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The 50th Anniversary of the Declaration of Helsinki: Progress But Many Remaining Challenges

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Since 1964, through 7 revisions, the World Medical Association's *Declaration of Helsinki* has stood as an important statement regarding the ethical principles guiding medical research with human participants. It is consulted by ethics review committees, funders, researchers, and research participants. It has been incorporated into national legislation and is routinely invoked to ascertain the ethical appropriateness of clinical trials.

There is much to praise about the revision process and the latest revision, which coincides with the declaration's 50th anniversary. The Working Group extensively consulted stakeholders and justified the proposed revisions. The result is a declaration that is better organized into clear sections, more precise, and likely to be more effective at protecting research participants.

For the first time, the declaration requires compensation and treatment for research related injuries (Paragraph 15), an explicit recognition that research participants should not bear the costs of research gone wrong.¹ The revised declaration's emphasis on the dissemination of research results, including negative ones, should increase the value of medical research (Paragraphs 23, 35, 36).

Nevertheless, the proposed declaration contains persistent flaws. While the document purports to be a statement of enduring ethical principles, the nearly continuous process of revision undermines its authority.² Moreover, it continues to assert that, "consistent with the mandate of the WMA," its primary audience is physicians (Paragraph 2). This is a mistake. Indeed, the document then offers recommendations for other health professionals (paragraph 9), research ethics committees (Paragraph 23), sponsors and governments (Paragraph 34), and editors and publishers (paragraph 36). It is time for the WMA to recognize that the declaration should address non-physicians: a statement of ethical principles does not require a mandate from the people who ought to follow those principles.²

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The revised declaration's treatment of informed consent remains inadequate. It fails to recognize the possibility of waiving consent for some research involving competent adults, even though such research is common and widely endorsed. Similarly, the declaration avoids providing guidance on when it can be appropriate to ask participants to give broad consent for their biological samples to be used in a wide range of future studies, rather than seeking consent for each specific study. This is a pressing issue on which researchers need clear guidance. Finally, it prohibits individuals who cannot consent from participating in research that does not address the condition that caused their incapacity (Paragraph 30) even when the research offers participants the potential for important medical benefit and there are no—or few—potential participants who can consent. This approach transforms a protection into a handicap.

Problems with Research Posing Net Risks

Research studies and interventions that pose risks without compensating benefits to participants—'non-beneficial' studies—are crucial to improving medical care. Yet, the revised Declaration offers conflicting and problematic guidance on this topic. It rejects placing participants at any net risk in order to collect data, no matter how valuable:

While the primary purpose of medical research is to generate new knowledge, this goal can *never* take precedence over the rights and interests of individual research subjects. (Paragraph 8, emphasis added).

Similarly, the Declaration permits research combined with medical care—an increasingly important category of research— only to the extent that “this is justified by its potential preventive, diagnostic or therapeutic value,” leaving it unclear whether individuals may be exposed to any net risks in this context (Paragraph 14). Even more puzzling, the Declaration seems to allow non-beneficial research only with individuals who are *unable* to give informed consent (Paragraph 28).

Clearly, the goal of generating new knowledge must not take precedence over the *rights* of individual research participants. And research participants should not be exposed to high net risks. Yet non-beneficial research can be ethical when the net risks to participants' *interests* are low and the benefits to society are sufficiently large. Indeed, in apparent conflict with Paragraphs 8 and 14, Paragraphs 16 and 28 seem to affirm that ethical research can pose some net risks to participants:

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects. (Paragraph 16)

The declaration's failure to provide clear and consistent guidance regarding when net risks are acceptable creates unnecessary confusion and fuels paranoia that all medical research is inherently exploitative.

Problems with Research in Poor Communities

The declaration rightly recognizes the importance of protecting the worst off, including populations which lack access to adequate healthcare. The revised Declaration calls for

special protections for groups and individuals who are “vulnerable and may have an increased likelihood of being wronged or of incurring additional harm” (Paragraph 19). It then delineates 3 conditions for research with vulnerable groups: (1) the research must be responsive to their health needs; (2) it must be impossible to carry out with nonvulnerable groups; and (3) the group should stand to benefit from the knowledge, practices, or interventions that result from the research (Paragraph 20).

The declaration is confused and mistaken about vulnerability and appropriate protections.^{3,4} First, the group the declaration has in mind that is in need of special protections is vulnerable because they are poor and have limited access to medical services, not because they are at higher risk of harms. Failure to make this clear undermines the protections. What is necessary to protect poor populations is very different from what is necessary to protect participants who are at higher risk of harm, cannot consent, or, because of their position, eg, being a student, are at increased risk of coercion.

Second and more importantly, the declaration is confused about what constitutes appropriate protections and the appropriate means to achieve those protections. To be clear and comprehensive, the declaration should state that populations who are vulnerable to exploitation should always receive a fair level of benefits. Providing fair benefits is the goal. The means to achieve it vary. In only a limited number of clinical trials, the requirement that vulnerable groups should benefit “from the knowledge, practice, or interventions that result from the research” (Paragraph 20) along with the requirement that participants have posttrial access to interventions identified as beneficial (Paragraph 34) can provide fair benefits, but only with respect to phase 3 trials in which an experimental intervention is found to be more effective. When research does not prove an intervention effective—phase 1 and 2, and negative phase 3 research trials—participants from poor countries with limited access to medical services are unlikely to benefit at all from these requirements. In these cases, a research project might supply clean water, new clinics, or build local medical and research capacity. If this level of benefits is fair, then the research will not be exploitative.

Problems with Placebos

The revised declaration fails to address the testing of interventions that may be beneficial to some groups, but are expected to be less effective than interventions that are available elsewhere—“the best proven interventions.” It asserts that placebos may be used only when the “patients” who receive them “will not be subject to additional risks of serious or irreversible harm *as a result of not receiving the best proven intervention.*” (Paragraph 33, emphasis added) How to interpret this last clause is unclear. The danger is that it may preclude vital research that promises to improve the condition of the worst-off. For example, past trials of single-dose nevirapine given to mothers during labor and their infants within 72 hours of birth demonstrated that this was a highly cost-effective means of reducing mother-to-child-transmission of HIV.⁵ However, it was known at the time that single-dose nevirapine would not be as effective as more comprehensive and much more expensive treatment regimens that also targeted transmission during pregnancy. Yet trials that used less than the best known treatment were ethical and had the potential to benefit mothers who otherwise would receive nothing. A future and better Declaration should allow such trials

under strict conditions, especially when no one is deprived of treatment they would otherwise receive and the research has the potential to save many lives and improve the care of poor populations.⁶

Conclusion

The revised declaration represents a significant improvement and the WMA and its Working Group are to be congratulated. Creating an international document to guide research around the world is an enormously difficult and complicated task. Nevertheless, important problems and confusions remain in this 50th Anniversary Declaration. The definitive guidance on research ethics and even better protection for research participants await responses to the declaration's remaining challenges.

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