vulnerable to criticism. Future revisions should therefore strengthen the Declaration in the following two ways.

Clarifying the Status of the Declaration

Like any other ethical guidance, the Declaration's provisions should be followed only if they are a statement of justified ethical principles, if they apply to the given situation, and if they are not outweighed by other significant ethical considerations. Ethics is not a rule-following activity, but necessarily involves the exercise of moral judgment. The Declaration should therefore eliminate its claim of ethical primacy in §10. It should also clarify the relationship between ethics and law in general terms, rather than suggesting that only the Declaration can trump legal or regulatory requirements. Further, the opening paragraph should be clearer that the Declaration provides a set of basic ethical principles which is intended to assist researchers in the process of reflecting upon and thoughtfully discharging their responsibilities, rather than providing solutions or an off-the-shelf set of uniformly applicable principles. The Declaration's principles should be seen as strong defaults, to be followed unless there is compelling ethical reason to do otherwise.

Improving the Declaration's Substance

In parallel, the Declaration's substance should be improved to strengthen its authority for researchers and others involved in medical research. The above analysis suggests several strategies towards achieving this goal. First, provisions that currently allow of too few exceptions should be specified to the extent this is compatible with a general guidance document. For example, the provisions on informed consent in research with competent subjects might specify conditions under which it can be acceptable to modify or waive elements of informed consent. Certain minimal risk interventions, such as a simple survey of behavioral health risks, would be one obvious candidate.

Second, vague provisions should be formulated more precisely. For example, it would be useful to define criteria that make post-trial access arrangements indispensable. It could be argued, for example, that subjects should have access to beneficial interventions if these interventions have a significant impact on subjects' health and/or well-being. Similarly, it would be useful to clarify the roles and responsibilities of the different actors necessary for realizing post-trial access arrangements, including researchers, sponsors, and health officials. Further specification, precision, and argument should also help to minimize internal inconsistencies.

Third, to foster and advance debate about controversial provisions, justifications for the positions taken in the Declaration should be laid out in a separate document. For example, as discussed above, reasonable people disagree about the appropriate standard of care in clinical research. Ongoing debates about this issue might be advanced if the reasons underlying the Declaration's position were clear. At a minimum, knowing the rationale would hopefully render ongoing controversy about the Declaration's respective provisions more focused and productive.

Conclusion

An urgent need exists for strong international guidance on the ethics of medical research. Due to its long and influential history, the Declaration of Helsinki is uniquely situated to provide such guidance. However, the Declaration's most recent claim of ethical primacy is problematic and makes the document unnecessarily

vulnerable to criticism. To truly become "first among equals" in research ethics, future revisions of the Declaration should clarify the document's normative status as a set of strong default recommendations and improve its substance through further specification, precision, and argument.

Note

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5. See Ashcroft, *supra* note 1.
6. World Medical Association (WMA), World Medical Association Declaration of Helsinki, *Ethical Principles for Medical Research Involving Human Subjects*, Ferney-Voltaire, 2008.
7. Confusingly, the Declaration uses the term "participants" for non-physician investigators and the term "subjects" for patients or healthy volunteers who participate in research. We adopt this terminology here exclusively for reasons of clarity.
8. Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Geneva, 2002; United Nations Educational Scientific and Cultural Organization (UNESCO), *Universal Declaration on Bioethics and Human Rights*, Geneva, 2005.
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