2.9 Prof. Dirceu Greco, Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil; Member of 2016 revision of the CIOMS Guidelines, WMA Associate member

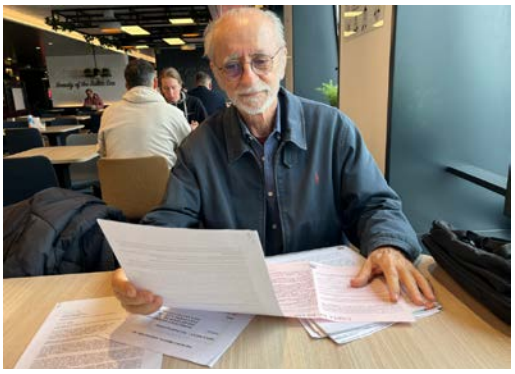
Interview: Kurihara C, Matsuyama K, Baroutsou V

①Placebo-controlled trials and post-trial access

Prof. Dirceu Greco, a member of the CIOMS 2016 Working Group, initially gave a brief history of the DoH: The 1964 DoH was a proposal aimed at doctors for ethical regulation in research. The 2000 version set the highest ethical standards, but notes of clarification were added in 2002 and 2004 for the paragraphs of placebo-controlled trials and post-trial access, respectively, and these notes were included in the main text in 2008. Then these texts were slightly modified in 2013 and 2024. The changes included meant a regression in ethical standards.

The controversy over placebo-controlled trials and the right to post-trial access dates back to 1994, when methods for preventing mother-to-child transmission of HIV/AIDS were already scientifically established. In the implementation of 15 ethically questionable clinical trials in developing countries, with the aim of evaluating the efficacy of less expensive regimens, placebo was used in the control group. These clinical trials were vehemently criticized by Peter Lurie and Sydney Wolf in their paper[1], and an editorial by Marcia Angel[2] supported Lurie and Wolf, both published in the *NEJM* in 1997. These publications gave rise to fierce debates and this was reflected in WMA and in the revision of the DoH.

In the 2000 GA in Edinburgh the approved version maintained the 1996 principles, which were based on principles already clarified in 1975, to allow a placebo control only when there was no proven treatment. And also, the principle of guaranteeing access to products that have shown to be safe and effective for the participants who still need them after the completion of the trial was included for the first time in the 2000 version.



Left: Prof. Greco and Chieko Kurihara, at the place of the hotel Scandic Grand Helsinki, where the second web meeting to agree on the Helsinki Statement, midnight of October 20, 2024. Photo was taken later. Baroutsou and Matsuyama also participated at the venue of Helsinki.
Right: Prof. Greco explaining brief history shortly after the 2000 revision of the DoH, showing related documents.

[1] Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *N Engl J Med*. 1997 Sep 18;337(12):853-6. doi: 10.1056/NEJM199709183371212.
[2] Angell M. The ethics of clinical research in the third world. *N Engl J Med*. 1997;337:847–9.

②The history leading to the 2016 edition of the CIOMS guidelines

Shortly after the adoption of this revision in October 2000, questions were raised, mainly by the US FDA and the pharmaceutical industry, arguing that the principles of placebo and post-trial access would not respond to the needs of science and, according to them, would make it difficult to implement many clinical trials. Then in March 2001 a conference was held in Pretoria, South Africa, by the WMA and relevant stakeholders, where the pros and cons of these paragraphs were debated[3]. Prof. Greco was one of the speakers, with the participation of well-known researchers and ethicists. Subsequently, a small subgroup was created by the WMA to discuss these paragraphs and as a result, clarification notes were issued, in 2002 for placebo and in 2004 for post-trial access, which reversed the 2000 principles. In the subgroup that discussed the 2004 note Dirceu Greco and Otmar Kloiber (who at the time represented the German Medical Association) were included. The minutes of the public consultation show that Chieko Kurihara and Ruth Macklin defended the same position as Dirceu Greco, which is the right to post-trial access. Macklin later joined with Greco in advocating for the protection and promotion of human rights in the Working Group for the 2016 CIOMS ethical guidelines.

The 2002 CIOMS guidelines adopted language similar to the current DoH regarding acceptable risk for placebo-controlled trials when there is a proven intervention (without increase of risk of serious or irreversible harm), but in the 2016 revision, this was substantially changed to "*minor increase above minimal risk*". There was a lot of discussion among the working group participants. Prof. Greco with Prof. Macklin advocated for this change. In fact, Prof. Greco's original position was that even "minor increase above minimal risk" is not acceptable, i.e., placebo-controlled trials are not acceptable when there is a proven intervention. This is also the basic stance of Latin American countries.

③Responses of Brazil and Latin American countries

Brazil brought the 2000 DoH principles into a national legislation in 2008[4]. This was decided shortly before the 2008 revision of the DoH, which incorporated the 2002 and 2004 notes of clarification into the main text. Other Latin American countries build consensus on a position similar to that of Brazil, in the form of statements by CONFEMEL (Confederación Médica Latinoamericana y del Caribe), an association of medical organizations in Ibero-America and the Caribbean, which represents around 500,000 doctors grouped in national associations)[5] and in international declarations from the federation of research institutions. For this reason, placebo-controlled trials, when there is a proven intervention, cannot be conducted in Brazil or Uruguay.

Where, then, do these placebo-controlled trials go in the world? If such trials, as some today claim, are no longer carried out anywhere, this is another reason for the WMA to return to the terms of the 2000 version, which is also consistent with its core principle that states that the purpose of the research never precedes the right of participant.

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[3] Pérez, A.C., Smith, R.N. The revised *Declaration of Helsinki*: interpreting and implementing ethical principles in biomedical research. *International Journal of Pharmaceutical Medicine. 2001; 15:* 131-43. https://doi.org/10.2165/00124363-200106000-00006

[4] Brazilian Research Ethics Commission Resolution 466/2012, which succeeded Resolution 404/2008.

[5] CONFEMEL. Intervención de la Dra. Zaida Arteta en la Asamblea General de la AMM. 16 octubre, 2024. https://www.confemel.com/intervencion-de-la-dra-zaida-arteta-en-la-asamblea-general-de-la-amm/

④Double standard

In fact, there were still cases of placebo-controlled trials in Vietnam even after effective vaccines against COVID-19 were developed, and other similar cases were reported[6]. Prof. Greco's position is that, especially to avoid exploitative studies carried out by big pharmaceutical companies, such as placebo-controlled trials in less-regulated, resource-limited countries when proven interventions exist, the DoH principles should return to the 2000 version.

In the current DoH the risks that may result from assignment to the placebo arm, which is much greater than in the 2016 CIOMS guidelines, i.e. prolonged pain and suffering, which is not serious or irreversible, can be left to the assessment of the research ethics committee or the individual participant.

But who would participate in a placebo-controlled trial that could increase the risk of long-lasting pain and suffering when an effective treatment exists?

They would be those who cannot access effective interventions without entering a clinical trial, particularly those who cannot adequate insurance coverage in the United States or those in areas without access to treatments that have been shown to be effective.

The WMA's position would be contrary to the "double standard". However, removing barriers to conducting placebo-controlled trials where there is a proven intervention characterizes a double standard, meaning that what is stated in the DoH (best proven) is different from what is stated in another item (no additional risks of serious or irreversible harm) actually allowing local standard.

The WMA's position is clear: "best proven" does NOT mean "best-proven intervention available in the region". Rather, WMA's position is "best proven intervention in the world". This was clearly sated by Dr. Jack Resneck, during the regional meeting of WMA in Sao Paulo, and also by Dr. Otmar Kloiber, WMA Secretary General[7].

[6] Kurihara C, Greco D, Dhai A, Matsuyama K, Baroutsou V. Vulnerability, social value and the equitable sharing of benefits from research: beyond the placebo and access debates. *Front. Med.* 2024; 11:1432267. doi: 10.3389/fmed.2024.1432267

[7] Kloiber O, Greco D, Watanabe H, Imamura K, Yamamoto Y, Matsuyama K, Saio T, Kurihara C. International collaborative research and new trends of research ethics: Follow-up session. *Clin Eval.* 2020 ; 48(1): 233-65.