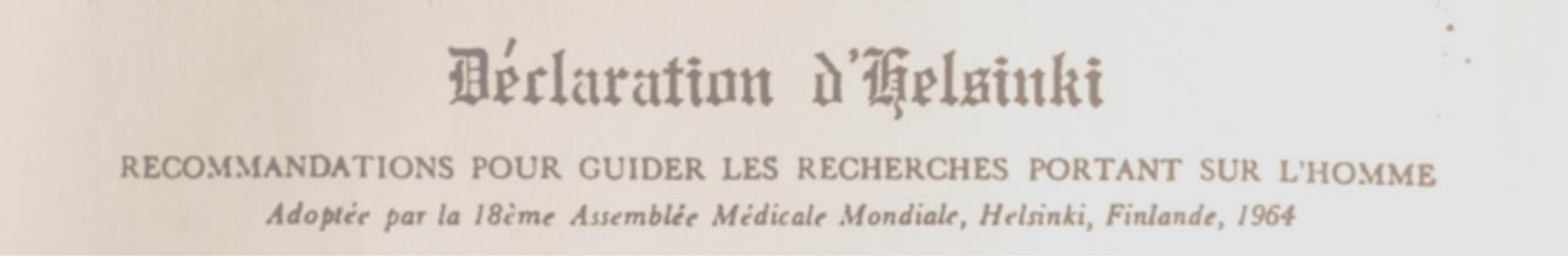


In Defense of the Most Vulnerable Research Participants

Sick Patients and the Need for Additional Principles for Therapeutic Research in the Declaration of Helsinki

Fernando Hellmann

Department of Public Health at the Federal University of Santa Catarina
Bioethics and Public Health Research Group (NUPEBISC)
Salud y Fármacos
Pandemic Ethics Research Consortium (led by the University of Oslo)
UNESCO Bioethics Network for Latin America and the Caribbean
Brazilian Bioethics Society

Understanding the Declaration of Helsinki: Past, Present, and Future

The history of the process of its revisions and its consequences

The need for including additional principles for therapeutic research — which must be differentiated from non-therapeutic research

The Genesis of the Declaration of Helsinki

- **1953** draft "Experiments on Human Beings."
- **1954** “Resolution on Human Experimentation” adopted in Rome - Less protective than the Nuremberg Code.
- **1959:** H. Clegg (UK), president of the WMA Medical Ethics Committee, reviews Rome Resolution.
- **1961:** First draft of the Declaration of Helsinki presented at XV General Assembly, Rio de Janeiro and Published in the British Medical Journal.
- **1964:**
  - Adoption at the 18th General Assembly, Finland.
  - Transition from a strict "Code of Ethics" to more relaxed "Recommendations."

Déclaration d'Helsinki

RECOMMANDATIONS POUR GUIDER LES RECHERCHES PORTANT SUR L'HOMME

Adoptée par la 18ème Assemblée Médicale Mondiale, Helsinki, Finlande, 1964

Introduction

La fonction sociale et naturelle du médecin est de veiller à la santé de l'homme. Il exerce cette fonction dans la plénitude de son savoir et de sa conscience.

Le Serment de Genève de l'Association Médicale Mondiale engage le médecin à "considérer la santé du patient comme son premier souci" et le Code International d'Éthique Médicale "interdit au médecin de donner un conseil ou de poser un acte médical prophylactique, diagnostique ou thérapeutique qui ne soit pas justifié par l'intérêt direct du patient et notamment d'affaiblir la résistance physique ou mentale d'un être humain, à moins de nécessité thérapeutique".

sonnalité du sujet peut être altérée par les médicaments ou les procédés d'expérimentation.

II. *Expérimentation thérapeutique*

1. Au cours du traitement, le médecin doit avoir la liberté de recourir à une nouvelle méthode thérapeutique s'il juge que celle-ci offre un sérieux espoir de sauver la vie, rétablir la santé ou de soulager les souffrances du malade.

Il doit, dans la mesure du possible et compte tenu de la psychologie du patient, se procurer son consentement libre et éclairé et, en cas d'incapacité juridique, celui de son repré-

The Genesis of the Declaration of Helsinki

- The 1964 DoH was divided into three parts:

  I. Basic Principles;
  II. **Clinical Research Combined with Professional Care; and**
  III. Non-Therapeutic Clinical Research.

- Unlike the Nuremberg Code, which considered consent to be 'absolutely essential,' the DoH allowed for consent 'whenever possible.'
- References to using "captive groups" (such as prisoners, orphans, institutionalized mental patients, and students) and "control trials were excluded from the final version;
- The British criticized the Americans' influence on the Declaration to align the final version with American research needs and legislation.
- From the start, the U.S. perspective on research ethics prevailed, generally weakening the principles protecting medical research participants.

Déclaration d'Hels

MANDATIONS POUR GUIDER LES RECHERCHE

Adoptée par la 18ème Assemblée Médicale Mondiale,

SOCIALE ET NATURELLE DU MEDECIN EST
nté de l'homme. Il exerce cette fonction
de son savoir et de sa conscience.

Genève de l'Association Médicale Mon-
édecin à "considérer la santé du patient
r souci" et le Code International d'Ethique
au médecin de donner un conseil ou de
ical prophylactique, diagnostique ou théra-
it pas justifié par l'intérêt direct du patient
ffaiblir la résistance physique ou mentale
à moins de nécessité thérapeutique".

sonnalité du su
les procédés d'

II.

1. Au cours
de recourir à
que celle-ci off
la santé ou de

Il doit, dans
psychologie du
et éclairé et, en

The Scandinavian Declaration (1975)

- **1974 Review** Initiated by the Scandinavian Medical Association.
- Draft discussed with national associations, WHO, and CIBA-Geigy (now Novartis) and adopted in Tokio, 1975.
- **Review Highlights:**
  - Quickest, most expansive, and progressive review.
  - Increased length without removing original content.
  - Introduced requirement for independent, multidisciplinary ethics committee reviews.
  - Made informed consent process more rigorous.
  - Established ethical guidelines for publication of results.
  - Introduced "best current" standard for diagnosis and treatment in clinical studies.

The Scandinavian Declaration

- **Criticism and Adoption:**
  - Criticism from European Medical Research Councils and the American Medical Association.
  - Issues with overemphasis on individual interests and impractical journal restrictions.
  - Decline in adoption by national medical associations due to higher ethical standards.
  - By 1979, only 24 international associations adopted the new version (down from 33 for the 1964 version).
  - American Medical Association disregarded the 1975 DoH.

The Review of the Century

- **1996:**
  - During AIDS epidemic, DoH clarified stance on placebo-controlled studies, alloweing placebo use in trials without proven methods,
  - WMA's ethics committee received a proposal from AMA for a comprehensive DoH review.
- **1997:**
  - AMA's draft sent to national medical associations for feedback without consensus.
  - The draft proposed abolishing distinction between therapeutic and non-therapeutic research.
  - Ethical double standards debate, especially over Zidovudine studies in low-income African countries.
- **1998:**
  - Prof. R. J. Levine (Yale University) led UNAIDS working group for HIV research guidelines.
  - Levine questioned DoH's validity on placebo use at UNAIDS meeting.
  - WMA President invited Levine to join DoH revision.

The Review of the Century

- **March 1999:**
  - Levine's draft proposed abolishing distinction between therapeutic and non-therapeutic research.
  - Aligned control arm with local medication availability and accepted placebos if scientifically justified and without severe participant harm
  - Draft criticized for flexible ethics standards (e.g., by Public Citizen).
- **1999:**
  - WMA formed a new committee, The "three wise women" to finalize the review, leading to the 2000 DoH version adoption in Edinburgh, Scotland.
- **2000 DoH Version:**
  - Maintained distinction between therapeutic and non-therapeutic research.
  - Placebos deemed ethical only without proven intervention.
  - Introduced guarantee of best intervention access post-study, sparking controversy.
- **Historical Impact:** Increased ethical requirements led to decreased adherence.

The Battle of Declaration of Helsinki (2001 – 2008)

2000 DoH Implementation:

- FDA chose not to adhere to the 2000 DoH.
- New Ethical Guidelines with with points diverging from the DoH
  US National Bioethics Advisory Commission guidelines (2001).
  UK's Nuffield Council on Bioethics guidelines (2002).
  CIOMS guidelines revised in 2002.

Clarification notes:

2002: Flexible provisions for placebo use introduced.

2004: Emphasized need for post-trial access.

- **2007 Formation of a committee with involvement from national medical organizations and stakeholders.**
- **2008** Resistance on placebo use, but **revised version adopted in Seoul**.

The Battle of Declaration of Helsinki (2001 – 2008)

2008 DoH Revision:

- Mandatory registration of clinical trials in a public database

- Big Pharma concerned about patent impact.

- Post-study access and placebo issues remained controversial.

Global Responses:

- US FDA abolished adherence to DoH for overseas research.
- Brazil's National Research Ethics Commission adopted 2000 DoH for stronger guidelines.

Formation of the Workgroup on Placebo in Clinical Trials.

2013

The Golden Jubilee Review

On its 50th anniversary in Fortaleza, Brazil, in October 2013, the DoH endorsed the removal of distinctions between therapeutic and non-therapeutic research.

It marked a decrease in protection for these patients' participants, leading to the development of two separate medical ethics:

- one for medical research (DoH), and
- another for medical care (Declaration of Geneva - The Physician's Oath).

In therapeutic research, participants are patients requiring treatment for existing medical conditions, necessitating additional ethical considerations, including the obligation to provide ancillary care and continue PTA to demonstrably effective therapeutic agents.

The Diamond DoH Anniversary

60th Anniversary (2024):

- Revision started in April 2022 to address current medical research challenges
- Led by American Medical Association with 12 national associations.
- Planned seven regional meetings (2022-2024).
- Two three-week public feedback periods.
- Increased regional participation and diversity of attendees.

Emphases on Social Value Highlighted as a goal of medical research

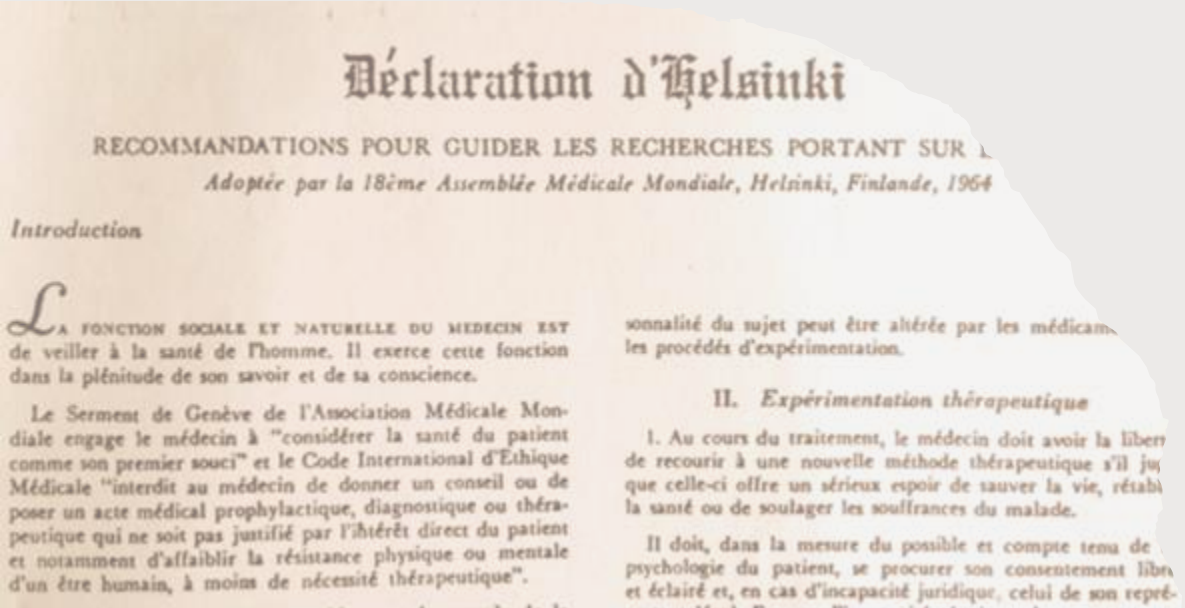
- If compliance with the principle of social value is maintained, a tendency toward researching "me too" drugs and conducting studies in resource-poor countries where the resulting treatments often remain inaccessible to the local population will be curtailed.

Considering the ongoing revision process, it is important to revisit and emphasize the thoughts and appeals related to the DoH made by a notable Latin American personality

The Pope Francis

- Advocated for solidarity and universal fraternity in medicine.
- Criticized economic interests overshadowing patient welfare in clinical research.
- Highlighted challenges and injustices in clinical research in LMICs.
- Emphasized equitable distribution of risks and benefits between poor and rich nations.
- Condemned the instrumentalization of individuals in science.
- Called for placing the sick person at the center of medical ethics, especially in medical research.

Final Considerations



Déclaration d'Helsinki

RECOMMANDATIONS POUR GUIDER LES RECHERCHES PORTANT SUR

Adoptée par la 18ème Assemblée Médicale Mondiale, Helsinki, Finlande, 1964

Introduction

LA FONCTION SOCIALE ET NATURELLE DU MEDECIN EST de veiller à la santé de l'homme. Il exerce cette fonction dans la plénitude de son savoir et de sa conscience.

Le Serment de Genève de l'Association Médicale Mondiale engage le médecin à "considérer la santé du patient comme son premier souci" et le Code International d'Ethique Médicale "interdit au médecin de donner un conseil ou de poser un acte médical prophylactique, diagnostique ou thérapeutique qui ne soit pas justifié par l'intérêt direct du patient et notamment d'affaiblir la résistance physique ou mentale d'un être humain, à moins de nécessité thérapeutique".

sonnalité du sujet peut être altérée par les médicam
les procédés d'expérimentation.

II. *Expérimentation thérapeutique*

1. Au cours du traitement, le médecin doit avoir la liber
de recourir à une nouvelle méthode thérapeutique s'il ju
que celle-ci offre un sérieux espoir de sauver la vie, rétabl
la santé ou de soulager les souffrances du malade.

Il doit, dans la mesure du possible et compte tenu de
psychologie du patient, se procurer son consentement libr
et éclairé et, en cas d'incapacité juridique, celui de son repré-

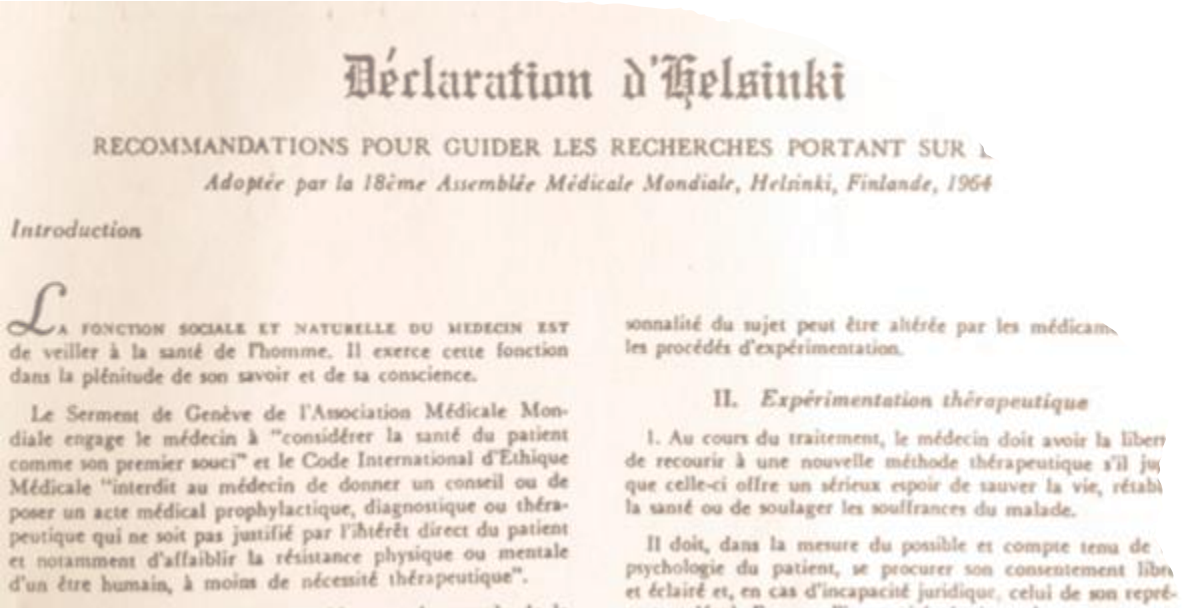
Some lessons can be learned from the history of the DoH

- Historical lack of consensus among global associations is a long-standing issue.
- The goal of revision processes has been to achieve a minimal ethical consensus, a lowest common denominator, rather than the highest ethical standard.
- Historically, there has been limited participation from Global South countries, a trend that continues when discussions are conducted solely in English rather than in other predominant languages.
- The American Medical Association has historically influenced the DoH, often accommodating its interests in research ethics and generally lowering ethical standards.
- It is essential for the WMA to include doctors without conflicts of interest with pharmaceutical companies in the revision process and more female participants.

Challenges in Expanding Participation

- Ongoing challenges include expanding participation of the Global South, including listening to them in the languages of their countries, and involving research participants directly in the revision process.

Final Considerations



Déclaration d'Helsinki

RECOMMANDATIONS POUR GUIDER LES RECHERCHES PORTANT SUR

Adoptée par la 18ème Assemblée Médicale Mondiale, Helsinki, Finlande, 1964

Introduction

LA FONCTION SOCIALE ET NATURELLE DU MEDECIN EST de veiller à la santé de l'homme. Il exerce cette fonction dans la plénitude de son savoir et de sa conscience.

Le Serment de Genève de l'Association Médicale Mondiale engage le médecin à "considérer la santé du patient comme son premier souci" et le Code International d'Ethique Médicale "interdit au médecin de donner un conseil ou de poser un acte médical prophylactique, diagnostique ou thérapeutique qui ne soit pas justifié par l'intérêt direct du patient et notamment d'affaiblir la résistance physique ou mentale d'un être humain, à moins de nécessité thérapeutique".

sonnalité du sujet peut être altérée par les médicam
les procédés d'expérimentation.

II. *Expérimentation thérapeutique*

1. Au cours du traitement, le médecin doit avoir la liber
de recourir à une nouvelle méthode thérapeutique s'il ju
que celle-ci offre un sérieux espoir de sauver la vie, rétabl
la santé ou de soulager les souffrances du malade.

Il doit, dans la mesure du possible et compte tenu de
psychologie du patient, se procurer son consentement libr
et éclairé et, en cas d'incapacité juridique, celui de son repré-

It is important to advocate for maintaining in the DoH the **"social value"** criteria in medical research and to condemn the exploitation of the bodies of the poor, especially in Global South countries. Frequently, these communities contribute to pharmaceutical research but lack access to the resulting medical treatments.

Finally, the differentiation between therapeutic and non-therapeutic research ethics is essential for ensuring that participants' rights, safety, and well-being are adequately and fairly protected.

Thank you!

Obrigado!　ありがとう！　Dankie!

fernando.hellmann@ufsc.br