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The 2024 Declaration of Helsinki:
Taking Forward Bioethics and Human Rights

Organizer/supporting organization
The Brazilian Society of Bioethics (SBB); The Japan Association for Bioethics (JAB); International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP); Clinical Evaluation. inc.; Clinical Research Risk Management Study Group

Ethics of placebo-controlled trials and post-trial access

international health research as a stepping-stone to universal public health care access

Dirceu B. Greco, MD, PhD
Federal University of Minas Gerais
Belo Horizonte, Brazil

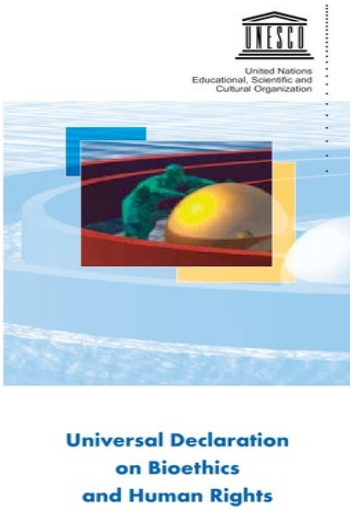
I declare no current or potential conflict of interest in relation to this presentation.

UFMG

Ethics of placebo use and post-trial access

Unesco 2005
CIOMS 2016
UNAIDS/WHO 2007
DoH -2000 to 2013
CONEP (Brazil) 2012

2005 UNESCO Universal Declaration on Bioethics and Human Rights



Article 15 Sharing of benefits

Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries.

...Benefits may take any of the following forms:

(a) special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research;

(b) access to quality health care;

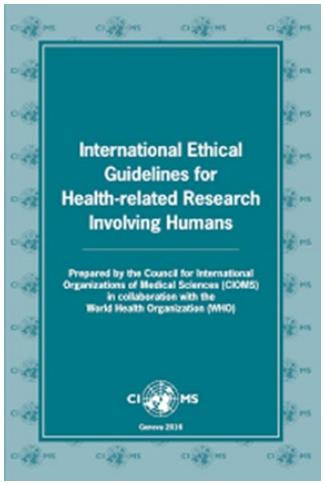
(c) **provision of new diagnostic and therapeutic modalities or products stemming from research** (emphasis added);

(d) support for health services;

(e) access to scientific and technological knowledge;

(f) capacity-building facilities for research purposes;

(g) other forms of benefit consistent with the principles set out in this Declaration



CIOMS 2016 - Guideline 6:
CARING FOR PARTICIPANTS' HEALTH NEEDS

2002 - Guideline 21

Ethical obligation of external sponsors to provide health-care services

Addressing participants' health needs requires at least that researchers and sponsors make plans for:

.How care will be adequately provided for the condition under study;

.How care will be provided during the research when researchers discover conditions other than those under study ("ancillary care");

.Transitioning participants who continue to need care or preventive measures after the research to appropriate health services;

.Providing continued access to study interventions that have demonstrated significant benefit; and

.Consulting with other relevant stakeholders, if any, to determine everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has demonstrated significant benefit in the study.

When access is provided after the research to investigational interventions that have demonstrated significant benefit, the provision may end as soon as the study intervention is made available through the local public health-care system or after a predetermined period of time that the sponsors, researchers and community members have agreed before the start of a trial.

Information on care for participants' health needs during and after the research must be included in the informed consent process

Commentary on Guideline 6

- **General Considerations**:

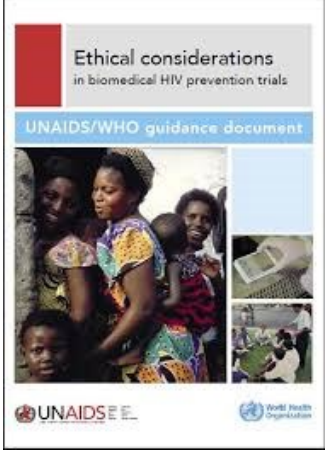
….. In some cases, participants may continue to need the care or prevention provided during the research after (the end of the study).

This may include access to an investigational intervention that has demonstrated significant benefit. In all these situations, researchers and sponsors **must show care and concern** for the health and welfare of study participants. **This is justified by the principle of beneficence, which requires researchers and sponsors to safeguard the health of participants when it is in their power to do so.**

It is also supported by the principle of reciprocity; participants assist researchers in generating valuable data and, in return, researchers should ensure that participants receive needed care or preventive measures to safeguard their health.

Importantly, the obligation to care for participants' health needs is not limited to research in countries with limited resources (see Guideline 2 – Research conducted in low-resource settings) but is a universal ethical requirement in research.

Furthermore, even though the provision of care during and after the trial may be an incentive for people in low-resource settings to enroll, **it should not be considered an undue influence.**



UNAIDS/WHO guidance document 2007 Ethical considerations in biomedical HIV prevention trials

Guidance Point 14 - Care and treatment
Participants who acquire HIV infection during the conduct of a biomedical HIV prevention trial should be provided access to treatment regimens from among those internationally recognized as optimal.

Commentary on G 14

- There is **consensus that sponsors need to ensure access to internationally recognized optimal care and treatment regimens, including antiretroviral therapy,** for participants who become HIV infected during the course of the trial.

- There is also agreement that prevention trials ought to contribute constructively to the development of HIV service provision in countries participating in biomedical HIV prevention research, **for the sustainable provision of care and treatment** after the completion of a trial.

Declaration of Helsinki

WMA General Assembly

Seoul, 18 October 2008, Fortaleza 2013

Post-trial access

Brazilian Medical Association and Brazilian Medical Council proposal* (defeated at the GA 2008)

Every patient entered into the study must be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

same as in DoH 2000

2013 Version

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

2024 WG Draft

Post-Trial Provisions

34. In advance of a clinical trial, post-trial provisions **must be arranged by sponsors and researchers to be provided by themselves, healthcare systems, or host country governments for all participants** who still need an intervention identified as safe and effective in the trial. **Exceptions to this requirement must be approved by a research ethics committee**. Specific information about post-trial provisions must be disclosed to participants during informed consent.

Declaration of Helsinki
WMA General Assembly
Seoul, 18 October 2008, Fortaleza 2013
Use of Placebo

Brazilian Medical Association & Brazilian Medical Council proposal (defeated at the GA 2008)*

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

- The use of placebo, or no treatment, is acceptable in studies where no proven method exists;

**same as in DoH 2000*

2013 Version

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

.Where no proven intervention exists, the use of placebo, or no intervention, is acceptable;

or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

2024 WG Draft

33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
If no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

If for compelling and scientifically sound methodological reasons the use of any intervention other than the best proven one(s), the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the participants who receive any intervention other than the best proven one(s), placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
Extreme care must be taken to avoid abuse of this option.

A CASE STUDY

Brazil's response to these pressures

Brazilian Research Ethics Commission
Resolution 466/2012*
Placebo and Post trial access

III.2 – Research involving human beings in any area of knowledge must:

ensure to the participants adequate conditions of follow up, treatment, access to new drugs (if shown to be safe and effective)

III.3 - In biomedical research:

b) when using placebo, such use shall be fully justified as to its non maleficence and methodology requirements, where the benefits, risks, difficulties and effectiveness of a new therapeutic method shall be tested, **comparing it to the best current prophylactic, diagnostic and therapeutic methods**. It is not included the use of placebo or any other treatment to studies where there are no proven methods of prophylaxis, diagnosis or treatment; **

d) At the end of the study the sponsors must ensure to all participants, access, free of charge and for all needed time, to the best prophylactic, diagnostic and treatment that have demonstrated to be efficacious

d.1) Access will also be warranted between the end of individual participation and the end of the study. In this specific situation access will be permitted through a study extension, according to a consubstantiated analysis of the participant's attending physician.

* ***Succeeded Resolution 404/2008 (1 August 2008), which also included:***
To propose further discussion on access to health and to the products that have showed efficacy to all who need them.

**** Brazilian Medical Council Code of Medical Ethics - Physicians are forbidden to have any participation in clinical trials where placebo is used as a control when there are efficacious and effective drugs for the disease on trial.**

Ethics of placebo-controlled trials and post-trial access DoH 2024

How the proposed draft of 2024 DoH addresses these issues?

Does it follow Highest Standards? (deontology, human rights)

Placebo: risk minimization (At least consistent with with Para 8; CIOMS 2016)
Post-trial access for all who need

Or does it focus on Minimum Requirements? (utilitarian, pragmactic)

Placebo: accepted if there is no increase of risk of serious or irreversible harm (DoH, ICH-E9)
Post-trial access: "it must be arranged by sponsors and researchers to be provided by themselves, healthcare systems, or host country governments"

Kurihara C, Greco D, Dhai A, Saio T, Tsubaki H. Ethics of placebo-controlled trials: historical analysis including experiences during the COVID-19 pandemic.
Kurihara C, Greco D, Dhai A. Post-trial access: historical analysis considering the experience of COVID-19 pandemic. *Ethical innovation for global health: pandemic, democracy and ethics in research*. Springer; 2023.

Modified from Chieko Kurihara

Established key concepts missing in DoH proposed draft comparing to other documents

Protection items	DoH	CIOMS *1	Patient group	CONEP Brazil	IFAPP*2	GL Japan	GCP (R3)
Social value	—	◎	◎	◎	○	◎	—
Community Engagement/Patient Public Involvement	△incomprehensible	◎	◎	○	◎	—	◎
Benefit Sharing	—	◎	◎	◎	○	—	—
Avoid Discrimination/Stigmatization (risk to target group)	—	◎	◎	◎	—	○	—
Consider Future Generations/Sustainability	—	—	◎	--	—	—	—
Inclusiveness for vulnerable people	—	◎	○	○	◎	◎	—
Right to know/not to know the result (including incidental findings up to the status of information)	— (△)	◎	◎	△	◎	◎	—
Broad informed consent/dynamic consent	—	◎*1	◎	○	◎	○	—
Fairness of REC/Patient Public Involvement(democracy)	—	◎	◎	○	◎	○	○
Best proven/risk minimization in comparative arms	—	○	◎	◎	◎	—	—
Post-trial access for participant (informed consent form), community (for those most in need globally)	△	○	◎	◎	◎	△	—

◎Strongly argued ○medium △weak or not explicit

*1: "Dynamic consent" is not in health research guidelines but in Report XI for patient engagement.
*2: Not official opinions of IFAPP, but of some members of IFAPP.

Modified from Chieko Kurihara

Norberto Bobbio
in *Fundamentals of Humans Rights*, 1964

- **“..the gravest problem of our times, in relation to the human rights, is not any more to set its foundations but to protect them.”**

..人権に関する現代の最も重大な問題は、その基盤を設定することではなく、それらを保護することです。

Conclusions

Time to globalize ethical principles
Conclusions 1

- Research with human subjects **must be scientific sound and have social value.** Clinical trials with these objectives can be performed where vulnerability is low;
- International ethical guidelines are necessary – Their principles **should be harmonized and approved by a world representative institution (such as UN WHO UNESCO);**
- In clinical trials, **access to best proven preventive, diagnostic and therapeutic must be provided, without double standards**.
- Participants have the **right to post-trial access** to a drug, vaccine or procedure that shows to be safe and effective
- **Placebo** can be used when there is no known comparator
- **If ethical standards are lowered it will certainly be difficult to eventually raise them;**
- **All researchers,** both from developed and developing countries, should participate in all stages of the study, from protocol development to the application of the results**.**
- **Participant's representatives should also participate**

In Public Health
Conclusions II

1. The discussion on access to care & treatment in research is outdated and the debates on participants rights to post trial access must be substituted with an objective of providing access to all efficacious products of research in public health.

2. Universal access to current established and future research products must be internationally sanctioned through international covenants and resolutions issued by the United Nations. **The *status quo* of inequality must not be an immutable fact, and we must fight for universal access to health,** which is recognized as a human right and not as an economic commodity.

3. And last but not least, we must be prepared for upcoming ethical challenges and to provide guidance for the expected difficult decisions related to new pandemics and to technological progress (Risks, inequalities, access, costs, AI)

Three examples of access in public health

2005 UNESCO
Universal Declaration on Bioethics and Human Rights

General provisions

Article 14 – Social responsibility and health

1. The promotion of health and social development for their people is a central purpose of governments that all sectors of society share.
2. Taking into account that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition,

progress in science and technology should advance:
(a) access to quality health care and essential medicines, especially for the health of women and children, because health is essential to life itself and must be considered to be a social and human good;

WHO 2010
Guidance on ethics of TB prevention, care and control
Access to care for all

Considerations are particularly important in designing an ethical research strategy.

- Research should be designed so that the populations in which it is carried out stand to benefit from the results.
- Research results should lead to **technology transfer**, whenever applicable, for the benefit of the affected population.
- Research protocols should provide attention **to how findings will be translated into public health policy, as applicable.**

Brazilian Constitution

Article 196.Health is a right of all and a duty of the State and shall be guaranteed by means of social and economic policies aimed at reducing the risk of illness and other hazards and at the universal and equal access to actions and serv ices for its promotion, protection and recovery.

I conclude with one quotation

- **Thucydites wrote* that: Justice will come only when those who are not subjected to injustice are as indignant as those who are.**

"Empowerment

I would argue that:

Justice will prevail when those affected and indignant by injustice are able to fight for their rights.

Emancipation

Peloponesian wars

Thank you

ありがとうございました

Muito obrigado

Dirceu Greco
dirceugreco@gmail.com