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Implementation of the DoH in the Americas:

Challenges and successes

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Outline

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Background and context

- The Declaration of Helsinki (DoH) is not a legally binding document under international laws.
- However, it exerts authority through the extent to which it has directly and indirectly influenced national and international legislation and regulations.
- In some cases, it has been codified into those laws and regulations.

- It is important to always keep in mind, however, that the Declaration is *morally binding* on physicians, and that this obligation is generally considered to override any national or local laws or regulations.
- Paragraph 10 of the 2013 version of the DoH states:
  - 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.

- Since the publication of the original version of the DoH in 1964, there has been a proliferation of numerous national and international research ethics guidelines and documents.
- While there is some degree of alignment and overlap between many of these documents, there are points of divergence as well, particularly in more controversial areas such as post-trial access and the use of placebos.

- Amongst international documents, the DoH is relatively unique in that it represents a set of ethical principles combined with some degree of proscriptive detail, while many of the other documents are more technical in nature.
- However, their presence has meant that a number of national regulatory bodies have decided to make reference primarily to **one** particular document or standard.
- For some, this has meant “choosing” between using the DoH as a standard versus another more static and/or technical document.

- Such documents include, but are not limited to
  - The World Health Organization (WHO) and its Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants
  - The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects
  - Good Clinical Practice standards developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP)

- The DoH is unique amongst these policies and guidelines in that it is written and updated by physicians for physicians and final approval of the document rests solely with the physician representatives of the World Medical Association.

United States of America

- In April 2006, the United States Food and Drug Administration (FDA) published a regulatory change ending the need for clinical trials conducted outside of the US to comply with the Declaration of Helsinki.
- Previous to this, the FDA had already rejected the 2000 version of the DoH and all subsequent revisions, recognizing only the 1989 version in its regulations.

- These decisions were made largely over the question of whether placebos should be allowed in clinical trials in resource-poor settings (and to a lesser extent on the issue of post-trial access).
- Representatives from the FDA have actively engaged on the placebo issue with the WMA, including during the DoH revision processes and as part of the placebo-control meetings held in Sao Paulo.

What the FDA says

- "We didn't think the World Medical Association understood you really do need placebos to learn something in a lot of cases. Fundamentally, in a lot of symptomatic conditions, it's common for studies that compare a new drug with placebo to fail. If doing the right design, or doing an informative design would mean denying somebody a therapy that would really save their lives, then you just can't do the study at all. Everybody agrees on that. But if it's just a matter of symptoms, having a headache a little longer, being depressed for a few more days, I would say most people and certainly we believe that you could ask a person to participate in a study [using placebos]. But it's not unethical to do a trial like that."

- "What I think has happened to some extent is that the Declaration has moved from a purely ethical document to a document that is increasingly interested in social justice. For example, they clearly are very upset that people in poor countries don't have really good medical care. And I'm upset by that too. But I don't think that determines the ethics of a trial."
  - Robert Temple, Director of the Office of Medical Policy at the FDA's Center for Drug Evaluation and Research, EBMO Reports, 2006

Pharmaceutical industry concerns

- *Fearing that these new obligations (to use a comparator other than placebo) would make it harder to prove the efficacy of a new drug and would drive up the costs of development, drug developers, particularly in the USA, are protesting.*
  - EBMO Reports, 2006

Criticism of the FDA decision

- "For the last 30 years, US organizations said they loved the Declaration of Helsinki. All of a sudden, people effectively lobbied to make some changes to the DoH after the HIV/AIDS trials. And now the FDA says, 'Helsinki? What is that? That doesn't mean anything.' It's just totally hypocritical on their part to follow the DoH as long as it says what they want it to say, and as soon as it's changed, say it doesn't mean anything."
  - George Annas, Chairman of the Health Law Department at Boston University's School of Public Health, 2006

- The FDA now references the ICH-GCP document instead, a change made in April 2008.
- Unlike the declaration, those standards are developed by regulators in Japan, the US and Europe, in conjunction with the pharmaceutical industry.

Concerns about pharma influence

- *Pharmaceutical companies ultimately look to see what are the regulations and laws they must comply with in whatever countries they are going to seek approval to market a particular product. To the extent that it's easier and perhaps less costly to conduct their research in settings that appear to have looser standards or less rigorous ethical processes, then we've seen a trend in which they have been moving more towards doing research in that setting.*
  - CMAJ November 6, 2012

- *The FDA's adoption of less morally stringent guidelines could encourage pharmaceutical companies to take ethical short cuts. It could also have practical consequences for trial ethics in developing countries, especially where research ethics committees may not be promoting high standards of protection for participants in clinical trials, due to lack of financial and human resources.*
- *Pharmaceutical companies may also pressurise research ethics committees to relax guidelines and legislation, in order to facilitate future clinical trials in developing and emerging countries that lack the resources to conduct their own clinical research on epidemics such as HIV/AIDS, which have devastating effects on their populations.*
  - South African J of Bioethics and Law 2012

The Common Rule

- Several US departments and agencies subscribe to subpart A of the relevant section of the Code of Federal Regulations, often referred to as the "Common Rule".
- The Common Rule is intended to establish a comprehensive framework for the review and conduct of proposed human research to ensure that it will be performed ethically.
- It includes provisions concerning research conducted in foreign countries.

- According to 45 CFR 46.10110:
  - When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy.
  - An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration of Helsinki (amended 1989) issued either by sovereign states or by an organisation whose function for the protection of human research subjects is internationally recognized.
  - In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy.

Canada

- Canada does not have a uniform and comprehensive legislative or regulatory framework pertaining to research involving human subjects.
- Two different sets of documents are the main sources that govern research involving human subjects in Canada.
- One of them (Health Canada's Food and Drug Regulations) addresses clinical trials that test new drugs or medical devices for approval in Canada, and the other (The Tricouncil Policy Statement, or TCPS) addresses studies that have received federal research funding.

- The Food and Drug Regulations do not reference the DoH.
- However, Health Canada has introduced the full text of the ICH-GCP Guideline (with its own references to the DoH) into its regulatory regime as a Guidance Document.

- In the Introduction to the Guidance Document, Health Canada states:
  - Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

- The TCPS applies to all research funded by the federal research granting agencies, and was most recently revised in 2010.
- It contains two references to the DoH, in the reference sections for Chapter 8 (Multi-Jurisdictional Research) and Chapter 11 (Clinical Trials).

South America

- **Uruguay**
- The Declaration of Helsinki is used in Uruguay as the main research ethics guideline by which all researchers must abide.
- National legislation incorporates the 2000 revised version of the document.
- Later modifications on the use of placebo are not part of the legislation.

- **Brazil**
- Following the 2008 revision, Brazil immediately contested the position adopted by the WMA concerning the use of placebo in research involving human beings.
- According to the position advocated officially by the Brazilian government, through a Resolution from its National Health Board, "the benefits, risks, difficulties and effectiveness of a new method should be tested by comparing them with the best present methods"

Double standard concern

- There remains in some parts of South America a concern about a “double standard” for research that they feel is not fully addressed by the DoH.
- Subjects in resource-poor settings may be exposed to placebo controls or to controls that are less then standard of care in more developed countries.
- Research may not be responsive to the needs of the community in which it is conducted.
- While revisions of the DoH have attempted to address some of these concerns, they have not done so to the satisfaction of all of those involved.

Declaration of Cordoba

- In November 2008, the Congress of the Latin-American and Caribbean Bioethics Network of UNESCO (Redbioetica) approved the *Declaration of Cordoba on Ethics in Research with Human Beings.*
- This document proposed that Latin American countries, governments and organisations should refuse to follow 2008 version of the Declaration of Helsinki, which was approved in Seoul, South Korea.
- It recommended instead as an ethical and normative frame of reference the principles of the *Universal Declaration on Bioethics and Human Rights* , proclaimed in October 2005 at the UNESCO General Conference.

- The Declaration of Cordoba states that:
  - The new version of the DoH can seriously affect the safety, well-being and rights of persons who participate as volunteers in medical research studies.
  - The acceptance of different standards of medical care, as well as the new possibilities for using placebo, are considered ethically unacceptable practices and are contrary to the idea of human dignity and human rights.
  - The lack of hard post-study obligations in relation to the persons who volunteered to participate in the studies and to the host communities, offends people's integrity and amplifies social inequity.

Summary

- The use and implementation of the DoH in the Americas is, to say the least, inconsistent and controversial.
- In the United States, the FDA does not endorse the document, and only references the 1989 version.
- In South American countries, there remains a concern that the DoH does not contain sufficient safeguards when it comes to the issues of placebo controls and post-trial access.

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