

Declaration of Helsinki

Controversies with Revisions 2000

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Welcome to Clinical Device Group's Web Publications series. In this publication, we discuss the controversial revisions made to the Declaration of Helsinki by the World Medical Association in October 2000 and look at some of the implications for medical device sponsors.

Revised October 2000

- **Continuous review.**
- **1996 version not appropriate for developing countries.**
- **Changing research environment: genetics, data privacy.**
- **Harmonize with other CIOMS, ICH, other guidelines.**

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The World Medical Association (<http://www.wma.net/>) issued the first Declaration of Helsinki in June 1964. Since then, the Declaration has been revised five times: October 1975, October 1983, September 1989, October 1996, and October 2000.

The Declaration undergoes continuous review to keep it appropriate for current situations. The 2000 revisions were undertaken to make the Declaration appropriate for research in developing countries, to keep pace with emerging issues such as genetics research and data privacy, and to harmonize the Declaration with CIOMS, ICH and other international guidelines. Many of the revisions are controversial, leave room for various interpretations, and cause problems with some well-accepted study designs.

Structure of 2000 Text

- **32 Articles.**
- **9 Introduction.**
- **18 Basic Principles for Medical Research.**
- **5 Additional Principles for Medical Research combined with Medical Care.**



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The structure of the 2000 text was substantially reworked from 1996. The text now consists of 32 independent articles: nine articles are introductory, 18 set forth basic principles for medical research, and five set forth additional principles for medical research combined with medical care. The changes include 12 minor rewordings, 12 substantial changes, and 8 new articles. The most important changes are discussed in the following slides.

Article 1-Scope

Medical research involving human subjects includes research on identifiable human material or identifiable data.



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Article 1 expands the scope of clinical research to include research on identifiable human material or identifiable data. This means, for example, that research on leftover tissue samples (even from deceased persons) that could be identified by genetic profile or other means is now subject to the guidelines of the Declaration of Helsinki. Registry data, where retrospective or prospective observational data are collected into a database, are also subject to the Declaration of Helsinki. Such research requires approval by an outside review board and informed consent. It will have a direct impact on in vitro diagnostic device manufacturers who use identifiable tissue samples, biotechnology companies who do genetics research, or implant companies who maintain registries.

Article 9-Legal Standing

- **1996: ...the standards...are only a guide; physicians are not relieved from criminal, civil & ethical responsibilities under the laws of their own countries.**
- **2000: ...No national, ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.**



The Declaration 1996 recognized itself as a guideline, with no legal standing outside of that conferred on it by national laws. Article 9 of the Declaration 2000 declares itself to override national, ethical, or regulatory requirements of any nation. It is not surprising that FDA doesn't agree with this statement, and indeed, many nations may have difficulty with the idea of an independent professional organization declaring itself above national law.

Article 13-ECs

Ethics committees:

- Have right to monitor ongoing trials.
- Must be given reports on SAEs.
- Must review information on funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

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Article 13 of the revised declaration describes the membership and responsibilities/authorities of Ethics Committees. The membership should be independent of the investigator, sponsor, or any other undue influence. The committee is responsible to review the protocol, has the authority to monitor ongoing studies, must be provided with reports of serious adverse events, and must review “information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.” US sponsors may not be familiar with providing information about investigative site funding to Ethics Committees.

Article 16-Availability

- **The design of all studies should be publicly available.**



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Article 16 states, among other things, “the design of all studies should be publicly available.” The World Medical Association has stated that their intent is not to force companies to disclose the details of their protocols. Rather, their intent is assure the design is available to the investigator, Ethics Committee and subjects (via an informed consent) pre-trial; and available through published results post-trial. Nevertheless, many sponsors are uncomfortable with the wording of this article, which will likely be interpreted as requiring full disclosure.

Article 17-Cease Investigation

- **Physicians should cease any investigation...if there is conclusive proof of positive and beneficial results.**



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Article 17 states that investigators should stop an investigation if there is conclusive proof of positive and beneficial results. Most sponsors are not comfortable with the idea of an investigator taking this kind of initiative independently. Such actions need to be carefully controlled. Investigators may have access only to data generated at their investigative sites, and there is a possibility they will terminate their sites prematurely, undermining the scientific and regulatory value of the entire study.

Article 19-Benefit to Populations

- **Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.**



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Article 19 states the populations in which the research is carried out must stand to benefit from the results of the research. Healthy volunteers rarely benefit from the research in which they participate, does this article mean to imply such research is no longer allowed? The World Medical Association has stated the article is aimed at research in developing countries, not healthy volunteers.

Article 22-Information to Subject

■ Each potential subject must be...informed of the...

*sources of funding,
conflicts of interest,
institutional affiliations...*



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Article 22 tells us that subjects must be informed of the sources of funding, conflicts of interest and institutional affiliations of investigators. This is new information for investigators to provide to subjects. Investigators may not be accustomed to disclosing to subjects the value of payments they or their clinics receive from sponsors, their financial or equity associations with sponsors, or (for those who are also the primary caregiver for a subject) to disclosing institutional affiliations to subjects. This new information may influence subjects if they suspect the researcher has other interests ahead of the subject's own well-being.

Article 24 & 25-Legally Incompetent

■ Now includes:

- ◆ Physically or mentally incapable.
- ◆ Legally incompetent minor.

■ Should not be included unless research necessary to promote health of population, cannot be performed on others.

■ Subject to give assent if possible.

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Articles 24 and 25 introduce the concept of “legally incompetent” and include the physically incapable, mentally incapable, and legally minor persons in this category. Research in these groups should only be conducted if it cannot be performed in other populations. Subject assent should be obtained whenever possible.

Article 26-Lack of Consent

If no consent, proxy, or advanced consent:

- **Physical/mental condition must be necessary to research.**
- **Protocol to explain reasons for inclusion.**
- **Protocol to be approved by IEC.**
- **Protocol to state consent to remain in study be obtained asap from subject or legal representative.**



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Article 26 allows for research in individuals who cannot give consent, including individuals who cannot give consent by proxy or in advance (say, in the early stages of dementia or prior to anesthesia). It states that such persons should serve as subjects only if their physical or mental condition is necessary to the research. The protocol must explain the reasons for their inclusion, the protocol must be approved by an independent ethics committee, and the protocol must state that *consent to remain in the study will be sought from subjects as soon as possible*.

Article 27-Publications

- Negative and positive results should be published.
- Sources of funding, institutional affiliations, conflicts of interest specified.
- Research not in accordance with Helsinki should not be accepted for publication.

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Article 27 is very problematic for medical device sponsors. It requires that both positive *and negative* results be published. Since medical device development is often iterative (design a device, test the device; re-design the device, test the device), many studies result in negative results. Sponsors may rightfully consider these data proprietary as they work out the best formulations and configurations for their products; and publishers may rightfully find the data uninformative, as the device that was investigated may never be available commercially.

Article 29-Placebo

- **...new method...should be tested against...*best proven prophylactic, diagnostic, and therapeutic methods...does not exclude use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.***



Finally, Article 29 states that investigational methods should be tested against proven methods, not placebos or no treatment. This is not really an issue for medical device sponsors, as most studies—if controlled—use active controls rather than placebos. FDA has a major problem with this provision for drug studies, however, requiring most pharmaceutical studies utilize placebo controls.

Article 30-Ongoing Treatment

- **At conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.**



Article 30 is a new article, requiring treatments be made available to subjects even after a study is ended. This is a major issue in developing countries where treatments are unaffordable otherwise. Device companies who manufacture products used for treatment or diagnosis, such as dialysis equipment, radiation equipment, or monitoring equipment, may find themselves obligated to continue providing parts and service.

Conflict

- **Ethics Committees deny approval for studies not in conformance with Declaration 2000.**
- **FDA will not accept clinical data that is in conformance with Declaration 2000.**



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Since October 2000, some Ethics Committees have denied approval for clinical studies whose protocols were not in conformance with the Declaration 2000. A problem for sponsors, some important research may be delayed or not conducted at all.

In March of 2001, FDA issued a guidance document entitled “Acceptance of Foreign Clinical Studies”. The message of this two-page document is that FDA will not accept foreign clinical studies conducted in conformance with the Declaration of Helsinki 2000. They have multiple problems with the guidance, the ban on placebos being only one.

Looking back to the version of the Declaration that was in effect at the time US regulations were passed, FDA has stated that pharmaceutical studies must be conducted in conformance with the Declaration of 1989, and device