Editorial:
Pandemic and research ethics
– Democracy, placebo, and post-trial access

This issue of the journal "*Clinical Evaluation*" features the proceedings of a two-day international webinar entitled "Pandemic and research ethics－Democracy, placebo, and post-trial access" co-organized by COVID-19 Task Force of the Japan Association for Bioethics and the Brazilian Society of Bioethics, held in June 2021. By then, a number of COVID-19 prophylactic vaccines had acquired emergency use authorizations (EUAs) and vaccination programs had been promoted worldwide. In this situation, we still need clinical trials because long-term efficacy and safety of these vaccines, or prophylactic effects of these or other candidate vaccines against variants have not yet been fully proven. Can we still justify placebo-controlled trials when we have vaccines with compelling scientific reasons? What are the principles to ensure fair access for participants enrolled in clinical trials, as well as those who most require the benefits from products developed to overcome this pandemic? We believe that revisiting the Declaration of Helsinki must be a driving force. It was a historic conference that brought together world-renowned experts with deep insights into these topics.

The World Medical Association (WMA) adopted the Declaration of Helsinki in 1964, and has been revised nine times until the 2013 version. During the 1990s, the HIV/AIDS pandemic raised international debates about the principles in the Declaration related to "placebo-controlled trials" and "post-trial access". The ethical principles to justify placebo-controlled trial when there is some proven intervention and the right of study participants to obtain access to proven interventions at the completion of the study were set forth in 1996 and 2000, respectively, in the Declaration. Although the 2013 revision of the Declaration reached some consensus, different wording was adopted in the 2016 version of the CIOMS (Council for International Organizations of Medical Sciences) Guidelines for health-related research. With the COVID-19 pandemic still ongoing, this webinar was organized to revisit these two important principles.

Dirceu Greco, Professor Emeritus of Infectious Diseases and Bioethics, Federal University of Minas Gerais, and Chair of the Brazilian Society of Bioethics, has been provoking international debates, has published on these issues and defends the stringent Brazilian Research Ethics Resolution related to the limits of placebo use and the rights to post-trial access. Chieko Kurihara and Takeo Saio, members of the COVID-19 Task Force of the Japan Association for Bioethics, have been publishing interviews with leaders in the World Medical Association, officials of the United States Food and Drug Administration, and others exploring the revision of the Declaration of Helsinki, and carried out case studies on this topic in Japan.

With the participation of Ramin Parsa-Parsi, Workgroup Chair of the 2013 revision of the Declaration and Otmar Kloiber, Secretary General of the World Medical Association, we could hold essential discussions. The International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP) and its Japanese National Member, Japanese Association of Pharmaceutical Medicine (JAPhMed) provided non-monetary support. Kyoko Imamura, past-President of the IFAPP

played a key role as a moderator.

Kloiber has emphasized that we are in the same storm but not in the same boat, and we need to address and effort for fundamental change of global, ongoing inequity. He critically discussed about the prevailing idea of existing business and trade and stated that "if we don't all engage, it will not change."

Parsa-Parsi stated that the next revision process of the Declaration of Helsinki will be undertaken in near future, although it has not been decided yet, and also promised that he will forward this feedback to the WMA Medical Ethics Committee for consideration as he took a lot of good thoughts from the discussion.

As if to symbolize the change of attitude of pharmaceutical companies in the 21st century, participants from the IFAPP expressed strong support for the ideas discussed in this webinar. Kurihara wrote a short report in the newsletter of IFAPP (IFAPP Today, No. 16). Its Japanese translation is included in this journal issue. One of the lay experts who participate in the patient public involvement activities organized by Imamura contributed her impression to IFAPP Today.

The most important points clarified through the discussion are as follows:

- **It is ethically unacceptable to conduct a placebo-controlled trial on the population with limited access to a proven intervention on the basis that this intervention is not available for them in their health system.**
- **Post-trial access provision is not only required to be disclosed for the study participants as a future plan, but must be assured for the host community of the trial, and then should be assured to those who need it most in the world.**

In addition to the discussions mentioned above, critically important perspectives were raised by each speaker and commentator, as outlined below.

● Day 1: Discussion focusing on placebo-controlled trials

Kurihara criticized the Japanese government for pre-ordering "best proven" vaccines for the entire population without participating in placebo-controlled efficacy trials of the COVID-19 vaccines. She also criticized the WHO (World Health Organization) experts' view to allow placebo studies in the settings of limited access to effective vaccines. Both cases are against the principle of "justice". The United States' statement to support the proposal of TRIPS (Agreement on Trade-Related Aspects of Intellectual Property Rights) waiver on intellectual property rights of COVID-19 related products could provide the basis for ensuring post-trial access to those in need of it worldwide. Finally, she presented points to be revisited in the Declaration of Helsinki.

Ruth Macklin is an American bioethicist of eminence as well as a global advocate expressing disagreement with the double standard, which is the idea to permit ethically unacceptable studies in developed countries to be performed in resource-limited settings. Whereas the 2013 revision of the Declaration of Helsinki set a risk threshold to justify placebo-controlled studies in the presence of proven interventions, the 2016 revision of the CIOMS Guidelines narrowed this threshold in its revised wording. She participated in the working group for this revision, with Greco. She clearly stated in this webinar that the view of the above-mentioned WHO experts violates both the Declaration of Helsinki and the CIOMS Guidelines.

Peter Lurie is an American physician leading a consumer advocacy group, who ignited international controversy over the placebo-controlled HIV perinatal transmission prevention studies in 1997. In this webinar, he presented a comparative analysis of COVID-19 vaccine trial ethics, comparing them to two historically important cases of ethically questionable placebo-controlled trials planned or conducted in developing countries even after effective interventions were available in developed countries. He presented some challenges to the design of future clinical trials of COVID-19 vaccines from ethical and scientific perspectives.

Ulf Schmidt is a German medical historian, who has been engaged in studying the history of the process of establishment of the Declaration of Helsinki and has recently published a book entitled "*Ethical research: The Declaration of Helsinki, and the past, present and future of human experimentation*", to which some of this webinar's speakers contributed. He presented various social and political factors which influenced the Declaration and emphasized the importance of the fact that the Declaration has been widely recognized as an international agreement on research ethics.

● Day 2: Discussion focusing on post-trial access

Ames Dhai, South African physician-bioethicist, has been co-Vice Chair with Greco of the UNESCO International Bioethics Committee which issued statements on enhancing global cooperation to end the pandemic, and presented an African countries' joint strategy to ensure access to vaccines, as well as a proposal for TRIPS waiver from South Africa and India. Based on the recommendations of *Nature*, *Lancet*, and other journals, she demonstrated that COVID-19 related products should be regarded as "global public goods" and presented the international community's criticisms of "vaccine nationalism" in wealthy countries.

Tammam Aloudat is a clinician from Syria, who has been engaged in humanitarian activities in the settings where medical resources are critically scarce. He has also been engaged until recently in the MSF (Médecins Sans Frontières) Access Campaign. He expressed a disagreement with utilitarian ethics and criticized the global health regime oriented by wealthy countries, differently from alternative regime oriented by humanitarian initiatives. He also pointed out the inadequate preparedness for the next pandemic which may be an inevitable result of climate change. He warned the essential problem of inequality and disparity caused by capitalist-democratic societies.

Dirceu Greco presented case examples of Brazil to adopt highest ethical standards on the ethics of placebo-controlled trial and post-trial access, in line with the 2000 version of the Declaration of Helsinki. He also stressed the need for the "emancipation" of the most oppressed people for the reformation of existing situations.

● Statements from commentators

Francis P. Crawley of the Good Clinical Practice Alliance – Europe (GCPA) and the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) discussed the role ethics has played thus far in the COVID-19 pandemic. He discussed the promise of global solidarity, the challenges of scientific evidence, and the need for data sharing in international vaccine, therapeutic, and diagnostic research during the pandemic. He asked if ethics has had a significant role and whether bioethics had failed the global community during this global public health emergency.

Sandor Karepel-Fronius, a Hungarian professor of clinical pharmacology, and Chair of the Working

Group on Ethics of IFAPP (2014-21), emphasized the importance of the regulatory authority's ethical decisions affecting the majority of the population.

Rihito Kimura, a Japanese professor, a global pioneer of bioethics, praised this webinar as suggesting a new direction of bioethics, based on our determination not to repeat the vice of human experimentation during World War II.

The "facts" surrounding the COVID-19 pandemic are changing rapidly, every day, but the "truth" described in this webinar is unwavering. The Declaration of Helsinki is based on the professional norm of physicians first considering the health and well-being of "my patient" and acting in the patient's best interest, as stipulated in the "Declaration of Geneva" and "International Code of Medical Ethics" proclaimed immediately after the World War II. Thus, the Declaration of Helsinki gains worldwide trust as pursues "dual responsibility" -- a physician/researcher must prioritize both the rights and interests of individual research subjects and promote the goal of research to generate new knowledge, as defined in the principle described in its paragraph eight.

While adhering to this principle, we must further explore and develop the principles of research ethics, especially revisiting "placebo use" and "post-trial provision". Such deliberation would be the basis of an alternative business model of research and development, overcoming the threat of new disasters, stressing that health is not an economic commodity but truly a right for all. We hope this publication spurs collaboration between participants of this webinar and readers of the proceedings.

Chieko Kurihara, Takeo Saio
Organizers, COVID-19 Task Force, Japan Association for Bioethics
Kyoko Imamura
Moderator, Past President of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP) and former President of the Japanese Association of Pharmaceutical Medicine (JAPhMed)
Dirceu Greco
Organizer, Chair of the Brazilian Society of Bioethics (2019-2021)
Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil

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Selected bibliography in *Clinical Evaluation*

Related information not cited in the proceedings

- Discussions and interviews with persons with important commitment to the 2000 revision and following note of clarifications of the World Medical Association (WMA)'s Declaration of Helsinki (DoH): Robert J. Levine, who led several working groups of international documents including the DoH; Peter Lurie, who ignited international debates; Stephan W. Lagakos, Harvard biostatistician, Delon Human, Secretary General in 2000 of the WMA, Eitaka Tsuboi, President in 2000 of the WMA. *Partially available in English*:
  http://cont.o.oo7.jp/26_3/p341-80.pdf (*Only in Japanese*)
  http://cont.o.oo7.jp/28_3/p409-22/report.html
  http://cont.o.oo7.jp/29_23/p307-13.pdf
  http://cont.o.oo7.jp/30_1/p99-107.pdf
- Interview with Otmar Kloiber, Secretary General of the WMA, on the 2013 revision of the DoH and related ethical issues.
  http://cont.o.oo7.jp/41_2/p351-72eng.pdf
- Report on the WMA Expert Conference in Tokyo for the 2013 revision of the DoH.
  http://cont.o.oo7.jp/41_2/p337-49eng.pdf
- Interview with Robert Temple, U.S. Food and Drug Administration on the 2013 revision of the DoH.
  http://cont.o.oo7.jp/42_2/p539-51eng.pdf
- Interviews and a report on WMA Taipei Declaration on health database and biobanks, complementing the DoH.
  http://cont.o.oo7.jp/46_1/46_1contents_e.html

Proceedings and video-recorded version of this Part 3 and the previous Part 1 of series of webinars entitled "COVID-19 and Bioethics"

- Part 1 was lecture by Dirceu Greco to introduce the Recommendation No. 01/2020 of the Brazilian Society on resource allocation in COVID-19 pandemic.
  http://cont.o.oo7.jp/sympo/covidandbioethics.html
  (Part 2 and Part 4 were Japanese versions to introduce the discussions in Part 1 and 3.)

Important references by supporting organization, IFAPP *

- IFAPP Today, a short report of this webinar
  https://ifapp.org/static/uploads/2021/07/IFAPP-TODAY-16-2021.pdf
- IFAPP Working Group on Ethics to propose linking DoH and Taipei Declaration
  https://www.frontiersin.org/articles/10.3389/fphar.2020.579714/full

* IFAPP: International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine