

# International Clinical Trials: Global Compliance Norms The Declaration of Helsinki

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# Goals of presentation

- To explain the role of the Declaration of Helsinki (DoH) in relation to other international research ethics guidance documents
- To update conference participants on the current revision process of the DoH

# Outline of Presentation

- Compliance vs. best practices
- The DoH among the international guidelines
- The current revision process
- Key issues
  - Double standards
  - Sharing of benefits
- The way forward

# Compliance vs. Best Practices

- Compliance: what **must** be done (law and binding regulations)
- Best practices: what **should** be done, even if not required (ethics and non-binding guidelines)
- Why do more than what is required:
  - Values (altruism, compassion, justice, etc.)
  - Reputation

# Principal International Compliance Guidelines

- ICH: *Guideline for Good Clinical Practice* (1996) and *Guideline: Choice of Control Group and Related Issues in Clinical Trials* (2000)
- European Commission: *Directive on Implementing Good Clinical Practice in the Conduct of Clinical Trials* (2001, 2005)
- Council of Europe: *Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research* (2004)

# Principal International Best Practice Guidelines

- World Health Organization (WHO): *Operational Guidelines for Ethics Committees that Review Biomedical Research* (2000)
- CIOMS: *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002)
- World Medical Association, *Declaration of Helsinki* (2004, currently under revision)

# The World Medical Association

- Established after WW2, mainly in reaction to atrocities involving physicians
- Global representative body for physicians
- 84 National Medical Associations, approximately 7 million physicians

# Roles of the WMA in Medical Research

- Establishment of high-level global ethical standards for medical research (*Declaration of Helsinki*)
- Bridge between physicians and researchers
- Advocate for patients serving as research subjects
- Participant in capacity-building initiatives (NEBRA, TREEE for Africa project, Strengthening the Capacity of Research Ethics Committees in Africa project)



# How Does the WMA Decide What is Ethical?

- Considers existing principles of medical ethics
- Extensive consultation on proposed new policies or amendments to existing policies
- Discussion at Medical Ethics Committee meetings; recommendations to Council and General Assembly
- 75% majority vote at Assembly to adopt or amend ethics policies

# WMA'S Legitimacy

- No legal authority
- Sources of its moral authority
  - Pioneer in guidelines development (DoH)
  - Members' experience in ethics and research
  - Extensive consultation/consensus building
  - Quality of its policies

# Declaration of Helsinki - Influence

- CIOMS Guidelines follow the DoH quite closely
- ICH-GCP Guidelines require adherence to “the principles that have their origin in the DoH”
- EC Directive on Clinical Trials and, until October 2008, the U.S. FDA require adherence to the principles of the DoH (not the current version, however)
- The UNESCO *Declaration on Bioethics and Human Rights* cites the DoH

# Declaration of Helsinki - Influence

- DoH is by far the most cited research ethics document by research ethics committees in Central and Western Africa (NEBRA, 2006)
- Standing Committee of European Doctors (CPME) “urges EMEA and national pharmaceutical authorities to no longer accept clinical trial data that are not in accordance with the Declaration of Helsinki.” (15 March 2008)

# DoH – Brief History

- First adopted in 1964
- Significant additions in 1975
- Minor amendments in 1983, 1989 and 1996
- Major revision and reorganization in 2000
- ‘Notes of clarification’ in 2002 and 2004
- Current revision begun in 2007; to be completed in October 2008

# Current Revision Process

- May 2007 – WMA Council establishes working group to guide process (Medical Associations of Sweden, Japan, South Africa, Brazil and Germany)
- May 2007 – Invitation to stakeholders to suggest changes
- October 2007 – WMA Medical Ethics Committee discusses the proposed changes

# Current Revision Process

- November 2007 – Working group prepares consultation draft, which is distributed widely
- February 25, 2008 – Deadline for comments
- March 10-11, 2008 – Stakeholders conference in Helsinki to discuss contentious points raised in the consultation
- March 11-31 – Working group revises its consultation draft

# Current Revision Process

- May 15-17 – Consideration of the revised draft by the WMA Medical Ethics Committee and Council
- May 31 – Call for comments on latest draft
- August 31 – Working group prepares its final draft
- October 15-18 – Final consideration of draft by WMA Medical Ethics Committee and Council; possible adoption by the General Assembly



# Proposed Amendments in the May 2008 Consultation Draft

- Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
- The research protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed.

# Proposed Amendments in the May 2008 Consultation Draft

- Every medical research study involving humans should be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

# Proposed Amendments in the May 2008 Consultation Draft

- Every clinical trial should be registered in a publicly accessible database before recruitment of the first subject.
- Participation by legally competent individuals in medical research involving humans must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual should be enrolled in a research study unless he or she freely agrees.

# Proposed Amendments in the May 2008 Consultation Draft

- For medical research using human tissues or data, physicians should seek consent for the collection, investigation, storage and reuse of samples. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research should be done only after consideration and approval of a research ethics committee.

# Double Standards

- When, if ever, should research that is considered unethical in developed countries be conducted in developing countries?
- In particular, should a placebo or no treatment arm be included in clinical trials when an effective treatment exists, even if it is not generally available where the research is to be conducted?

# Double Standards

- CIOMS provides arguments for and against the use of a comparator other than an established effective intervention in developing countries but does not decide the issue.
- Should the issue be decided in terms of the way things are now (enormous inequalities between developed and developing countries) or the way they might be with some additional efforts (e.g., externally financed provision of best available treatments)?

# Proposed Rewording of Para. 29

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best proven current method, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no proven current method exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of a method and the patients who receive placebo or no treatment will not be subject to any additional risk of serious or irreversible harm.

# Sharing of Benefits

- Do individuals and communities that participate in medical research have a right to share in the benefits of the research if it is successful? Do researchers and sponsors have an obligation to provide such benefits? If so, what benefits, to whom, for how long, etc.?
- Research sponsors (e.g., NIH, pharmaceutical industry) generally deny such a right and obligation.



# Sharing of Benefits

- One view - Ethical obligations are binding only if they can be implemented ('ought' implies 'can'). Requirements to provide ongoing benefits would place an impossible burden on researchers and/or sponsors, particularly in countries where medical treatment is not readily available.

# Sharing of Benefits

- Another view - The ethical principle - that those who take on the potential risks of a medical research study should, wherever possible, receive the benefits that result from the study - is valid. Attention to this principle represents an important step in overcoming international disparities in research and health care. If there are practical problems to its implementation, every effort should be made to overcome them.

# Proposed Rewording of Para. 30

- [Addition to new para. 13] The protocol should describe arrangements for post-study access by study subjects to methods identified as beneficial in the study or access to other appropriate care or benefits.
- At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study.

# Proposed Rewording of Para. 19

- Medical research involving a disadvantaged population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

# Conclusions

- These are complex issues that admit of no easy resolution
- Consensus is difficult to achieve because of different perspectives and interests
- These differences occur not only between industry/regulatory agencies and ethics guidelines developers but among the guideline developers themselves, some of whom are more principled and others more pragmatic
- Developing countries are rightly concerned about exploitation

# The Way Forward

- Consensus building on points of disagreement (not an easy task because of different interests at stake)
- Exploration of relationship between ethics/best practices (what *should* be done or avoided) and law/regulations (what *must* be done or avoided)

# In the Meantime...

- Consider carefully the different positions on the points of disagreement and only deviate from the highest standards if there are convincing reasons for doing so (ethics/best practices)

Thank You !!

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