U.S. Department of Health and Human Services
Perspectives on the Revision of the Declaration of Helsinki
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The Declaration of Helsinki (DOH) has been an important source of ethical guidance in the conduct of clinical research throughout the world for nearly half a century. The DOH is highly regarded and respected for its reflection of fundamental principles and widely-held values. As the process to revise the 2008 version of the Declaration of Helsinki begins, we wish to commend the World Medical Association (WMA) for the integrity and transparency of its consultative and deliberative processes and for giving due consideration to the perspectives of all stakeholders and interested parties.

DOH's strength and influence lies in its articulation of basic ethical guidance for the conduct of clinical research. While ethical principles are enduring, clinical research is a dynamic enterprise. New frontiers of clinical science and new opportunities to address human diseases and advance human health can raise ethical questions. We support efforts to augment the DOH where new ethical challenges arise and to adjust current content to reflect new research practices and directions. At the same time, it is important to resist calls to add procedural specifics to the DOH. Prescribing specific procedural steps leads to conflicts between the DOH and the mandatory procedures that countries have in place to protect human research participants. Such conflicts weaken DOH's influence and diminish its value as a source of fundamental ethical guidance.

We appreciate the opportunity to provide our perspectives on the specific topics being discussed at this Expert Conference, to raise several issues with regard to the content and structure of the current document, and to listen to the thoughtful perspectives of other participants. We also look forward to providing further input during the next phases of the revision process when specific revisions to the current version will be considered.

Discussion Topics

Vulnerable Groups

In the current DOH, attention is given to the ethical issue of vulnerability in two separate paragraphs, 9 and 17. Taking note of the definition provided in Paragraph 9, we would recommend that the reference to disadvantaged populations in Paragraph 17 be dropped. Its inclusion effectively and, in our view, inappropriately characterizes every disadvantaged population or community as incapable of giving or refusing consent for themselves or as vulnerable to coercion or undue influence. In addition, the second "if" clause currently makes no reference to the fact that research participation in itself can be beneficial to a population or community. We would suggest that this issue be addressed by dropping the phrase "results of the."

Post-Study Arrangements

The current DOH approach to post-trial arrangements, expressed in Paragraphs 33 and 14, warrants reconsideration and revision, particularly Paragraph 33. The expectation in Paragraph 33 that investigators will provide access to interventions identified as beneficial or to other appropriate care or benefits is a standard that most investigators cannot meet. Especially troubling is the statement that study participants "are entitled" to share in the benefits that result from the study. Investigators may face any number of challenges and impediments to providing access to such benefits, including lack of funding, insufficient supplies, the country's health care situation and its national regulations and health care policies. Moreover, requiring post-study access may restrict the number of countries where research involving potentially beneficial interventions can be conducted and could have profoundly adverse consequences across the globe on the ability of the public and private sectors to carry out research on investigational therapies, diagnostics, and preventive measures.

Certainly, researchers must be attentive to the ongoing health needs of research participants, but establishing a standard that is largely impossible to achieve does not advance the ethical conduct of research. We urge WMA to consider a more reasonable articulation of the investigator's obligations to the future well-being of the participants enrolled in their studies. In our view, the WMA should adopt a more measured ethical approach that would call upon researchers to consider the issue of post-trial access in the context of local needs, the local healthcare infrastructure, national regulations and health care policies, and the availability of effective treatments and, where such access is possible, to describe arrangements for access to interventions identified as beneficial in the study, such as continued therapy with an investigational intervention or other appropriate care or benefits.

For reasons we will describe later, the concepts in Paragraph 33 should be moved to Part B.

Biobanks

Biobanks raise many important ethical issues, and they will likely play a role of growing importance in the world of research. The debate with regard to the ethical issues surrounding biobanks is ongoing, and there is as yet no consensus. It is premature to establish ethical requirements in areas where a consensus on the appropriate ethical course to take has not been established.

Ethics Committees

One important element regarding the composition and role of ethics review committees is missing from Paragraph 15. Language should be added to specify that Ethics Review Committees should be comprised of members with the appropriate expertise to review the research protocols that are submitted to them. Addressing this gap would strengthen the DOH.

Enhancement

HHS does not see a need for the DOH to address the ethical issues related to physical or cognitive enhancement research. To the extent that such research involves the same ethical

issues that apply to other types of research, the DOH already provides guidance. If there are unique ethical issues with enhancement research, those issues have not yet been identified or resolved. As such, it would be premature to attempt to articulate specific ethical guidance.

General Consultation Topics

HHS looks forward to learning more about the specific aspects of the four consultation topics that may be under consideration for inclusion into the DOH. As the thinking advances and the intentions become clearer, we will likely have more specific comments. Below are some of our preliminary thoughts.

Insurance/Compensation/Protection

We agree that clinical researchers have an ethical obligation to provide for treatment of individuals who experience adverse events or injuries as a result of their participation in research. Compensation for harms or costs of long-term care is a much more complex issue. In this regard, the U.S. Presidential Commission on the Study of Bioethics Issues addressed the issue in a recent report, which is currently under consideration by HHS. Articulating the ethical principle that research participants should not bear the cost of unforeseen harms related to their study participation may be an appropriate addition to the DOH. However, given the different approaches that nations take in addressing this issue, it would be counterproductive to go farther by attempting to identify a specific implementation mechanism.

Use of Unproven Interventions/Off-label Use

HHS does not see a need to modify or expand on the current text in the DOH that addresses unproven interventions. Paragraph 35 speaks to the issues that should guide a physician's decision-making when considering the use of an unproven intervention. Moreover, existing national regulations and guidance provide more detailed explanation of requirements for the use of unproven interventions with therapeutic intent for an individual patient. More detailed text on this topic is likely to conflict with national regulations that vary in their requirements for dealing with the use of investigational drugs for therapeutic purposes.

Also, we advise against addressing the topic of off-label use of approved products. It is a medical practice, rather than a research, matter. Moreover, attempting to address the issue of off-label use in the DOH is likely to lead to conflicts with national regulations that vary in their policies or requirements.

Broad Consent

The ethical acceptability of the use of broad consent in certain types of research is an important and timely issue. HHS is currently considering regulatory changes to allow the use of broad consent for research involving biospecimens and data. Such a change will facilitate important research and, if properly designed and implemented, would be in keeping with applicable ethical principles.

Medical Research Involving Children

Specific ethical guidance on research involving children need not be added to the DOH. The principles outlined in the DOH generally apply to research with children and, together with the principle outlined in Paragraph 17 that covers vulnerable populations, the DOH provides sufficient ethical guidance for studies involving pediatric populations. Articulating detailed standards for pediatric research would require a significant expansion of the DOH. However, such an expansion would be inappropriate because adding specific details in this area to the DOH may conflict with specific and comprehensive regulations for pediatric studies already in place for many countries.

Other Issues with the 2008 Version of the DOH

Deference to National Human Subjects Protections Requirements on Specific Details

While much of the DOH appropriately remains at the level of broad principles, there are provisions that detail specific requirements. Some of these are, moreover, at odds with national laws and/or regulatory requirements. Excessive specificity undermines the value of DOH as a source of basic ethical guidance and leads to unnecessary conflicts with national approaches that are based on the same fundamental ethical principles. This problem is exacerbated because of language in the DOH that claims moral supremacy over national requirements and standards.

We urge WMA to modify Paragraphs 10 and 15. Both Paragraphs include statements that inappropriately call on researchers to disregard their obligations to follow their national laws and regulations when they conflict with the provisions of the DOH. Paragraph 10's statement 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" and the similar statement in Paragraph 15 should be deleted.

Clarifying the Intent of Paragraph 6

Paragraphs 6 conflates medical research with medical care and, in so doing, incorrectly creates a standard for the well-being of the subject that is akin to that which applies to patients in clinical care. That standard is not the one that is currently being applied in the research setting, for if it were, much of the research conducted today would be in violation of the standard. Paragraph 6 should be revised and combined with paragraph 21, which more closely reflects the applicable standard.

Registration of Clinical Trials

HHS agrees with the importance of the goals of transparency and accountability articulated in Paragraph 19 and that information about clinical trials should be available through registration in a publicly accessible database. However, specifying a timeframe for registration does not relate to an ethical principle, i.e., whether the registration occurs before recruitment or sometime after recruitment begins is not important for the protection of the study participants. Moreover, there is no international consensus on best practices about the scope and timing of registration.

Accordingly, Paragraph 19 should be revised to become a statement of principle that "Every clinical trial should be registered in a publicly accessible database as early as possible in order to facilitate transparency and accountability."

Artificial Distinction between Medical Research (Section B) and Medical Research Combined with Medical Care (Section C)

The distinction that the DOH is drawing between "medical research" and "medical research combined with medical care" is confusing. In fact, there do not appear to be conceptual differences that would warrant separate ethical guidance sections. As such, we recommend deleting Part C "Additional Principles for Medical Research Combined with Medical Care," and incorporating sections of Paragraphs 31-35 into sections A and/or B, as follows.

- Paragraph 31 repeats concepts already covered in Paragraphs 3, 6, and 16 and can be deleted altogether.
- Paragraph 32 addresses the use of placebos and should be moved to follow Paragraph 16.
- Paragraph 33 should be deleted. An exhortation to inform participants of the outcome of the study should become part of Paragraph 14 (this should not be worded as an entitlement since it may not always be possible). For reasons discussed above in Post-study Arrangements, the second part of Paragraph 33 that reads "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" should be deleted.
- The second sentence in Paragraph 34 regarding refusal to consent and withdrawal repeats concepts in Paragraphs 4 and 9 and should be deleted. The concept in the first sentence that care and treatment should be distinguished should be addressed in Paragraph 24.
- The guidance regarding the use of unproven interventions in Paragraph 35 should be moved to follow Paragraph 18.

Enhancing DOH's Readability

The paragraphs in Section B should be reorganized so that related issues are presented together and in a logical order. It would be helpful to add descriptive topic headings as well. Currently, related items are scattered throughout Section B. A restructuring would help readers navigate the document more easily, enhance its readability, and facilitate adherence to ethical guidance in the DOH. For example, the information in Paragraphs15, 25 and 29 concerning the responsibilities of Research Ethics Committees could be grouped together under the topic heading "Research Ethics Committees."

Exceptions to Requirements for Informed Consent

Paragraph 22 should allow for the fact that, in certain limited circumstances, some research involving competent subjects can ethically be conducted without consent. Specifically, Paragraph 22 should be expanded to state that the requirement for informed consent may be waived or altered in situations where risk to research subjects is no more than minimal and consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research.

Emergency Research

Changes should be made to clarify Paragraph 29. Although the text applies to pre-planned emergency research situations, its focus is not evident until midway through the paragraph. Pre-planned emergency research includes, for example, studies to evaluate the effectiveness of automated defibrillators in reducing mortality in out-of-hospital cardiac arrest. Since people who have suffered cardiac arrest are incapable of providing consent for themselves and the urgent need for the intervention does not, in most instances, permit additional time to seek consent from a legally authorized representative, the research cannot be carried out without a waiver of consent. Specifically, Paragraph 29 should be reorganized and revised to make clear that it pertains to the waiver of consent in pre-planned emergency research situations and not to an individual emergency situation. These revisions, which are shown below, will also distinguish it from Paragraph 35 which addresses consent from the patient or a legally authorized representative for administering an unproven intervention to an individual in an emergency situation.

> "29. The requirement for informed consent may be waived in certain emergency research situations. These waivers of consent are justified when all the following conditions are met: research involves subjects in life-threatening situations where there are no proven or effective treatments and the initiation of the experimental intervention cannot be delayed; research involv~~inges~~ subjects who are ~~physically or mentally~~ incapable of giving consent due to the life-threatening situation; ~~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.~~ Participation in the research holds out the prospect of direct benefit for the subjects; ~~If~~ no such legally authorized representative is available to provide informed consent; ~~and if the research cannot be delayed, the study may proceed without informed consent provided that~~ the research cannot practicably be carried out without a waiver of consent; and 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.

Placebo Controls in Clinical Research

Although the use of placebo controls in clinical trials was the subject of much discussion and debate in the past, we are pleased with the consensus wording achieved in 2008. The 2008 version appropriately outlines the ethical criteria that justify the use of placebos when a proven intervention exists, including that the study has scientific merit and clinical value and that it does not pose risks of serious or irreversible harm. Paragraph 32 thus offers appropriate ethical guidance as currently written, and the WMA should resist calls for substantive changes.

Conclusion

We appreciate the opportunity to present HHS perspectives on the DOH and the additional topics under discussion and to hear thoughtful perspectives from colleagues around the world. We stand ready, during the next phase of the revision process, to provide additional perspectives as well as more specific comments regarding revisions to the 2008 DOH.