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臨床評価

Clinical Evaluation Vol. 49, Suppl XXXVIII 2021

COVID-19 and bioethics Part 3: Pandemic and research ethics – Democracy, placebo and post-trial access

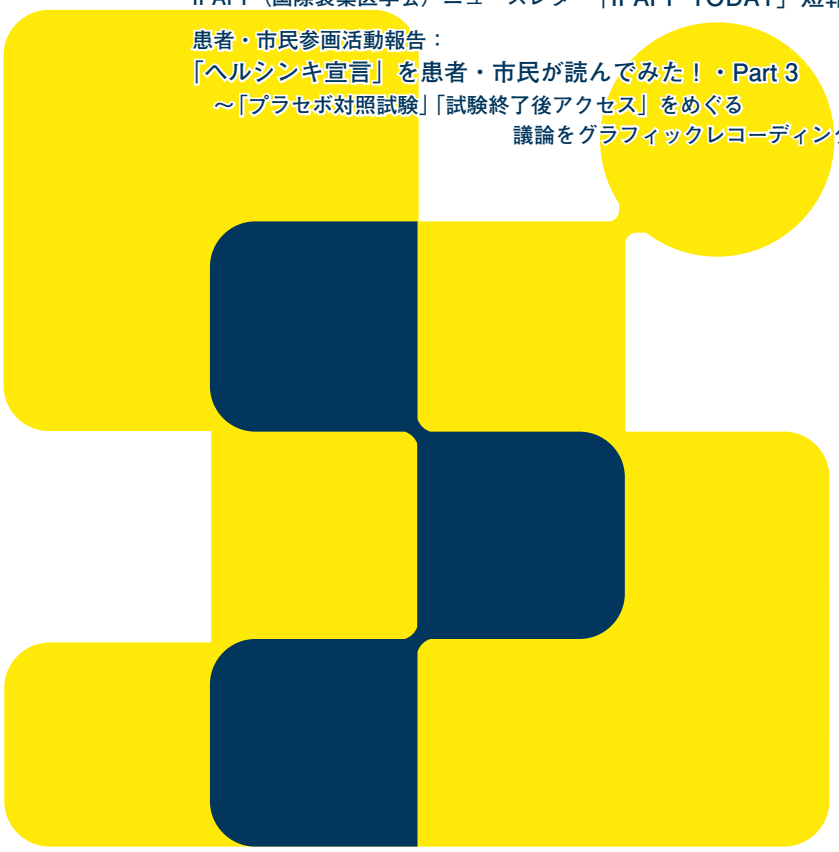
Japanese translation of a short report in IFAPP Today

A group of Patient Public Involvement (PPI) shared their feelings after reading "DECLARATION OF HELSINKI": Part 3
Graphic Recording of the discussion on placebo-controlled trial and post-trial access

COVID-19と生命倫理 Part 3：
パンデミックと研究倫理 ― 民主主義，プラセボ，試験終了後アクセス

IFAPP（国際製薬医学会）ニュースレター「IFAPP TODAY」短報翻訳

患者・市民参画活動報告：
「ヘルシンキ宣言」を患者・市民が読んでみた！・Part 3
～「プラセボ対照試験」「試験終了後アクセス」をめぐる
議論をグラフィックレコーディングする～



臨床評価刊行会

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Vol. 49, Suppl XXXVIII 2021

もくじ

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

(Published November 15, 2021)

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

Proceedings

COVID-19 and bioethics Part 3 : Pandemic and research ethics – Democracy, placebo and post-trial access*1

Lecturers: Day 1

Chieko Kurihara[1] Specially-appointed Professor, Kanagawa Dental University, Japan
Ruth Macklin Distinguished University Professor Emerita at Albert Einstein College of Medicine in New York City, the United States
Peter Lurie Center for Science in the Public Interest, Washington, DC, the United States
Ulf Schmidt Professor of Modern History, University of Hamburg, Germany

Lecturers: Day 2

Ames Dhai[2] Professor of Bioethics, University of the Witwatersrand, Johannesburg, South Africa
Tammam Aloudat Managing Director, Global Health Center, Graduate Institute of International Development Studies, Geneva, Switzerland
Dirceu Greco[3] Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil
Francis P. Crawley Executive Director of the Good Clinical Practice Alliance – Europe (GCPA) and Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), Leuven, Belgium

Special guests

Ramin Parsa-Parsi Workgroup Chair of the 2013 revision of the Declaration of Helsinki, World Medical Association; German Medical Association
Otmar Kloiber Secretary General, World Medical Association

Discussants

Rihito Kimura[4] Professor Emeritus of Bioethics, Waseda University, Japan
Sandor Kerpel-Fronius[5] Professor of Clinical Pharmacology, Semmelweis University, Hungary

Moderators

Takeo Saio[6] COVID-19 Task Force, Japan Association for Bioethics
Kyoko Imamura[7] 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)

Co-organized by the COVID-19 Task Force, Japan Association for Bioethics and the Brazilian Society of Bioethics
Supported by the Japanese Association of Pharmaceutical Medicine (JAPhMed) and the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)
Cooperation: Clinical Evaluation; Bioethics Policy Study Group; Pharmaceutical Study Group; Clinical Research Risk Management Study Group

(Friday, 4 and Friday, 11, June, 2021, Webinar by Zoom system)

*1 This is a record of the webinar, of which related information and video-recorded version is available at: http://cont.o.oo7.jp/sympo/covidandbioethics.html
Japanese translation is published in this journal issue: http://cont.o.oo7.jp/49sup38/49sup38contents.html

Abstract

In the 1990s, the HIV/AIDS pandemic raised substantial discussions of research ethics, mainly a long-lasting debate on placebo-controlled clinical trials and post-trial access after the establishment of safe and effective interventions. In 2019, some argued that this debate was outdated and that we should drive ourselves forward to a new trend of research ethics. Just at this occasion, the world was confronted with the COVID-19 pandemic. In this webinar we have discussed to explore what is the internationally agreed ethical standard on placebo-controlled clinical trial and post-trial access considering the COVID-19 situation.

The invited speakers and special guests who took historically critical roles in the above discussion made presentations and engaged in debate exploring and clarifying local and global situations. The discussion provided insights into (1) future direction for possible revisions of the paragraphs in the World Medical Association's Declaration of Helsinki on placebo use and post-trial access; and (2) emphasized need for global, collaborative efforts for structural reformation of the mechanisms of research and development to correct inequity and to achieve access to necessary medicines for all who need it.

Key words

The Declaration of Helsinki, COVID-19, human rights, global health, clinical trial, placebo, post-trial access

Rinsho Hyoka（*Clinical Evaluation*）. 2021；49 Suppl XXXVIII：9-109.［Epub ahead of the issue publication］

[1] COVID-19 Task Force, Japan Association for Bioethics; Working Group on Ethics, International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP); National Institutes for Quantum and Radiological Science and Technology

[2] Founder of the Steve Biko Centre for Bioethics, University of the Witwatersrand, Johannesburg, South Africa; Member and Vice-chair of International Bioethics Committee of United Nations Educational, Scientific and Cultural Organization (UNESCO) (2018-2021)

[3] Chair of the Brazilian Society for Bioethics (2019-2021); Member and Vice-chair of International Bioethics Committee of United Nations Educational, Scientific and Cultural Organization (UNESCO) (2018-2021)

[4] Faculty Affiliate, Kennedy Institute of Ethics, Georgetown University; Past President, Japan Association for Bioethics (2009-2012); President , Keisen University (2006-2012)

[5] Chair of the Working Group on Ethics of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP) (2014-2021)

[6] Department of Internal Medicine and Psychiatry, Fuji Toranomon Orthopedic Hospital

[7] Project Professor, Social Cooperation Program of IT Healthcare, The Graduate School of Pharmaceutical Sciences, The University of Tokyo; Japanese Institute for Public Engagement

COVID-19 and bioethics Part 3:
Pandemic and research ethics – Democracy, placebo and post-trial access

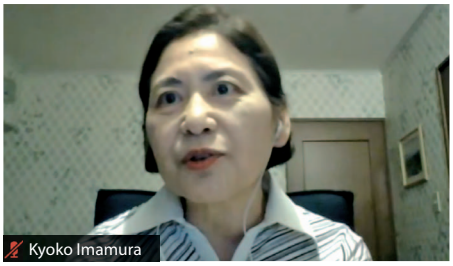
Agenda and participants

❖ Opening Remarks by organizers and moderators

Opening Remarks of the Day 1 (page 14) and Day 2 (page 61)

Takeo Saio, MD
COVID-19 Task Force, Japan Association for Bioethics
Department of Internal Medicine and Psychiatry, Fuji Toranomon Orthopedic Hospital

Dirceu Greco, MD, PhD
Chair, Brazilian Society of Bioethics
Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil



Kyoko Imamura, MD, PhD
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)
Project Professor, Social Cooperation Program of IT Healthcare, The Graduate School of Pharmaceutical Sciences, The University of Tokyo; Japanese Institute for Public Engagement

❖ Special guests

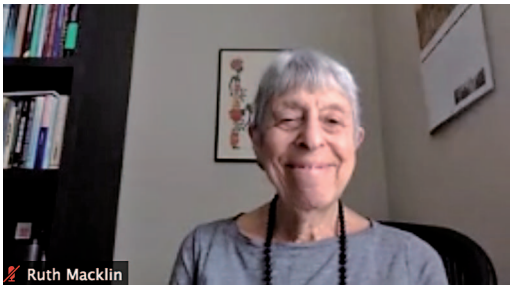
Comments at the Day 1 and Day 2 discussion sessions (page 42, 51, 78, 103)

Ramin Parsa-Parsi, MD, MPH
Workgroup Chair of the 2013 revision of the Declaration of Helsinki, World Medical Association; German Medical Association

Otmar Kloiber, MD, PhD
Secretary General, World Medical Association

❖ Presentations in Day 1

Chieko Kurihara, BSocSc
COVID-19 Task Force, Japan Association for Bioethics
Specially-appointed Professor, Kanagawa Dental University, Japan
"Opening remarks and situation in Japan and the world: Proposal on ethics of placebo-controlled trials and post-trial access in the Declaration of Helsinki" (page 16)



Ruth Macklin, PhD
Distinguished University Professor Emerita at Albert Einstein College of Medicine in New York City, the United States
"Ethics in vaccine research: the COVID-19 pandemic" (page 24)

Peter Lurie, MD, MPH
Center for Science in the Public Interest, Washington, DC, the United States
"Revisiting the debate over placebo use in developing countries in the age of COVID-19" (page 30)

Ulf Schmidt, PhD
Professor of Modern History, University of Hamburg, Germany
"From Nuremberg to Helsinki: Historicising Research Ethics during Health crisis" (page 45)

❖ Discussants

Comments at the Day 1 and Day 2 discussion sessions (page 51, 103)

Rihito Kimura, LLM, PhD
Professor Emeritus of Bioethics, Waseda University, Japan
Faculty Affiliate, Kennedy Institute of Ethics, Georgetown University, the United States

Sandor Kerpel-Fronius, MD, PhD
Professor of Clinical Pharmacology, Semmelweis University, Hungary

❖ Presentations in Day 2

Ames Dhai, MD, PhD
Professor of Bioethics, University of the Witwatersrand, Johannesburg, South Africa
"Ethics in vaccine allocation in developing countries" (page 63)

Tammam Aloudat, MD, MPH
Managing Director, Global Health Center, Graduate Institute of International Development Studies, Geneva, Switzerland
"Médecins Sans Frontières (MSF) Access Campaign for equitable access in the world" (page 72)

Dirceu Greco, MD, PhD
Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil
"Post-Trial Access for All: Perspective of achieving universal access to adequate public health" (page 82)

Francis P. Crawley
Executive Director of the Good Clinical Practice Alliance – Europe (GCPA) and Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), Leuven, Belgium
"Learnings for ethics from COVID-19" (page 94)

❖ Special thanks to

We express special thanks to organizers and supporting organizations.

Co-organized by the COVID-19 Task Force, Japan Association for Bioethics and the Brazilian Society of Bioethics
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Cooperation:
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Clinical Research Risk Management Study Group

Video-recorded versions and other related information can be accessed from the following web-site:
http://cont.o.oo7.jp/sympo/covidandbioethics.html

Opening Remarks of the Day 1 session

Takeo Saio
COVID-19 Task Force, Japan Association for Bioethics
Department of Internal Medicine and Psychiatry, Fuji Toranomon Orthopedic Hospital, Japan

Good evening from Kyoto. I am Dr. Takeo Saio, practicing physician, one of the organizers of this webinar, and a member of COVID-19 Task Force of Japan Association for Bioethics. This is Part 3 of the series of webinar entitled "COVID-19 and Bioethics" co-organized with Brazilian Society of Bioethics chaired by Prof. Dirceu Greco. Prof. Greco is a globally well-known professor of infectious diseases and bioethics.

Today, we discuss about the critical issue of research ethics in the situation of pandemic. All speakers of this webinar have played historically important role in the international debates on the related topics of Declaration of Helsinki of the World Medical Association (WMA). It is our great honor that Dr. Ramin Parsa-Parsi, who chaired the recent revision of the Declaration of Helsinki, and Dr. Otmar Kloiber, the Secretary General of the WMA, are joining us.

I hope everyone enjoys our discussion.

Dirceu Greco
Chair, Brazilian society of Bioethics
Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil

Good morning, good afternoon, and good night to all. It's my pleasure and honor to be part of this very important meeting. It's very nice to see some people that I have not seen for a long time due to this COVID situation.

I will start by thanking Prof. Kurihara and Dr. Saio, because they have had most of the work to make possible our debate today. I am saying this in the name of the Brazilian Society of Bioethics. It's very nice to see again people that I know very much including Prof. Kyoko Imamura, Prof. Rihito Kimura, who participated in the symposium of the Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT) in Tokyo [1], and with Prof. Kimura we have debated about Paulo Freire (Brazilian educator/philosopher). It was at the end of 2019. Dr. Otmar Kloiber, who was there too, and we were together in the symposium of JSCPT, Tokyo, just before the start of the COVID-19 pandemic and in many other related meetings throughout the years.

It's good to see Prof. Ruth Macklin. Thank you for accepting, Prof. Macklin, whom I have the honor of sharing her friendship for a long time. Last time we saw each other was in 2019. It's good to see Dr. Peter Lurie too. It has been long time no see. I am seeing my friends from Brazil, including Tania Cotrim, coordi-

1) *Clin Eval*. Vol. 48, No. 1.
http://cont.o.oo7.jp/48_1/48_1contents_e.html

nator of Communication at the Brazilian Society of Bioethics.

I am giving the floor to start this meeting. I hope you can be with us again next week at the same time when we are going to have another debate. We wish us all have a very good meeting. Hope you all keep safe and healthy. We will keep fighting against not only COVID-19, but against all the things that are happening with this very bad situation facing the world including the inequity that has been even more unacceptable than before. Thanks very much.

Kyoko Imamura
Japanese Association of Pharmaceutical Medicine (JAPhMed)/Past President, International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)
Project Professor, Social Cooperation Program of IT Healthcare, The Graduate School of Pharmaceutical Sciences, The University of Tokyo, Japan

I am Prof. Kyoko Imamura. I am Project Professor of Social Cooperation Program of IT Healthcare at the Graduate School of Pharmaceutical Sciences at the University of Tokyo. I am glad to meet Prof. Greco again and our colleagues at the World Medical Association.

Today, I am representing two organizations. One is the International Federation of the Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP). This is a worldwide group of people who are trying to promote pharmaceutical medicine. We have Ethics Working Group in our organization which is strongly driving the ethical conduct of medicines development and appropriate use of medicines in the market. Prof. Kurihara has been the strongest activist in this Ethics Working Group. This program has been supported by our organization IFAPP. Also I am representing Japanese National Member Association, the JAPhMed, Japanese Association of Pharmaceutical Medicine. I am happy to meet you all here in this online meeting this week and next week as well.

Today, I am going to help Dr. Saio to moderate all these presentations and trying to keep in mind that we need to be strict on the scheduled time. In the interest of time, we better accelerate the presentation. Let me ask Prof. Kurihara, who prepared all these events spending many weeks. Please start your presentation.

(Published November 15, 2021)

* * *

臨床評価　49巻　別冊　2021

Opening remarks and situation in Japan and the world: Proposal on ethics of placebo-controlled trials and post-trial access in the Declaration of Helsinki

Chieko Kurihara [1, 5) * 1, 2]　**Takeo Saio** [2) * 2]
Kotone Matsuyama [3, 5)]　**Kyoko Imamura** [4, 6)]

1) Specially-appointed Professor, Kanagawa Dental University, Japan
2) Department of Internal Medicine and Psychiatry, Fuji Toranomon Orthopedic Hospital, Japan
3) Professor, Department of Health Policy and Management, Nippon Medical School, Japan
4) Project Professor, Social Cooperation Program of IT Healthcare, The Graduate School of Pharmaceutical Sciences, The University of Tokyo, Japan
5) Working Group on Ethics, International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)
6) Past President, International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)

1. Opening remarks: Justice principle in bioethics

Our presentation will make some proposals for the future revision of the Declaration of Helsinki [1)], focusing on placebo and post-trial access, especially considering global experience of this pandemic. The presentation is based on our recent paper [2)].

We have no conflict of interests. First, we will describe about the "***justice***" principle in bioethics. Ethics of "placebo-controlled trials" and "post-trial access" is related to justice principle of bioethics. Japanese government is going to purchase COVID-19 prevention vaccines to cover its whole population without participating in phase 3 placebo study. This is against justice principle. Some vaccines have been proven to be effective at the time of half a year from the vaccination in high-risk populations but have not been proven in Japan.

＊1　Presentation at the webinar.
＊2　Organizer at the COVID-19 Task Force, Japan Association for Bioethics

1) World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research involving Human Subjects. Adopted Jun 1964, last amended in Oct 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
2) Kurihara C, Saio T, Matsuyama K, Imamura K. Science and ethics of clinical trial of COVID-19 preventive vaccines: Consideration on placebo and post-trial access. *Clin Eval*. 2021; 49(1): 93-108. Japanese.
http://cont.o.oo7.jp/49_1/p93-108.pdf

2. Morbidity, mortality and vaccine availability in Japan and the world

In this pandemic situation, morbidity and mortality is higher in American and European continents, but lower in Eastern Asian Countries (Table 1, as of 1 year from the onset of epidemic in Japan)[3]. High-efficacy

Table 1 Statistics of COVID-19 infection and status of clinical trial and approval of COVID-19 prevention vaccine of each country, one year from the onset of the pandemic

Statistics was downloaded on January 1, 2020, from the following web-site of the World Health Organization (WHO), and information of phase 3 trial and approval of COVID-19 prevention vaccine were surveyed by the authors.
WHO Coronavirus Disease (COVID-19) Dashboard
https://covid19.who.int/
EU countries were given the mark of ○ because vaccine approval of each of EU country has not been surveyed but EU gave central approval.

- *Italic*：Deaths-cumulative total per 1 million population>100
- ***Bold & Italic***：Deaths-cumulative total per 1 million population>1,000
- Gray background：ASEAN＋Japan, China, South Korea, Taiwan

※Data of Taiwan is not included in WHO web-site thus complemented by the data from Japanese Ministry of Health, Labour and Welfare.

Name of country	Conduct of phase 3 trial	Approval	Cases - cumulative total	Cases - cumulative total per 1 million population	Deaths - cumulative total	Deaths - cumulative total per 1 million population
Global			**85,929,428**	**11,008**	**1,876,100**	**240**
USA	●	●	20,870,913	63,054	354,286	***1,070***
India	●	●	10,395,278	7,533	150,336	*109*
Brazil	●		7,810,400	36,745	197,732	*930*
Russian Federation	●	●	3,332,142	22,833	60,457	*414*
UK	●	●	2,836,805	41,788	77,346	***1,139***
France		○	2,660,740	40,763	66,184	***1,014***
Italy		○	2,201,945	36,419	76,877	***1,272***
Spain		○	1,982,543	42,403	51,430	***1,100***
Germany		○	1,835,038	21,902	37,607	*449*
Colombia			1,702,966	33,468	44,428	*873*
Argentina	●	●	1,662,730	36,790	43,785	*969*
Turkey	●	●	1,469,593	17,425	22,070	*262*
Mexico	●	●	1,466,490	11,374	128,822	*999*
Poland		○	1,356,882	35,852	30,241	*799*
Iran			1,261,903	15,024	55,830	*665*
South Africa	●		1,149,591	19,383	31,368	*529*
Ukraine			1,099,493	25,141	19,505	*446*
Peru	●		1,022,018	30,997	37,925	***1,150***
Netherlands		○	841,163	49,091	11,999	*700*
Czechia		○	794,740	74,212	12,621	***1,179***
Indonesia	●	●	788,402	2,882	23,296	85
Belgium		○	655,732	56,579	19,883	***1,716***
Romania		○	654,007	33,996	16,299	*847*
Chile	●	●	625,483	32,720	16,816	*880*
Canada		●	618,646	16,391	16,233	*430*
Iraq		●	599,965	14,916	12,865	*320*
Bangladesh		●	518,898	3,151	7,687	47
Pakistan	●		492,594	2,230	10,461	47
Philippines			480,737	4,387	9,347	85
Sweden		○	469,748	46,513	8,985	*890*
Switzerland		●	468,427	54,124	7,400	*855*
Israel		●	457,721	52,882	3,503	*405*
Morocco	●		447,081	12,113	7,618	*206*
Portugal		○	446,606	43,799	7,377	*723*
Austria		○	371,657	41,266	6,454	*717*
Saudi Arabia		●	363,377	10,438	6,272	*180*
Serbia		●	352,120	50,565	3,444	*495*
Hungary		○	334,836	34,661	10,325	***1,069***
Jordan	●	●	302,856	29,683	3,955	*388*
Nepal			263,193	9,033	1,899	65
Panama		●	259,770	60,205	4,238	*982*
Japan			258,393	2,043	3,791	30

Data of ASEAN＋Japan, China, South Korea and Taiwan were extracted.

Indonesia	●	●	788,402	2,882	23,296	85
Philippines			480,737	4,387	9,347	85
Japan			258,393	2,043	3,791	30
Myanmar			128,178	2,356	2,785	51
Malaysia			125,438	3,876	513	16
China		●	97,217	66	4,795	3
Republic of Korea			66,686	1,301	1,046	20
Singapore		●	58,780	10,047	29	5
Thailand			9,636	138	67	1
Viet Nam			1,505	15	35	0
Taiwan			819		7	
Cambodia			385	23	0	0
Brunei Darussalam			172	393	3	7
Laos			41	6	0	0

As of January 6, 2021.

Source: Kurihara C, Saio T. 2021 Jun 15[3].
https://www.covid19-jma-medical-expert-meeting.jp/topic/4068
Reproduced from: The 6th Congress of Asian College of Neuropsychopharmacology—Neuropsychopharmacology to the next generation: New wave from Asia—. *Clin Eval*. 2021; 48(Sup 37). P.146.
http://cont.o.oo7.jp/48sup37/p73-146.pdf

rates of some vaccines at 6 months from vaccination have been shown in Phase 3 studies and in real-world evidence (Table 2). However, there is just one concern in a blog of *BMJ*[4] on this high efficacy rate (Table 2). Placebo studies have been conducted in high prevalence areas. But there is no participation from Japan (Table 2), and the Japanese government is going to purchase these vaccines to cover its whole population. This is against the principle of justice. There are many Chinese vaccines with not so high efficacy rate[5], but people in some countries can access only these vaccines.

There are many countries with no access to effective vaccines. Meanwhile, there is "***scientific compelling reason***" to continue placebo studies, e.g., to prove long-term efficacy, long-term safety, and efficacy for some specific populations. Therefore, we have to clarify ethical principles to provide effective vaccines to people who need it in the world. In this regard, discussion on the Declaration of Helsinki will provide driving force (Table 3).

Table 2　Two mRNA vaccines and their efficacy and their confirmatory trials

BNT162b2　Generic name: Tozinameran		**Bland name：Comirnaty**	**Developed by BioNTech＋Pfizer**		
Phase 3		**BNT162b2 (21,720)**	**Placebo (21,728)**	**efficacy**	NCT04368728
NEJM	**PCR Positive:**	**8**	**162**	**95%**	**US, Argentina, Brazil, Germany, South Africa, Turkey**
DOI: 10.1056/NEJMoa2034577		(7 days after the 2nd dose)			
	Severe:	**1**	**9**		
		(any time after the 1st dose)			
***BMJ* blog** (concern by Doshi P.)	**Symptoms** (with/without PCR)	**8＋1,594**	**162＋1,816**	**19%**	
Press Release Pfizer	**Confirmed**	**77**	**850**	**91.30%**	
		(7 days to 6 months of 2nd dose)			
	Severe	**0** (CDC definition)	**32** (CDC)	**100%**	
		1 (FDA definition)	**21** (FDA)	**95.30%**	
Real World Data, Israel		**Vaccinated (596,618)**	**Unvaccinated (596,618)**		
NEJM	**Infection**	**4,460**	**6,100**	**94%**	
DOI: 10.1056/NEJMoa2035389	**Symptomatic**	**2,389**	**3,607**	**94%**	
	Hospitalization	**110**	**259**	**87%**	
	Sever	**55**	**174**	**92%**	
	Death	**9**	**32**	**84%**	
Real World Data, US		**Vaccinated (2,961)**	**Unvaccinated (989)**		
MMWR	**PCR-confirmed**	**8** (Partially)	**161**	**80%**	
doi: 10.15585/mmwr.mm7013e3	**PCR-confirmed**	**3** (Fully)	**161**	**90%**	
mRNA-1273　Bland name：Moderna COVID-19 vaccine　Developed by Moderna＋NAID					
Phase 3		**mRNA-1273 (14,134)**	**Placebo (14,073)**	**efficacy**	NCT04470427
NEJM	**Symptomatic**	**11**	**185**	**94.1%**	**US**
DOI: 10.1056/NEJMoa2035389	**Severe:**	**0**	**30**		

3) Japan Medical Association COVID19 Expert Meeting. Kurihara C, Saio T. Ethics in COVID-19 prevention vaccine development: a milestone toward post-corona era. 2021 Jun 15.
https://www.covid19-jma-medical-expert-meeting.jp/topic/4068

4) Thebmjopinion. Peter Doshi: Pfizer and Moderna's "95% effective" vaccines – we need more details and the raw data. January 4, 2021 [cited 2021 Oct 5].
https://blogs.bmj.com/bmj/2021/01/04/peter-doshi-pfizer-and-modernas-95-effective-vaccines-we-need-more-details-and-the-raw-data/

5) Mallapaty S. China's COVID vaccines are going global: But questions remain. *Nature*. 2021 May 4, update 2021 May 12.
https://www.nature.com/articles/d41586-021-01146-0?utm_source=Nature+Briefing&utm_campaign=6b10e58cc9-briefing-dy-20210504&utm_medium=email&utm_term=0_c9dfd39373-6b10e58cc9-44721677

Table 3 Need for strengthened Declaration of Helsinki (DoH)

- There are **many countries of No Access** to effective vaccines.
- And there is "***scientific compelling reasons***" to continue placebo studies to prove:
  - ➢ Longer term efficacy;
  - ➢ Longer term safety;
  - ➢ Efficacy for some specific populations.
- We have to find ethical principles to provide effective vaccines for **people who need it in the world**.
- Discussion on the DoH will provide **driving force**.

3. Placebo-controlled trials after EUA

Next, we will discuss about placebo study after Emergency Use Authorization (EUA).

The Declaration of Helsinki states that new intervention must be tested against "***best proven intervention***" (Paragraph 33). There have been arguments that if this "best-proven intervention" is not available in some communities, new intervention can be tested against locally available intervention ("***local standard of care***" argument).

This idea is ***against*** "***justice***" principle when placebo study is conducted in "no access" areas and only rich countries can purchase products proven to be effective.

For this reason, the principle of "***best-proven intervention***" must be strengthened.

4. WHO's comment on EUA and need for placebo-controlled trials

Due to some "***scientific compelling reasons***" to continue phase 3 placebo study under EUA, the study design of placebo-controlled clinical trial of BNT162b2 was changed by Pfizer/BioNTech (Table 4). Hence, participants are able to switch from a placebo to active group when due to their condition, when they become

Table 4 A strategy by Pfizer · BioNTech: Change of study design (Dec 22, 2020)

●Vaccination of Placebo recipients with BNT162b2 - Stage 1
- Participants ≥16 years of age who originally received placebo and are eligible for COVID-19 vaccination following any local or national recommendations will be offered the opportunity to receive BNT162b2 as part of the study.

●Vaccination of placebo recipients with BNT162b2 - Stage 2
- Participants ≥16 years of age who originally received placebo will be offered the opportunity to receive BNT162b2 at defined points as part of the study.

NCT04368728
https://clinicaltrials.gov/ct2/history/NCT04368728?V_22=View#StudyPageTop

Supported by authorities and scientific communities, e.g. US-FDA; WHO

Scientific compelling reasons to continue placebo study.
Participants in placebo group can switch to active group.

eligible for vaccination.

WHO (World Health Organization) stated in December, 2020 [6] that Emergency Use Authorization does not in itself render the "***best-proven intervention***" in the Declaration of Helsinki [1], or "***established effective intervention***" in CIOMS guidelines (Guideline 5) [7]. However, worldwide roll out of vaccines has been based on the fact that ***half a year efficacy has been proven***.

WHO experts also stated [8] that countries with limited or no access to an effective vaccine could ethically permit placebo-controlled trials. This is against the principle of the Declaration of Helsinki in that "***new intervention must be tested against the best proven intervention*** (in the world)". This statement is similar to the French doctor's statement in last year (2020) that WHO protested against [9]. In April of last year, this French doctor had posed a provocative question, "Why not conduct vaccine study in Africa where there are no masks, no treatments?"

5. Our opinion on "use of placebo" (Paragraph 33) of the DoH (Table 5)

To avoid such confusion, the meaning of "best proven" must be clarified as it means "*the best proven intervention* ***in the world***". The Declaration of Helsinki does not permit placebo study on the ground of "no access" in the host countries.

Still now, there is "***scientific compelling reason***" to conduct placebo studies of COVID-19 vaccine. It can be permitted in lower prevalence areas or on some specific untested populations. It should also be clarified that "*the best proven in the world*" means "*the best proven intervention in the world* ***on some specific populations***".

The question still remains about the risk threshold. In a situation where there is "*the best proven intervention in the world*," the Declaration of Helsinki permits placebo study if it does not cause "***additional risks of serious or irreversible harm***". However, this risk threshold is questionable, because CIOMS guidelines took this wording in their 2002 version but changed in its 2016 revision to "***minor increase above minimal risk***" (Guideline 5) [7]. Hence, we should discuss more about this risk threshold in terms of ***physicians' obligation to prioritize patient's interests to the goal of research***, which is the core principle of the Declaration of Helsinki (Paragraph 8).

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6) World Health Organization. Emergency Use Designation of COVID-19 candidate vaccines: Ethical considerations for current and future COVID-19 placebo-controlled vaccine trials and trial unblinding Policy brief 18 December 2020. https://apps.who.int/iris/bitstream/handle/10665/337940/WHO-2019-nCoV-Policy_Brief-EUD_placebo-controlled_vaccine_trials-2020.1-eng.pdf?sequence=1&isAllowed=y

7) Council for International Organizations of Medical Sciences). International Ethical Guidelines for Health-related Research Involving Humans. 2016. https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

8) WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation, Krause PR, Fleming TR, Longini IM, Peto R, Beral V, Bhargava B, Cravioto A, Cramer JP, Ellenberg SS, Figueroa JP, Halloran E, Henao-Restrepo AM, Ryan MJ, Levine MM, Nason M, Nohynek HM, Plotkin S, Rees H, Singh JA, Swaminathan S. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. *N Engl J Med*. 2021 Jan 14;384(2):e2. doi: 10.1056/NEJMp2033538. Epub 2020 Dec 2. PMID: 33264543.

9) Coronavirus: Africa will not be testing ground for vaccine, says WHO. BBC News. 2020 Apr 6. https://www.bbc.com/news/world-africa-52192184

Table 5 Problem and proposal on principle of "Use of placebo" in the Declaration of Helsinki (DoH)

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s) in the world on specific population, 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.

To be compatible with para 8 of DoH
– DoH 2000*
– CIOMS 2016

【Problem of current principle】

- Meaning of "best proven" is not clear and cause misunderstanding and confusion (e.g.WHO [8, 9]).
- Risk threshold of "***no additional risk of serious or irreversible harm***" is inconsistent with DoH's core principle to prioritize patient's right and welfare to the goal of research, as well as threshold in CIOMS 2016.

【Our proposal】

- Meaning of "*best proven*" should be clarified as "***best proven in the world, for specific population***".
- Risk threshold ("***not be subject to additional risks of serious or irreversible harm***") of placebo should be discussed again to go back to 2000 version or CIOMS 2016.

Source: World Medical Association. Declaration of Helsinki. 2013 [1]. Proposed revisions are by authors.
* According to Prof. Dirceu Greco, Brazil does not allow this risk threshold even in the range of CIOMS 2016, and keep the principle in the 2000 version of the DoH [10].

6. Current situation of post-trial access

Next, we will discuss about "***post-trial access***". The Declaration of Helsinki states that "*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*" (Paragraph 34).

In case of COVID-19 prevention vaccines, ***sponsors*** are going to provide post-trial access not only for study participants, but also for people who need it in host countries as well as other people in the world.

The obligation of ***individual researcher*** is to provide best available care to study participants at the completion of each period of study participation.

Meanwhile, ***host country governments*** which have invested substantial public money, collaborating with all related stakeholders (industries, healthcare workers, study participants), have been struggling to meet their ethical obligations to achieve global access. For example, waiver from certain provisions of TRIPS agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights) has been discussed to over-

10) Greco D. Shimoda K, Watanabe H, Organizers. The Past, Present, and Future of Ethics of International Health Research: Research as a stepping-stone to Universal Public Health Care Access. *Clin Eval.* 2020; 48(1): W29-W53. http://cont.o.oo7.jp/48_1/w29-w53.pdf

come obstacle of intellectual property rights.

The biggest progress in this topic has been the statement from the United States [11] to support the proposal from developing countries [12]. Japanese companies' association protested against it, worrying about uncontrolled manufacturing and supply without assurance of safety and quality [13]. But this is a questionable statement because safety, quality, and supply are not controlled by patent system but controlled by pharmaceutical regulations.

7. Rapid development of effective vaccines

United States' "Operation Warp Speed" [14] achieved rapid development of effective vaccines. Now global version of Operation Warp Speed is needed. It should be collaborated with NGOs and governments of Low- and Middle Income-countries (LMICs), as well as COVAX initiative.

This paper [15] is not about COVID-19. It shows lower rate of product approval in lower-income countries that hosted clinical trials, comparing higher rate of product approval in higher income countries that hosted clinical trials.

8. Our opinion on "post-trial access" (Paragraph 34) of DoH (Table 6)

We should assure post-trial access not only to study participants but also we must assure "***fair***" access for people who need it in host community and in the world. Thus, it is not enough to provide information of post-trial provision to research ethics committee and candidate participants. Post-trial provisions should be discussed involving relevant stakeholders, in order to actually achieve post-trial access in health system of each country and in the world.

This is the finding from the experience of this world pandemic, but it is applicable to all kind of studies involving human participants.

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11) Office of the United States Trade Representative. Statement from Ambassador Katherine Tai on the Covid-19 Trips Waiver. 2021 May 5 [cited 2021 Oct 5].
https://ustr.gov/about-us/policy-offices/press-office/press-releases/2021/may/statement-ambassador-katherine-tai-covid-19-trips-waiver

12) Council for Trade-Related Aspects of Intellectual Property Rights. Waiver from certain provisions of the TRIPS Agreement for the prevention, containment and treatment of COVID-19: Communication from India and South Africa. 2 October 2020; IP/C/W/669.
https://docs.wto.org/dol2fe/Pages/SS/directdoc.aspx?filename=q:/IP/C/W669.pdf&Open=True

13) Japan Pharmaceutical Manufacturers Association (JPMA). On the WTO-TRIPS waiver. 2021 May 7 [cited 2021 Oct 5]. Japanese.
https://www.jpma.or.jp/news_room/release/news2021/210507.html

14) US Dept of Defense. Trump Administration Announces Framework and Leadership for 'Operation Warp Speed'. 2020 May 15.
https://www.defense.gov/News/Releases/Release/Article/2310750/trump-administration-announces-framework-and-leadership-for-operation-warp-speed/

15) Miller JE, Mello MM, Wallach JD, Gudbranson EM, Bohlig B, Ross JS, Gross CP, Bach PB. Evaluation of Drug Trials in High-, Middle-, and Low-Income Countries and Local Commercial Availability of Newly Approved Drugs. *JAMA Netw Open*. 2021 May 3;4(5):e217075. doi: 10.1001/jamanetworkopen.2021.7075. PMID: 33950209; PMCID: PMC8100865.

Table 6 Problem and proposal on principle of "post-trial access" in the Declaration of Helsinki (DoH)

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions ~~for~~ to assure post-trial access fairly for all participants, people of host community, and then in the world, who ~~still~~ need an intervention identified as beneficial in the trial.

~~This information~~ This provision should be developed in advance involving relevant stakeholders and must also be disclosed to participants during the informed consent process.

※Disclosure to Research Ethics Committee in protocol is defined in paragraph 22.

【Problem of current principle】

- This is mixture of obligations of sponsors, researchers and governments.
- It mentions obligations only in advance of clinical trial; what about post-trial? (See DoH 2000, 2004 and 2008)
- Post-trial access should be assured not only for participants, but also host community; then people who need it in the world.

【Our proposal】

- Not only to assure post-trial access to study participants but also we must assure "***fair***" access for people who need it in host community, and then in the world.
- It is not enough to provide information of post-trial provision to ethics committee and candidate participants.
- Post-trial provisions should be discussed ***involving relevant stakeholders***, in order to ***actually achieve post-trial access*** in health system of each country and in the world.
- This is finding from the experience of the world pandemic, but it is applicable to any research involving human participants.

Source: World Medical Association. Declaration of Helsinki. 2013 [1]. Proposed revisions are by authors.

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Ethics in vaccine research: The COVID-19 pandemic

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1. Covid-19: Two key ethical issues

We are discussing today two key ethical issues that arise in COVID-19 vaccine research (Table 1). These are not the only ethical issues, but they involve long-standing controversies in research ethics. The first issue is the acceptability of placebo controls in current and future vaccine research. One argument relies on the difference between countries with wide access to vaccines that are already approved for emergency use and those countries with limited or no access to these vaccines.

I use the phrase "approved for emergency use" because at the time of this presentation, all seven or eight vaccines that are currently in use throughout the world have been approved only for emergency use. This is the case for the ones that have been approved by the European Union Medicines Agency and the United States' Food and Drug Administration (I remain uncertain about the vaccines manufactured in China and India). This means the vaccines can be used, but they are not yet licensed.

The second ethically controversial topic is post-trial access. I will say a few words about the COVAX agreement, which was proposed to ensure access to vaccines in low- and middle-income countries (LMICs); however, difficulties arose in seeking to ensure proper distribution. The question arises: whose obligation is it to provide access in those countries? Two respected international ethical guidelines address this question.

2. Controversies of placebos in research

The use of placebos can be controversial in research with human beings. Two well-known and highly

Table 1　Covid-19: Two key ethical issues

- **Design of preventive vaccine research**
  - Acceptability of placebo controls
    - In countries with wide access to vaccines approved for emergency use
    - In countries with limited or no access to vaccines approved for emergency use
  - Post-trial benefits
    - In countries with limited or no access to vaccines
      - COVAX agreement
      - Whose obligation?

respected international ethical guidelines provide guidance on placebos. Those are the Declaration of Helsinki (DoH), issued by the World Medical Association (WMA) in its most recent iteration in 2013 [1] and the 2016 CIOMS International Ethical Guidelines for Health-related Research Involving Humans, prepared in collaboration with the World Health Organization [2]. I was a member of the working group that issued the CIOMS International Ethical Guidelines. Those were prepared with informal input from the WMA, since key participants who worked on the 2013 version of the DoH were present at all of the meetings of the CIOMS group that prepared the 2016 guidelines.

We should recall that international guidelines are not legally binding. There is no way of enforcing them because by themselves, they do not have the status of international law. However, some countries do incorporate international guidelines into their own domestic laws.

3. Use of placebo in the Declaration of Helsinki

Paragraph 33 of the Declaration of Helsinki, entitled "Use of Placebo," states:

"***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."

Several words and phrases in that paragraph require unpacking or elaboration, and need further discussion. What are the compelling and scientifically sound reasons? What are the interventions that are less effective than placebo? What are the additional risks of serious or irreversible harm? And, how serious does the harm have to be?

One example of a compelling and scientifically sound methodological reason why a placebo might be necessary is to get a clear result in a study. Some diseases have the characteristic of being "exacerbating and remitting." What that means is that the strength of symptoms increases and decreases naturally—as a characteristic of the disease, not as a result of treatment. An example is one form of multiple sclerosis. The argument is that without a placebo control, it would not be clear whether the experimental treatment is working or the disease symptoms subsided on their own. However, this disease attribute does not occur with COVID-19.

A key question is: what counts as "serious" harm? Patients may have a different view from that of research-

1) World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research involving Human Subjects. Adopted Jun 1964, last amended in Oct 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
2) Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-related Research Involving Humans. 2016.
https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

ers concerning what should be considered serious. There is a proverbial humorous reply to the question, "what is minor surgery?". The answer is: "minor surgery is surgery on someone else." Moreover, patients themselves may disagree on whether COVID-19 is a disease that carries serious harm. This is one reason why so many people in many countries have refused to be vaccinated: their belief that the disease would not cause serious harm to them.

4. CIOMS guideline 5 on placebo use

CIOMS guideline 5 makes the same point:

"***As a general rule, the research ethics committee must ensure that research participants in the control group ..... receive an established effective intervention.***
Placebo may be used as a comparator when there is no established effective intervention for the condition under study, or when placebo is added on ....."

CIOMS uses different words from those in the Declaration of Helsinki. Helsinki uses "best proven" while CIOMS uses "established effective," but both intend to convey the same idea.

5. Determining minor increase above minimal risk

The CIOMS guideline goes on to say:

"***When there is an established effective intervention, placebo may be used as a comparator without providing the established effective intervention to participants only if:***

- ***there are compelling scientific reasons for using placebo; and***
- ***delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures.***"

The phrase describing the level of risk requires further explanation. What is a "minor increase above minimal risk"? I find it difficult to quantify. Those of us who were members of the working group that revised the CIOMS guidelines had multiple debates and discussions about the meaning of that phrase and whether it is useful. People disagree, for example, about what constitutes minimal risk, and they are similarly likely to disagree over what counts as a "minor increase." That is clearly something that requires further work and explanation.

6. Unethical proposal in *NEJM* Article

A controversial article was published in the *New England Journal of Medicine* (*NEJM*)[3] in January 2021. The authors were external experts brought together by WHO. Three WHO staff members were on the com-

3) WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation, Krause PR, Fleming TR, Longini IM, Peto R, Beral V, Bhargava B, Cravioto A, Cramer JP, Ellenberg SS, Figueroa JP, Halloran E, Henao-Restrepo AM, Ryan MJ, Levine MM, Nason M, Nohynek HM, Plotkin S, Rees H, Singh JA, Swaminathan S. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. *N Engl J Med*. 2021 Jan 14; 384(2): e2. doi: 10.1056/NEJMp2033538. Epub 2020 Dec 2. PMID: 33264543.

mittee that authored the article, including the principal scientist from WHO. The article argues that new vaccine research using placebo controls should be carried out in countries lacking access to the COVID-19 vaccines that have already been approved in other countries. It says the use of placebos is still "ethical and feasible," but this claim is not convincingly argued in the article. The authors say the purpose of the placebo control study is "to obtain pivotal data to improve regulatory and public health decision making" but they do not clearly explain why the research cannot be conducted using the COVID-19 vaccines already in use.

The proposal in this article to use placebos when there already exist highly effective vaccines violates a long-standing practice in research to do one of two things: either stop ongoing placebo-controlled trials when a successful product becomes available outside the trial, or inform the trial participants that such vaccines exist, thereby enabling them to leave the trial and possibly obtain the vaccine. It is true, however, that COVID vaccines are currently available in poor countries only to a very limited extent. Nevertheless, if sponsors seek to test new vaccines in those countries using placebo controls, it constitutes a "double standard": one standard for rich countries and another for poor countries. It takes advantage of the inhabitants' lack of access to existing vaccines. Probably the strongest condemnation of that practice is to say that not only does it involve a double standard, but it amounts to exploitation of people in lower- and middle-income countries.

7. *NEJM* article violates guidelines and WHO policy

The proposal in the *New England Journal of Medicine* article violates the CIOMS and Declaration of Helsinki guidelines. It violates a provision in Helsinki in that participants in the placebo group would be "***subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.***" "***Serious or irreversible harm***" in this case would be infection with the virus for COVID-19. With regard to CIOMS: "***Delaying or withholding the established effective intervention,***" (the vaccine) will likely result in more than a minor increase above minimal risk to the participant; and in the case of COVID-19, that risk is the possibility of serious illness or death.

Perhaps most surprisingly, this article violates WHO's own policy. The WHO website says, "***The ERC*** [Ethical Review Committee at WHO] ***is guided in its work by the World Medical Association Declaration of Helsinki as well as the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 2016)***." The ERC is the research ethics committee that reviews all research submitted to WHO for approval. The 2016 CIOMS guidelines document cites WHO as a collaborator in drafting its guidelines. CIOMS says in an acknowledgment: "Prepared by CIOMS in collaboration with WHO." As already noted, key members of WHO staff were present at all of the meetings of the CIOMS work group, and additional WHO staff were involved in reviewing the final document. In the end, the final version of the CIOMS guidelines was reviewed by the WHO ERC. As already mentioned, the ad hoc group of experts included key WHO staff among the authors of the article published in the *NEJM*. They should have been aware of WHO's involvement in preparing the CIOMS guidelines, as well as WHO's endorsement of the completed guidelines.

8. Puzzling question

So, the question arises: how could three WHO staff members who served on the expert group of authors

convened by WHO conclude that it is “still feasible and ethical” to conduct a placebo-controlled trial when vaccines for COVID-19 have become available? Were they not familiar with the WHO ERC’s adherence to the Declaration of Helsinki and CIOMS? Were they relying on the excuse that the currently available vaccines had received only “emergency use approval”? As mentioned earlier, that may be a key point in the argument here. Eight different vaccines have received such approval and millions of people around the world have been vaccinated. Although the leading vaccines in the US and EU are not yet licensed at this time, can they still be thought of or properly be called “experimental”?

9. Inequitable post-trial access

The second key ethical issue addresses the question of access to any benefits that arise from current and future vaccine research. Both the Declaration of Helsinki and CIOMS include guidelines that address providing successful results of research to trial participants and others. It has become abundantly clear that wealthy countries can afford to purchase COVID-19 vaccines, but many LMICs cannot. The result is an inequitable balance of available vaccines in the world.

Here is what the Declaration of Helsinki says:

> “***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***” (Paragraph 34).

It’s clear from this that according to the Declaration of Helsinki, the benefits are limited to trial participants. There is no mention of benefits to others in the country where trial is conducted.

This paragraph places the burden on sponsors, researchers, and host country governments to make provisions for post-trial access. The Declaration of Helsinki is intentionally a brief document, so the details would have to be worked out by these parties. But the question here is who has the greatest obligation? How can the researchers fulfill such an obligation? Are they supposed to take money out of their pockets? Obviously not. Sponsors are very often pharmaceutical companies that obviously have lots of money, but they maintain that their obligation is to their shareholders. And for their part, some countries in which vaccine trials take place are LMICs. The details of any such arrangements would have to be worked out among these various parties. The DoH does not mention benefits to others in addition to research participants in the countries where trials are conducted.

10. CIOMS guideline 2

CIOMS guideline 2 on this point is entitled “Research Conducted in Low-resource Settings”.

> “***Before instituting a plan to undertake research in a population or community in low-resource settings, the sponsor, researchers, and relevant public health authority must ensure that the research is responsive to the health needs or priorities of the communities or populations where the research will be conducted***.”

That part of the guideline is intended to prohibit research on a disease or condition that doesn’t exist in that

country and so there could never be any benefits to the population from the research.

An additional point in CIOMS guideline 2:

"***As part of their obligation, sponsors, and researchers must also:***
make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out...."

Unlike the DoH, CIOMS calls for providing post-trial benefits to the wider population in the country or the community. That is, the benefits are not limited to trial participants only.

11. COVAX global initiative

COVAX is a recently formed initiative specifically related to the COVID-19 pandemic. The program is jointly carried out by WHO, a global organization called the Global Alliance for Vaccines and Immunization (GAVI), and the Coalition for Epidemic Preparedness and Innovations (CEPI), a newly formed organization after the pandemic began. UNICEF is also a partner but is not as centrally involved essential as the other three organizations. At least 184 nations signed on to the COVAX program.

The aims of this initiative are to accelerate development and manufacture of COVID-19 vaccines, and to guarantee fair and equitable access for every country in the world. However, although high-income countries did not explicitly violate provisions in the initiative, they circumvented the agreement. They signed on to the agreement but then went ahead and made independent contracts with vaccine manufacturers. Then these high-income countries (the United States was one of them) stockpiled vaccines for their own citizens, which resulted in inequitable access and too little supply for LMICs. This behavior has come to be known as "vaccine nationalism."

12. Eliminating patent protections

An entirely new development is a movement to eliminate patent protections for COVID-19 vaccines. For obvious reasons, vaccine manufacturers oppose the idea but many public health advocates are in favor. The US government has stated its support for waiving patent protections for COVID vaccines, which is a historic move by the current US President, Joseph Biden. It is highly likely that some factions in the US and other countries do not support this innovation.

13. Conclusion

Both of the key ethical issues addressed in this presentation are elaborated further by other speakers in these two international programs.

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COVID-19 and bioethics Part 3:
Pandemic and research ethics－Democracy, placebo and post-trial access【Day 1, June 4, 2021】

Revisiting the debate over placebo use in developing countries in the age of COVID-19

Peter Lurie
Center for Science in the Public Interest, Washington, DC, the United States

1. Opening remarks

What I would like to do is try and put this debate over the use of placebos in developing countries in the context of concrete historical examples. I will talk about three examples of clinical trials that have raised these kinds of ethical questions. The first is the perinatal HIV prevention with zidovudine case. The second is the treatment of Respiratory Distress Syndrome (RDS) with Surfaxin. My colleague Dr. Sidney Wolfe and I brought these first two to public attention when I was with the group Public Citizen [1, 2].

Then, I am going to compare these two circumstances against a third one, which is our current circumstance with regard to COVID-19 vaccines.

I will compare them in four different ways: One is the risks of placebo use, i.e., the risk of not getting an effective intervention. Second is the presence of alternative study designs or the lack thereof. Third is the existence of constraints on product availability. Fourth is whether the "constancy assumption" has been met and how that relates to the feasibility of alternative study designs.

2. Review of well-known cases

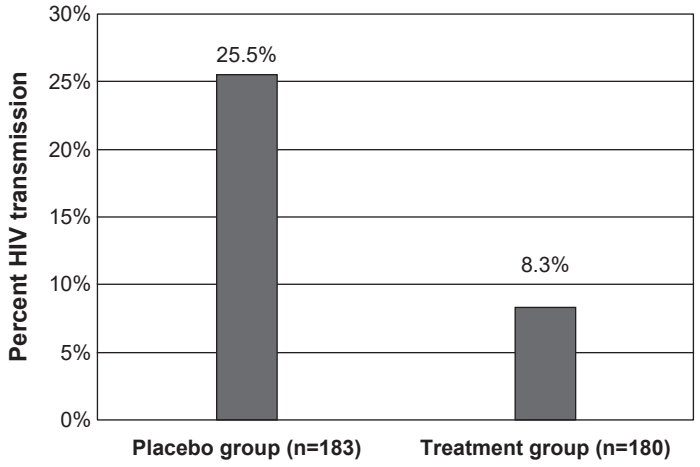
I will start off with a review of other fairly well-known cases. If we start with the perinatal case, we are looking at a placebo-controlled trial that was done with HIV positive pregnant women in the early 1990s using the drug (Fig. 1) [3] zidovudine or AZT with an object of preventing HIV transmission from the pregnant women to her fetus. At the time, there was no intervention known to be effective in preventing that transmis-

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. PMID: 9295246.

2) Levine RJ, Lurie T, Lagakos SW. Organized by Kurihara C. Interview with Robert J. Levine, Peter Lurie and Stephan W. Lagakos-Discussion on the Declaration of Helsinki and its background-. *Clin Eval*. 2001; 28(3): 409-22. Japanese. http://cont.o.oo7.jp/28_3/p409-22/report.html

3) Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. 1994 Nov 3; 331(18): 1173-80. doi: 10.1056/NEJM199411033311801. PMID: 7935654.

Fig. 1 Results of U.S./French perinatal HIV transmission trial ACTG 076



Source: *NEJM*. 1994; 331:1173-80[3].

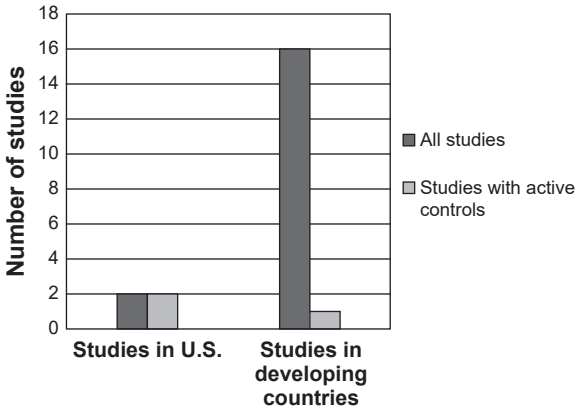
sion and so the use of a placebo was ethical, and this is the result was reported in *New England Journal of Medicine*[3].

In the placebo group, there was about a 26% transmission rate to the infant; in the treated group, it was down all the way to 8.3%. This is a very striking degree of efficacy, and I will make the argument in a moment probably about as effective as any intervention in the history of medicine.

3. Provision of antiretroviral drugs in perinatal trials

Dr. Wolfe and myself got interested in this when I made a trip to West Africa and heard about a placebo-controlled trial that was being done in Cote d'lvoire in the years after the initial placebo-controlled trial, which I should say, took place in the United States and France. The idea was that the regimen proved effective in the original US-France trial would be unaffordable in developing countries. So if one could develop a less costly intervention, an easier to administer intervention, then that would be of benefit to people in developing countries, which is true. The question really was what clinical trial design would you use in trying to identify this putatitively less expensive and effective intervention?

Fig. 2 Planned perinatal trials, 1997



What we discovered ultimately was that there were a large number of studies that were being conducted in the aftermath of the original trial in the United States and France (Fig. 2). Two of them were being conducted in the United States,

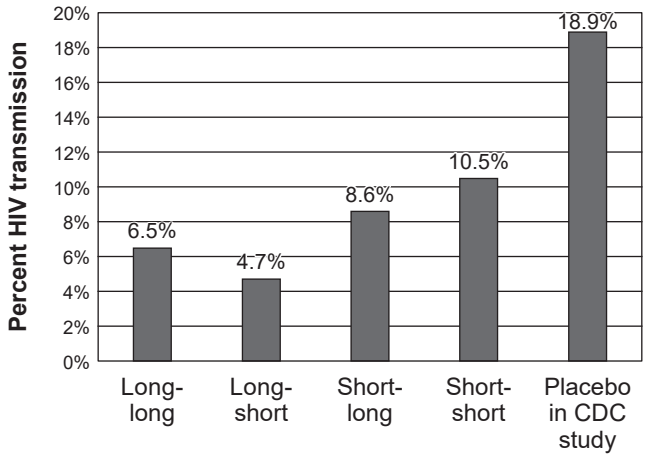
and in those two trials in each case, active controls were being used. No placebo was being used in two out of two. In the developing world, however, there were 16 trials and in 15 out of 16, a placebo or some other intervention not known to be effective was being employed. This is the double standard right here on a single slide (Fig. 2). Do one thing in the United States and simultaneously do something very different in the rest of the world. These studies were funded by very well-known institutions like the United States Centers for Disease Control (CDC), United States National Institute Health (NIH), and the World Health Organization (WHO) itself.

4. Thailand equivalency study

One of the interesting aspects of this was that there was, in fact, one trial which did not use a placebo-controlled trial and that was done by a group from Harvard with NIH money operating in Thailand (Fig. 3). This is the result of their trial[4]. What they did was instead of using a placebo, they had four different arms of AZT. The idea of long and long in the slide has to do with the duration of AZT administration prior to delivery and then after delivery. Long and long means for a long time before and a long time after. Then you have Long-short, Short-long, Short-short, and from these, you can see that there was quietly clearly effectiveness, remembering that the historical control from the earlier trial had a transmission rate of 25%. These were in all groups well below those.

Indeed, when the CDC study unfortunately was completed with its placebo group, the transmission rate in the placebo group was about 19%. The people in the Thai trial were protected, because they got some version

Fig. 3　Results of Thailand equivalency study



Source: Lallemant , et al. *NEJM*. 2000; 343: 982-91[3].

4) Lallemant M, Jourdain G, Le Coeur S, Kim S, Koetsawang S, Comeau AM, Phoolcharoen W, Essex M, McIntosh K, Vithayasai V. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med*. 2000 Oct 5; 343(14): 982-91. doi: 10.1056/NEJM200010053431401. PMID: 11018164.

at least of the effective regimen, but all the people who were receiving placebos were losing this degree of effectiveness, and seeing as though the infection was invariably fatal at that point, the consequences are clear. This design, of course, allowed a very nice comparison between different strategies, with different prices, and different degrees of toxicity as well.

5. Second example of an unethical clinical trial

A less well-known controversy, which some people are able to understand more readily, is this one involving a drug company called Discovery Laboratories in the United States. I say it's easier for people to understand, because one reason that people did not see the ethical problems in the perinatal trials was because they were done by people who were inarguably trying to help out people in developing countries and I would never contest that. They were well-intentioned people trying to make a difference in resource-poor settings. People found it easier to understand this second example, because there was a clear profit motive involved, the way there is in the situation now with COVID-19, because these are mostly private companies seeking profit ultimately.

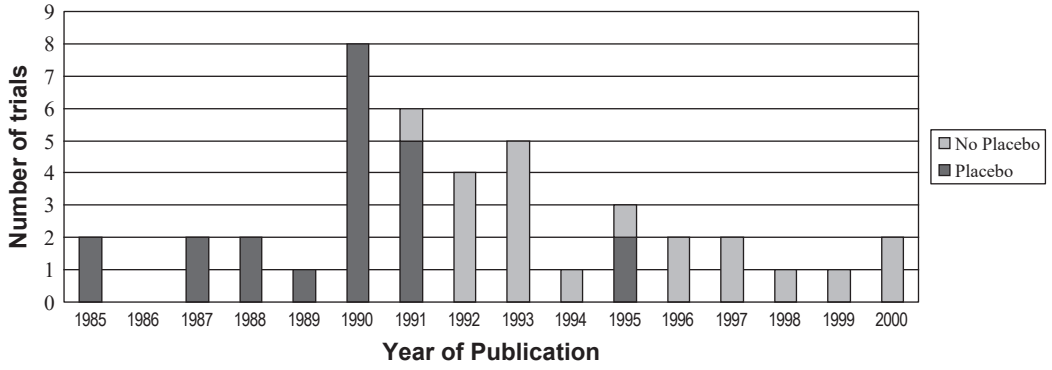
The product was called Surfaxin which is one of a series of surfactants, which are products instilled into the lungs of neonates and which can help the lung inflate if they have a condition called respiratory distress syndrome, which has a very high mortality. At the time of this study, which was in the late 1990s to early 2000s, there were already four surfactants on the market in the United States. Extraordinarily, there was so much research that there had already been a Cochrane meta-analysis done which showed a 34% relative reduction in neonatal mortality compared to placebo. A review in the *New England Journal of Medicine* stated that this was "without doubt the most thoroughly studied new therapy in neonatal care." Cochrane went on to say that "Further placebo-controlled trials of synthetic surfactant are no longer warranted." In an internal meeting, the U.S. FDA (Food and Drug Administration) stated that "Conduct of a placebo-controlled surfactant trial for premature infants with RDS is considered unethical in the USA."

The company needed a way to bring this product to market. One thing they did was conduct a study in Europe, which unsurprisingly did not have a placebo group. It was considered to be an equivalency or non-inferiority study in which Surfaxin was compared to one of the four already approved surfactants.

This is quite an interesting study slide because it shows the history of the development of these four surfactants (Fig. 4). You can see that the early studies in '85, '87, '88 all of them used placebo controls, and then starting somewhere in the early 90s, you start to see non-inferiority or other non-placebo-controlled trials starting to be published. There are a couple of exceptions in '95, but after that nobody is doing placebo-controlled trials anymore. Yet, here in 2001, when this placebo-controlled study was proposed, we have a company proposing to set back the ethical clock by about 10 years, by conducting this study on the ground that it's taking place in a developing country.

The FDA convened a meeting to discuss this. Somebody leaked us the internal documents from that. It showed just how unthinking people can be when they consider these issues. The name of the meeting was "Use of placebo-controls in life-threatening diseases: is the developing world the answer?" Somebody needs a little bit of help in deciding what their meetings are to be called. The location in which the studies were to take place was quite unclear. It was a protocol in search of a location and made a mockery of argument that

Fig. 4　42 Randomized trials of natural and synthetic Surfactant in the treatment of neonatal respiratory distress syndrome



we sometimes hear, which is that the local people want this trial.

We brought that trial to public attention and the placebo-controlled trial never happened. The study was redesigned. They found a way to prove effectiveness and to my understanding, the product eventually came to market despite the lack of a placebo control.

6. Availability of COVID-19 vaccines

Let's turn to vaccines for COVID-19. First, I will give you some background on those and then go through the exercise of comparing these two situations to COVID-19.

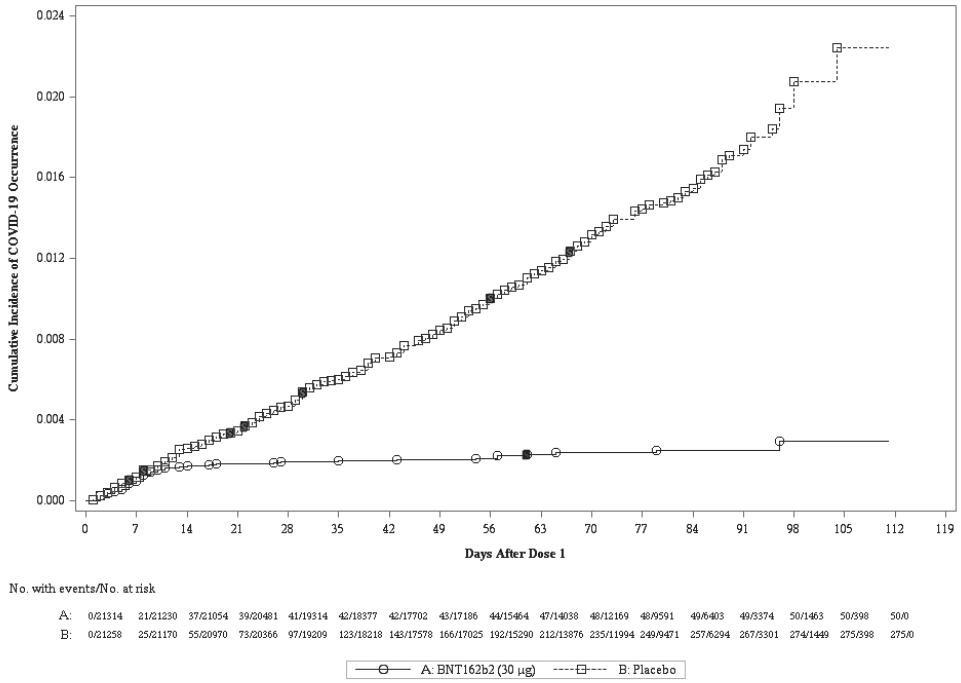
There are 17 vaccines that are now authorized in at least one country. A fair number of them are authorized only in their home country. There are eight of them that have substantial presence in the international market in that they have been authorized in at least 10 countries. There are over 100 countries with at least one authorized vaccine and with striking degrees of efficacy up to 95%. Although there have been some safety issues, generally speaking, the safety profiles have been acceptable. So far, 2 billion doses have been administered, that is, about 26 doses for every 100 people in the world. Of course, some people have gotten two. It is a little bit hard with this amount of vaccine availability to make a blanket argument that there is no available product on an international scale.

7. COVID-19 vaccine efficacy and vaccination rates

This slide shows the efficacy data on Pfizer/BioNTech vaccine and the Moderna vaccine (Fig. 5)[5, 6]. Both have about 95% effectiveness against symptomatic COVID-19 infection. These are extraordinary efficacy findings, and they both represent an enormous opportunity from a public health point of view, but also at the root of the ethical question that is before us.

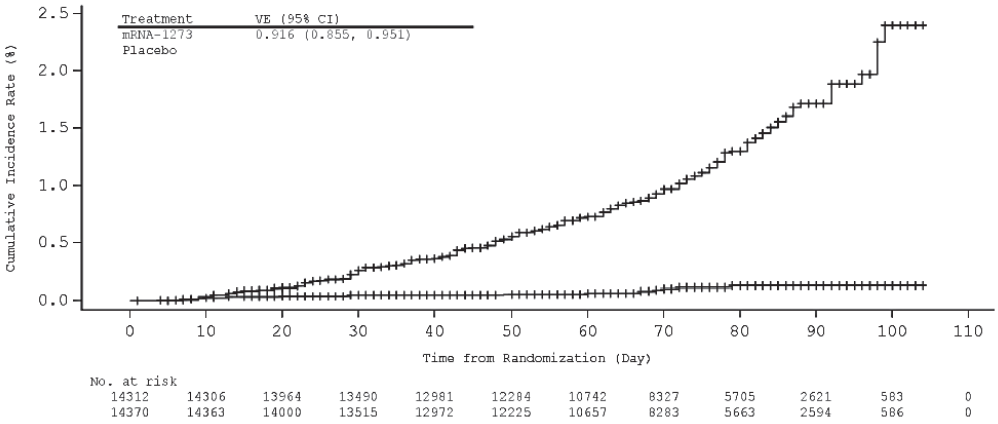
As of June 4, 2021, there was clear evidence of widespread disparities in vaccination rates. The per capita rate of vaccination is highest in North America, Chile, Uruguay, Europe, China, Mongolia, and some countries here in the Middle East, but very few countries with nothing. In places like Brazil and Argentina, there

Fig. 5 Pfizer/BioNTech and Moderna COVID-19 vaccine efficacy



Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 17NOV2020 (21:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: /nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_f001_km_d1_aai

Source: FDA Briefing Document Pfizer-BioNTech COVID-19 Vaccine. Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020. Sponsor: Pfizer and BioNTech
https://www.nejm.org/doi/full/10.1056/nejmoa2034577
Published in Polack, et al. *NEJM*. 2020[5].



Source: FDA Briefing Document Moderna COVID-19 Vaccine.
Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020.
Sponsor: ModernaTX, Inc.
https://www.fda.gov/media/144434/download
Published in Baden, et al. *NEJM*. 2020[6].

is a fair amount of vaccination. It's a bit hard to make an argument of complete lack of vaccine availability. On the other hand, you have Africa, in particular, where the rates of vaccination are alarmingly low, and Prof. Macklin has gone through some of the reasons why that is the case.

8. Comparing the risks of placebo use

I said I would compare these products on four different dimensions, and this is the first (Table 1). This is an attempt to place the risk that all of us I hope agreed was unacceptable in the perinatal and the Surfaxin case in the context of the currently available COVID-19 vaccines, or at least the more effective ones.

Here I have calculated the difference between the event rates in the treated and placebo groups. It was about 25% transmission in the placebo group in the original perinatal study versus about 8% in the treated group. So the difference is 17%. There is an index which is the number needed to treat which is the inverse of the difference in the two groups. That tells you the number of patients that need to be treated in order to prevent one outcome. For the perinatal, it was 5.8, which is why I happen to believe that this is the most astonishing intervention perhaps in the history of medicine.

For every six infants who are treated, with an intervention that is now inexpensive, you save a life. This is an infant who then gets an entire lifespan. If you compare that to things like interventions for stroke, cardiovascular disease, it's not even remotely in this ballpark. This is an extraordinarily effective intervention and makes the provision of the placebo in a trial like the perinatal ones all the more problematic.

In the Surfaxin case, the difference between the treated and the placebo in the meta-analysis of earlier trials was 5.2% and that translates to a number needed to treat on 19.1. The number needed to prevent one event is

Table 1　Comparing the risks of placebo use

	Perinatal	Surfaxin	Pfizer	Moderna
Difference in event rates	17.20%	5.20%	0.84%	1.24%
Number Needed to Treat to prevent one event	5.8	19.1	119	80.6
Number Needed to Treat to prevent one death	5.8	19.1	11,900	8,060

Assumes COVID-19 fatality rate = 1%
In Pfizer and Moderna trials, there was one death due to COVID-19 among 32,398 placebo patients

5) Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020 Dec 10. doi: 10.1056/NEJMoa2034577. Epub ahead of print. PMID: 33301246.

6) Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Kehtan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2020 Dec 30. doi: 10.1056/NEJMoa2035389. Epub ahead of print. PMID: 33378609.

the same as the number to prevent one death for both the perinatal trials and Surfaxin because HIV infection was assumed to be invariably fatal and because the Cochrane meta-analysis, on which the estimates for Surfaxin was based, used mortality as an outcome.

Now, let's turn to the situation with COVID-19. The differences are much smaller. The sample sizes in these trials are very large, in the tens of thousands. In a group of 10,000 to 20,000 people, there would be only a limited number of people in a 2-month period who will acquire symptomatic infection. But when you look at this difference which for Pfizer was 0.84% over a 2-month period, Moderna 1.24%, and then you do the math on those, you wind up with the number needed to treat to prevent one event of 119 and 80.6, so about 100. Quite a bit higher than the perinatal trials and Surfaxin, but not enormously higher and remember that COVID itself is not a fatal infection. Applying a crude 1:100 fatality rate to a case of symptomatic COVID, which was the outcome in these two trials, you get a number needed to treat to prevent a death of about 12,000 in Pfizer case and about 8,000 in Moderna, so you can say 1:10,000.

That says a couple of things. One is that the excess risk due receiving a placebo in these vaccine trials is really considerably lower than it was in the first two cases. But that doesn't answer the question of whether or not this is an acceptable risk. It just places a number on it, and we can have a conversation about whether this is still too high a risk. I probably would argue that it is, but reasonable people can probably disagree over that. Certainly, it's very different than the situation in these two earlier cases.

9. Comparison using alternative study designs

The second dimension on which I wanted to compare these three trials has to do with the availability of alternative study designs (Table 2). As Prof. Macklin indicated with the multiple sclerosis example, there are occasional situations where there is simply no other way to do this other than a placebo control. You do not want the research to stop completely. But if, in fact, there is an alternative design, then the ethical calculus is altered.

In the perinatal example, the alternative design that we put forth was in fact the one that was used in Thailand: a non-inferiority trial. As we have seen, it provided a very convincing display of effectiveness, and was able to unpack the regimen in ways that wouldn't have been possible with a simple placebo. A non-inferiority trial design basically says this new product you are testing is no more than a specific amount less effective than the already available product. You establish this non-inferiority margin called "ε" which is some amount less than the standard. If it's not too much less effective than the standard, then you call it for all intents and purposes non-inferior, and from a clinical point of view, this is a product that is suitable for

Table 2 Alternative study designs, perinatal and Surfaxin

●Perinatal
• Non-inferiority trial
• Conducted in Thailand
●Surfaxin
• Non-inferiority trial (conducted in Europe)
• Superiority trial (FDA: "a clinical efficacy hurdle that the sponsor deems too high for this drug.")

use, assuming that the initial product had clinical benefit. That was the design that we put forward in the perinatal study.

In the Surfaxin case, it was a little bit more complicated. There was a non-inferiority trial that was done in Europe and that again was evidence of double standard. There was also consideration of a superiority trial. A superiority trial is a case where you are comparing two things and you try to prove that your new product is better than the old product. The placebo-controlled trial is a special case of a superiority trial in which the comparator is a placebo. It was suggested that the company could do a superiority trial in which its product might be proved more effective than one of the existing surfactants, but interestingly enough, the FDA said that the superiority trial was "a clinical efficacy hurdle that the sponsor deems too high for this drug," which is a polite way of saying they didn't want to do it that way.

Those are alternative designs for the previous trials and they crop up again when we start thinking about COVID-19 vaccines.

10. Alternative study designs of COVID-19 vaccines

Here the alternative designs are greater in number and more diverse (Table 3). One possibility is a superiority trial as was considered in the Surfaxin case. Here the sample sizes are truly formidable, at least if you use the Pfizer or Moderna products as the comparator, because you are looking at 95% effectiveness. It's very hard to be more effective than 95%, and if you wanted to actually prove that, I have not done the sample size calculations, but they would certainly be in the hundreds of thousands and quite possibly even more than that.

A second option would be a non-inferiority trial. This is interesting because when the FDA and the WHO put out their guidance on what would be an adequately effective COVID vaccine, they stated that the product should be more than 50% effective. You don't want minimally effective vaccines on the market. We are happy to say that has not turned out to be a problem. But efficacy should be greater than 50%, and if you were to use a non-inferiority margin, according to the FDA and WHO, that ε that I referred to earlier, would be

Table 3 Alternative study designs, COVID-19 vaccines

●Superiority trial
• Formidable sample sizes
●Non-inferiority trial
• FDA stipulated 10% non-inferiority margin based on >50% efficacy
• But with 95% efficacy, considerably larger non-inferiority margin may be acceptable
• May require 2-3 times as many subjects but "may enable reliable randomized evaluations of efficacy and safety"
• Constancy assumption (met in perinatal and Surfaxin trials)
●Challenge trial
• Greatly reduced sample size
• Unique ethical issues
●Correlates of immunity
• Reduced sample size
• Area of active research

10%. The problem with those guidances is that they never really contemplated 95% effectiveness. It's one thing to say your product is, let's say, 60% effective and you don't want ε to be more than 10%, in other words, vaccine efficacy no less than 50%, but it's a totally different thing if you are starting from 95% efficacy, you have a much more effectiveness to "give away" and still remain above 50% effectiveness.

One could imagine a non-inferiority margin or ε that could be much higher than 10%, say 20%, even 30%, and you would still have a vaccine that with a high degree of confidence would be quite effective and more effective than the 50% people originally required. That would still require more subjects than a placebo-controlled trial. There is one study by some eminent statisticians [7] who estimated perhaps 2 to 3 times as many subjects depending on the exact inputs, but they did conclude that such a design "may enable reliable randomized evaluations of efficacy and safety using a non-inferiority trial design." One caveat though is the so-called "constancy assumption", which is the idea that the original product would be as effective in this new setting as it was in the old setting in which it was proved effective. That assumption was met in the perinatal and Surfaxin trials. Here it is a little bit more complicated. We will return to that shortly.

A third potential design is a challenge trial. That is a situation in which people are intentionally infected with the pathogen. This reduces sample size because you don't have to wait for people to be exposed. Most people will not be exposed in a 2-month study as we can tell from the relatively low incidences of COVID-19 in those large trials. So the challenge trial takes away the waiting period, if you will, and everybody is exposed and the results are enormously decreased sample sizes. But, it creates a whole set of unique ethical issues of its own, particularly, the lack of consistently effective treatment for COVID-19 and the fact that in a subset of cases the infection will be fatal. It's a whole issue unto itself.

The big hope in vaccine development is that we will identify what are called "correlates of immunity", for example, neutralizing antibodies, in which one could simply look at antibody levels as opposed to infection levels, and that would also reduce sample size and allow products to come to market quicker. To state the obvious, any delay in getting a product to market in the context of a pandemic is an ethical issue itself.

11. Reconsidering product availability

The third dimension is reconsidering product availability. So, in the perinatal and Surfaxin situations, the drugs were largely unavailable in the settings the studies were to be conducted. There was very little zidovudine available in Africa to be sure. Note that even in countries without widespread availability of any of these products it's highly likely that local wealthy people were getting access to these products. You have this disparity that is within countries as well as between countries.

As was suggested in the earlier presentations, the lack of availability leads to the standard of care argument, which argues that the lack of local availability results in a situation where the researcher has no ethical obligation to provide anything more than what is locally available. Seeing that little was locally available in the perinatal and Surfaxin studies, in the view of some, justified the use of placebo. Of course, not in my view, but that was the argument.

7) Fleming TR, Krause PR, Nason M, Longini IM, Henao-Restrepo AM. COVID-19 vaccine trials: The use of active controls and non-inferiority studies. *Clinical Trials*. 2021. Feb 3; 1740774520988244. Doi: 10.1177/1740774520988244.

Let's ask the question of product availability with respect to COVID-19 vaccines. It's a bit more complicated, because laid on top of the usual disparities between countries and within countries, we do have a legitimate problem which is the rollout problem. The products are only now being identified as effective. The companies are starting small in terms of the number of products that they can produce, and there is an inevitable ramp-up as more comes to market, but the result is that we are in a period even in the wealthiest countries where there is not enough vaccine to go around and there is prioritization based on public health need that the authorities ought to be making. I don't think any of us are troubled by such prioritization in the context of legitimate shortages based on non-economic circumstances.

But the problem in COVID-19 is that you have a mixture of what are true shortages related to lack of production laid on top of those long-standing socioeconomic disparities. Those phenomena become essentially impossible to disentangle at a certain point. Because, at the end of the day, even in a country, say, South Africa where there is a certain amount of vaccine availability, they are in a different place with respect to their public health prioritization than say, the United States, because of the underlying disparity in the way that the product is being distributed. It may be a good ethical decision within a country with scarcity to start with older people, but the reason that they are providing the vaccine only to older people whereas in the United States we are on to vaccinating 12-year-olds is because of these disparities in economic status leading to greater leverage in negotiating contracts with vaccine manufacturers. This should not be used to justify placebo controls.

12. The constancy assumption

The last thing I want to touch on is the constancy assumption (Table 4). This is the idea that the product will work as well in the new location, developing countries, let us say, as it did in the location where the product was proved to work. That was not an issue for the perinatal and Surfaxin cases, although I did hear people try to raise that in the perinatal case, arguing that somehow AZT would lose its effectiveness when it went to West Africa. I never thought that that made much sense, and at the end of the day, when the trial results came in, it wasn't an issue.

But it is more of an issue in our current circumstance in COVID-19 primarily because of the variants, not because of differences between local populations. You have to evaluate the constancy assumption in the

Table 4　The constancy assumption

- ●Perinatal, Surfaxin: not an issue
- ●COVID-19 variants
  - • Continually evolving.
  - • Dependent upon vaccine characteristics, variant prevalence, the degree of variant resistance, and the acceptability of immune-bridging studies.
  - • Oxford/AstraZeneca vaccine ineffective in South Africa where B.1.351 is prevalent.
  - • True equipoise over whether any vaccine would be effective in a given country could justify placebo use.
  - • Requires continued reassessment.

context of the characteristics of the vaccine, how prevalent the variants are, the degree of resistance that the variant imposes, and whether or not you have these immune-bridging studies, which we don't yet have, but which might get us out of the box altogether.

This can be a real issue. The Oxford/AstraZeneca vaccine which was effective in studies conducted in western countries proved to be ineffective in South Africa where the B.1.351 variant was prevalent. So you have to assess how much variant you have and how likely is it that that variant would not respond to the vaccine, in order to justify a placebo. So there would have to be true equipoise over whether *any* vaccine was effective before you could justify using a placebo. Obviously, this requires continuing reassessment as the variant situation continues to evolve.

13. Conclusion

In summary, the risks of placebo use were extremely high in the perinatal and Surfaxin circumstances, certainly lower for COVID-19 vaccines (Table 5). There is a question of whether they are low enough to justify a placebo control in the circumstance of COVID-19 vaccines. Alternative designs were available in the perinatal trials and Surfaxin and potentially in COVID as well, certainly if we have correlates of immunity. The constraints on product availability were economic and clearly so in the perinatal and Surfaxin cases. In COVID, it's a more complicated combination of both economic and production shortages. Finally, is the constancy assumption met? Yes, in the first two circumstances. Here in COVID, mostly yes at this point but the situation does require ongoing monitoring.

In conclusion, to determine the ethical acceptability of placebo use in a given situation, you have to do a case-by-case assessment. These assessments need to be revised over time and we need to keep those who would propose placebo controls on their toes as the situation continues to evolve.

I hope that this comparison has proved helpful and puts the overall ethical debate in context.

Table 5 Summary

	Perinatal	Surfaxin	COVID-19 Vaccines
Risk of placebo use	High	High	Fairly low
Alternative designs?	Yes	Yes	Potentially yes
Constraints on product availability	Economic	Economic	Economic Production shortages
Constancy assumption met?	Yes	Yes	Requires ongoing monitoring

Conclusion: To determine the ethical acceptability of placebo use in a given situation, case-by-case assessments, revised over time, are necessary.

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Discussion (Day 1 No. 1)

Ramin Parsa-Parsi
Workgroup Chair of the 2013 revision of the Declaration of Helsinki
German Medical Association

Thank you so much for these extremely interesting presentations. I especially appreciated the excellent examples and references to different studies. It was very helpful and I took a lot of notes. This event and today's discussion will be very valuable for the World Medical Association (WMA) looking ahead to a possible next revision of the Declaration of Helsinki [1]. We do not know yet when exactly the revision process will be initiated, but the WMA usually revises its documents every 10 years, or, if necessary, even earlier. The last revision of the Declaration of Helsinki (DoH) lasted a couple of years and culminated in the formal approval of the WMA General Assembly in 2013. The next revision would therefore be expected to take place in 2023, which is soon, and it's possible that the WMA would even start a little bit earlier in order to have begun the process by then. However, no decision has been made so far.

The WMA is currently revising its International Code of Medical Ethics (ICoME) [2], which is also one of the core documents of the WMA and a very important one. We have a large international working group focused on this. Of course, this document also deals with clinical research in some paragraphs, as it reflects the core ethical principles in medicine, but obviously, it doesn't go into as much detail as the DoH. That's not its purpose. Instead, the ICoME is a foundation of ethical principles for the medical profession in a globalized world. It is intended to serve as a template for national codes. The revision is a rather work intense endeavor for the workgroup and the WMA Medical Ethics Committee. We very recently completed a public consultation. Maybe one or two of you even participated. Even though the Medical Ethics Committee will be very focused on the revision of the ICoME until its scheduled completion in October 2022, given the need to ensure that the DoH remains up to date, I would assume that the WMA will embark on another revision sooner rather than later. Certainly, it will be extremely important to look at the topics of placebo and post-trial access in more depth. They were already the subject of intense and comprehensive discussions during the last revision. In fact, in preparation for the DoH revision, the WMA installed a dedicated workgroup to deal exclusively with the placebo issue. We even organized an international expert conference to discuss possible different approaches with the medical ethics expert community. Back then it was quite difficult to come to a consensus about the exact wording we currently have. Because the revision was a truly international and

1) World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research involving Human Subjects. Adopted Jun 1964, last amended in Oct 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
2) The World Medical Association. International Code of Medical Ethics. Adopted in 1949, last amended in 2006.
https://www.wma.net/policies-post/wma-international-code-of-medical-ethics/

inclusive endeavor, we considered very different points of view, which therefore involved quite a bit of compromise. We will most likely need to revisit the two paragraphs dealing with placebo and post-trial access during a next revision process, and I foresee that it will once again be an interesting challenge to discuss the wording in light of the current pandemic situation and these evolving and very pressing issues.

I have heard and taken note of the proposals Prof. Chieko Kurihara made in the very beginning of our session today in terms of new wording that could be a possible solution. I have also heard the concerns of Prof. Ruth Macklin and appreciate the excellent examples she provided. I am very much looking forward to the discussions involving these topics within the WMA. Of course, I don't know how they will develop. I can only say that from my point of view it will certainly be important to discuss whether current trials are still in line with the two documents in question - the DoH (Declaration of Helsinki) [1] and the CIOMS (Council for International Organizations of Medical Sciences) [3].

Otmar Kloiber

Secretary General, World Medical Association

First of all, thanks for these three very interesting presentations. I liked very much the different approaches to the use of the placebos that have been taken by Prof. Macklin and by Dr. Peter Lurie, one of the kinds of a principle approach and one of a pondering approach. Yet, the question remains which approach to take. I am very happy that we are the policy-setting body for the Declaration of Helsinki, but we are not the one to judge each and any application of it. It's also very clear to me that the Declaration of Helsinki is a little weak on the side of prevention research. We obviously have to look a little bit into the requirements of prevention research to the use of the placebos. That may be a part of the development that has to come among other points in the revision of the Declaration of Helsinki which I see coming up soon.

Clearly, with a disease that is potentially deadly and that has no therapeutic, there are question marks about the challenge trials that are out there, as well as the use of trials without placebos, especially in poor settings. Prof. Macklin mentioned the concept of "post-trial benefit". Meanwhile, the concept of "additional benefits" have been one of the topics discussed with the Declaration of Helsinki [4]. Many of us thought it was something to add to the Declaration of Helsinki, but it was rejected very clearly by the representatives coming from resource-poor countries. They reasoned that those trials easily may become something different when some see them as a method to gain material profit from. Finally, the concept of "additional benefits" was not included in the Declaration.

There also was the question about double standards. We discussed these examples of trials that Dr. Lurie reported very elegantly with a very good analysis. Like with the additional benefits approach we received a very affirmative answer from our colleagues, especially from Africa, saying "no" double standards at all.

I do however accept the argument that has been brought up by Dr. Lurie, having a principle is nice, but,

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3) Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-related Research Involving Humans. 2016.
https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

4) Page 558 in the interview with Dr. Margaret Mungherera; Page 571 in the interview with Dr. Otmar Klober.
Mungherera M, Kloiber O, Doppelfeld E, Kumar A, Jorge MR. Kurihara C, Saio T, Interview. The WMA Council Session in Tokyo, 2014: Globalized medical ethics and research ethics: – Interview with Dr. Margaret Mungherera, Dr. Otmar Kloiber, Dr. Ajay Kumar, Prof. Dr. Elmar Doppelfeld, Dr. Miguel R. Jorge. *Clin Eval*. 2014; 42(2): 553-90.
http://cont.o.oo7.jp/42_2/p553-90eng.pdf

you have to look into each and every case. To me, it makes a difference whether a decision on the acceptable standards has been taking by sponsors in the rich world in kind of a paternalistic way judging risks and benefits for others, or whether **that is a decision** by the community that is affected. Because the pondering **that has to be done** is not only based on facts, but it's also a question of community values and community acceptance.

I am also aware of all the problems of creating an undue incentive by just creating the mere opportunity to treatment which without a trial would not exist. In the end, those were the reasons that made us saying no to double standards. And in that context I agree with Prof. Macklin: This brings up some of questions with the paper issued by the experts of the WHO (World Health Organization)[5].

I have a question for Prof. Kurihara: I have not quite understood what problem you have with vaccination trials that have been done outside of Japan. I agree with you that there are different horizons you can look for, endpoints you can select. We can say the endpoints have been extremely short. We are looking only at 6-month and we are looking only at certain variants of the virus, all of this may produce limited applicability of results. Let's put those questions aside for a moment and let's accept for the moment that we are in an emergency.

Why would it not be acceptable for a country like Japan to accept good studies from other countries like the United States or European countries?

Chieko Kurihara

Specially-appointed Professor, Kanagawa Dental University, Japan

My argument is that it is possible for Japan to accept the results tested in some Western or some developing countries where already efficacy rate was proven. Actually, in Japan "bridging study", pharmacological studies with surrogate endpoint have been conducted for approval of the two mRNA vaccines. What I wished to say is that there are some things that people in the world want to know, as I said, long-term efficacy or long-term safety, because the original protocol was designed to prove two years efficacy and safety. That is the reason why Pfizer/BioNTech has been continuing placebo study permitting switching from placebo group to active group. There is some "compelling reason" to continue placebo study. Japan and maybe some other Asian countries are, theoretically, not so eager to get vaccine to decrease morbidity and mortality. It would be possible for Japan and other Asian countries to conduct global placebo study to find longer efficacy or longer safety assessment. This is my opinion.

My argument is not that it is necessary for Japanese people to enter into placebo studies to get the evidence for Japanese population. My argument is that Japan should contribute to and participate in world-wide efforts to generate something which have not been proven globally. Japanese government is thinking only to get vaccine for whole population. This is against the "justice" principle, which is the point I wanted to argue.

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5) WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation, Krause PR, Fleming TR, Longini IM, Peto R, Beral V, Bhargava B, Cravioto A, Cramer JP, Ellenberg SS, Figueroa JP, Halloran E, Henao-Restrepo AM, Ryan MJ, Levine MM, Nason M, Nohynek HM, Plotkin S, Rees H, Singh JA, Swaminathan S. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. *N Engl J Med*. 2021 Jan 14; 384(2): e2. doi: 10.1056/NEJMp2033538. Epub 2020 Dec 2. PMID: 33264543.

COVID-19 and bioethics Part 3:
Pandemic and research ethics－Democracy, placebo and post-trial access【Day 1, June 4, 2021】

From Nuremberg to Helsinki: Historicising research ethics during health crisis

Ulf Schmidt
Professor of Modern History, University of Hamburg, Germany

1. Opening remarks

I hope I will be able to contextualize some of these issues in relation to some of the history also in relation to the history of biomedical ethics standards, the Declaration of Helsinki [1], and the Nuremberg Code [2] on the one hand, but also some of the issues relating to politics which have been touched on by some of our previous speakers before.

The work which I am discussing here is related to research which I and more than 20 colleagues around the world have been doing over the last couple of years many of who are present here today and which we called "Ethical Research" (Table 1) [3] in which we try to lay down some of the issues which have affected human medical ethics and human protection regimes.

Table 1 Ethical Research: Questions

Is our current human protection regime adequately equipped to deal with new ethical challenges resulting from high-tech biomedical science?
How important has the Declaration of Helsinki been in non-Western regions, for example in Eastern Europe, Africa, China, and Latin America?
How does the Declaration negotiate complex contestations around conflicts of interest and the use of placebos?

Oxford, OUP, 2020 [3]

1) World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research involving Human Subjects. Adopted Jun 1964, last amended in Oct 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
2) The Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, October 1946-April 1949. Vol. 2, p. 181-2.
https://www.loc.gov/rr/frd/Military_Law/pdf/NT_war-criminals_Vol-II.pdf
3) Schmidt U, Frewer A, Sprumount D, eds. *Ethical research: The Declaration of Helsinki, and the past, present and future of human experimentation*. Oxford University Press; 2020.

Among others, we have been asking about the importance of the Declaration in different regions, for example, Eastern Europe, Africa, China, and Latin America and how it's actually being implemented in some of those contexts. It's an attempt to contextualize the Declaration of Helsinki both historically and contemporarily in a much broader global framework.

2. Worldwide pharmaceutical market

Let me start with looking at the actual field, the broader aspects. I do think they are relevant in some of the discussions we are having. Let us talk about money for a moment. Revenues for the global pharmaceutical market are beyond most people's wildest imagination. The revenue generated increased from around $390 billion in 2001 to over $1.1 trillion in 2016, which at that time was the nominal GDP of Russia. The main markets, North America including the United States and Canada, account for almost 50% of the global pharmaceutical market revenue followed by Europe with 21.5%, Africa and Asia excluding Japan and Australia with 16.4%, Japan with 8.3% and Latin America with 4.7%.

You can see where the global pharmaceutical revenue is generated primarily and that puts things into a little bit of context here when we are also speaking about issues beyond current vaccination issues. The top three world companies are Pfizer, Novartis, and Roche at least according to these figures, which may already be outdated, but I am sure that Pfizer is still among the most prominent ones. In 2017, Pfizer sold prescription drugs worth $45.3 billion and invested $7.6 billion into R&D. Novartis sold prescription drugs of $41.8 billion and invested $7.8 billion into R&D. Now for everybody, these are quite staggering figures. Once updated for the sale of COVID vaccines for some companies at least, they will be eye-watering.

Now one would think that unambiguous uniform regulations ensuring the safety of participants and continued public confidence in human research would be in everyone's interest. Yet little is further from the truth. We are living in a society or in a global community which according to Tony Judt, the author of Postwar[4], is profoundly wrong. Ruth touched on the issues very tangentially, issues such as vaccine nationalism, vaccine populism. These are issues which we will have to deal with in the near future. According to Judt, in our world today, people no longer asks whether everything is good, fair, or just, or whether it improves the lives and the health of the many, or whether indeed it is true or untrue. He is arguing that our world has not only left ideologies, and he means the Cold War ideologies behind, but it has become post-ethical.

3. The Nuremberg Code

Now, the Postwar world had other ideas and also other hopes. More than 70 years ago, in 1947, the Judges and the Doctors trial formulated 10 principles for the ethical conduct of human experiments which are today known as the Nuremberg Code and which is probably very familiar to you. Most of you may not be as familiar to the principle one about informed consent as they think, but it is extremely comprehensive, and as some have argued, slightly legalistic.

Over 60 years ago in 1964, the World Medical Association (WMA) adopted the first version of the

4) Judt T. *Postwar: A History of Europe since 1945*. Penguin Books; 2006.

Declaration of Helsinki, which we all agree is another landmark in the history of biomedical ethics. Yet it is far from certain whether our existing global framework, and here we come to issues, for example, the extent to which some of these guidelines are legally binding, which are clearly not, but nonetheless, they are extremely important, whether these guidelines and frameworks are actually sufficient and provide sufficient guidance for tomorrow's research practices.

Also, experts are just becoming aware of the enormous implications and demands on the current system of research governance, particularly in what is increasingly confusing research environment which requires adaption and near-constant reform. As pointed out by some of the participants, we may be looking at another revision of the Declaration of Helsinki in the near future. The historical and contemporary relevance of both documents offer ample reasons to historicize and reflect for a moment about research ethics more broadly.

4. The Nuremberg Doctors' Trial

Encouraging medical professionals to reflect about existing and emerging risks involved in medical science was a very long process that required great efforts on the part of experts and organizations such as the WMA. The Doctors' trial which opened in 1946 charged 23 German doctors and official with war crimes, crimes against humanity for their involvement in unethical and often lethal camp experiments.

The images of the women presented during that trial went around the world. They were testifying and became a recurrent theme in debates about some of the atrocities committed during the Second World War. What you see here is one of the medical experts in 1946 at the relative start of the trial, Leo Alexander. He was a Jewish refugee scientist, who had immigrated to United States and then returned to Germany at the end of the World War II to investigate some of the crimes which had been committed, and he presents one of the witnesses from Holland and their particular scars.

5. The World Medical Association 1949

Following the post war condemnation of Nazi medical war crimes, the WMA reaffirmed its support for Hippocratic medical ideals in the Declaration of Geneva [5], and as we have all already heard a very important International Code of Medical Ethics [6] from 1949 originally, yet at the time, the organization was initially reluctant to extend the discussion further into the field of human experimentation insofar that it did not want a more detailed document.

However, war crime trials after 1945 contributed to a climate in which public debate about the role of research ethics became inevitable. Harsh sentencing of German scientists, for example, during the Struthof medical trials in the 1950s prompted the French National Academy of Medicine and the Medico-Juridical Commission of Monaco, which had a mixed membership of lawyers and physicians to take a firm stand on

5) The World Medical Association. Declaration of Geneva. Adopted in 1948, last amended in 2017. https://www.wma.net/policies-post/wma-declaration-of-geneva/

6) The World Medical Association. International Code of Medical Ethics. Adopted in 1949, last amended in 2006. https://www.wma.net/policies-post/wma-international-code-of-medical-ethics/

medical misconduct in clinical research. They proposed that they might draw up a new code of ethics in human experimentation, which indeed would have legal applicability.

By doing that, they set themselves on a collision course at the time with the WMA. WMA officials at the time made it clear that if others including lawyers persisted in drafting such a document, and I quote, "this document will not be accepted by the medical professional of the world." So at the time, there was a clear resistance against having others encroaching on what the WMA regarded as their area of competence. Yet by insisting that it was the only legitimate body with a moral authority to draft such as a text, the organization found itself under pressure to produce a more authoritative text.

Moreover in continental Europe at least, the memory of the Holocaust showed no signs of waning. Delegates such as Lambert Hulst himself involved in the Dutch resistance, who later became president of the WMA, raised awareness of the risks involved in clinical research, which at that point was funded with considerable new resources, investments in science and technology. Experiments have to be voluntary, he noted, and were only permissible if participants were informed about their rights to consent or refuse, he argued. He called on the WMA to define more clearly the boundaries within which research could be legitimately performed.

6. Western research ethics transformation after Nuremberg Code

In the decade after the promulgation of the Nuremberg Code, the ethics of western research culture underwent a process of profound transformation. It was a period in which ongoing human and civil rights violations went hand in glove with the realization in the field that further resistance to change could lead to damage to the medical profession.

Making enormous investment in medicine science, public agencies in North America and Western Europe had created a situation, as some authors have argued, where available resources were "greater than the supply of responsible investigators." By beginning of 1960s, in light of evermore frequent revelations about unethical research on vulnerable populations and after the widely publicized thalidomide tragedy, it was increasingly difficult to oppose the reform of existing research practices. By 1961 and as you can see here published in 1962, the WMA's Medical Ethics Committee produced what they called a Draft Code of Ethics on Human Experimentation. This is from October 1962.

7. Last minute changes on the Draft Code

Two years later, in June 1964, the WMA adopted the Declaration during its General Assembly in Helsinki but not after making last minute changes. On 14th June, only days before the inauguration ceremony, the WMA Ethics Committee agreed to change the name of the document from Ethical Principles to Recommendations Guiding Doctors in Clinical Research thus making the guidelines somewhat less binding for the medical community. The Committee also decided to delete Clause III(c) which states "no clinical research should be undertaken when the subject is in a dependent relationship to the investigator" and replace it instead with an addition to Clause 4a which said "the investigator must respect the right of each individual to safeguard his personal integrity," now comes the addition, "especially if the subject is in a dependent rela-

tionship to the investigator".

Within less than 2 hours, the character of the WMA's Ethics Code at least in part had changed. Experiments on institutionalized children, asylum inmates psychologically or physically handicapped or the elderly while requiring due care in detention were no longer ruled out. The final version dated 18th of June 1964 known as the Declaration of Helsinki was also silent on the subject of prisoners and vulnerable population.

You can see here the representatives of the Finnish Medical Association handing over the document to the president of Finland. In the summary of it and for the year 1964, the WMA hardly mentioned the document at all. There are two or three lines mentioned, but otherwise, very little was said. It seems to be that the organization did not anticipate the impact the Declaration would have at least at that point on medical research ethics over the next 50 years. Here is the actual document, the typed version of the Declaration of Helsinki as we have uncovered it in the Finnish Medical Association archive.

8. Present situation: 2007 Novartis clinical trial in Poland

Have things improved? As discussed today, the jury is still out. Let me give you one example which I came across during the recent research project. In 2007, the Swiss based company Novartis commissioned a Phase III trial with a newly developed bird flu vaccine to be used as a prophylaxis of influenza prior to the outbreak of a pandemic. With the WHO warning about an imminent bird flu pandemic and governments beginning to place orders for vaccine stocks, here was a chance to boost revenue by selling an existing yet modified flu vaccine, provided market approval could be secured quickly. The trial which had not been authorized by the Polish Health Authorities took place at a clinic South of Gdańsk. As many as 350 participants including people from the local homeless shelter and at least one pregnant women received between one €40 and eight €30 for testing what they believed to be a conventional flu vaccine.

The raised mortality rate among the inmates of the homeless shelter so far have not been conclusively been attributed to the trial. Yet in 2017, 10 years later, three physicians and six nurses from that clinic received suspended prison sentences for falsifying documents and misleading participants about the nature of the vaccine. One of the participants at the time recorded, "I never agreed to be used as a guinea pig. If I had known what the vaccinations were, I would not have participated". Responding to the allegations, Novartis insisted that it was "following a research ethics set out in the Declaration of Helsinki."

Observers of this case have claimed that the case only presents a tip of the iceberg, shining an unwelcome light on to the impoverished National health services in Eastern Europe. Large-scale western funded trials are today an important part of that part of the continent and their economy. Health clinic doctors and participants depend on them for additional income and access to medicines. Moral and legal blame if things go wrong, as in this case, can easily be apportioned to those running the clinic or to the contract research organization charged with that trial. In 2015, the Novartis company sold its vaccine business to GlaxoSmithKline for $7.8 billion, a move which it might retrospectively have regretted.

9. Conclusion

Today, the world scientific community is engaged in a continuous process of revising the Declaration of

Helsinki which rather than undermining its authority as some have argued, aims to ensure that it's protective potential for human participants and vulnerable communities can be maintained. It is ultimately one of the most important documents we have. At the same time, and I hope some of the things I have said here today have shown that we need to recognize that the Declaration is not just a reflection of moral and ethical norms in the field of research ethics, but is in itself a product of medical interest groups, who were at the time at least determined to implement a carefully phrased, codified regulation as a way to legitimize the continued use of humans and experimental trials across the globe.

(Published November 15, 2021)

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Discussion (Day 1 No. 2)

Otmar Kloiber
Secretary General, World Medical Association

What Prof. Ulf Schmidt's presentation tells us is that the ethics research has to be seen on the background of the contemporary development. It is not isolated. Take vaccine research, for instance: If nowadays somebody would do an experiment as Edward Jenner had performed, you would simply go to prison. Yet, at the time being, it was a reasonable scientific experiment, in a time while "wild" inoculations were going on in Great Britain. It is also very clear that we had setbacks in the application of ethical standards, for instance, during the Third Reich, but not only there. The Tuskegee study is one example, others are sterilizations for social reasons in Europe that have been done until long into the '70s or discrimination against certain groups, like patients with Hansen's Disease, still going on.

Yet, I would like to remain a strong advocate of physicians being the driver of ethical standards because it means taking responsibility for what we are doing. It is correct and I agree with Prof. Schmidt the weight of the Declaration of Helsinki [1] has shifted quite a bit from enabling research in the beginning to the protection aspect that dominates today. But that is not only about the patients, but also about those participating in the research. This protection aspect is double: Adhering to the Declaration of Helsinki protects those who are subject to the research, but also those who participate as researchers and physicians.

The aspects have certainly shifted and there is much more cognizance. For instance, there is more distance to the industry nowadays. The closeness to the industry in the 50s and 60s was much bigger than it is now. That does not mean that there is not a reason for cooperation, discussion and integration. Everybody who has a legitimate interest in being part of a healthcare system must also have a voice at the table and must be included. But we see this with much more distance today.

The question has been raised whether the guidelines or the principles are sufficient. They are never sufficient. Sufficient is the ethical behaviour that is being applied to respect these guidelines. The guideline itself is just one tool in the application of experimentation and medical practice in general. Questions of applicability, enforceability, and the completeness of guidelines, remain. We all know: the moment we have accepted a new version of the Declaration of Helsinki we realize already the first deficits of that new version. We are continuously learning from mistakes, we recognize gaps. We currently have to revisit the Declaration to maintain ownership and take responsibility for its continuing development. This is as important as the document itself. The moment we stop working on it, we lose ownership and it also loses its relevance to medicine.

1) World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research involving Human Subjects. Adopted Jun 1964, last amended in Oct 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

On the other side, we also can be proud of it. There has been no other professional group that has taken such leadership. Coming from Germany, and thinking of the jurisprudence or other groups, like artists, technicians, other researchers, they have not taken this challenge and have not taken this responsibility as we have. We can take pride in this work, knowing that nothing is perfect and nothing has come to an end.

Ramin Parsa-Parsi

Workgroup Chair of the 2013 revision of the Declaration of Helsinki

German Medical Association

I would like to echo that it is the ethical behavior that indeed counts, more so than the guidelines per se and whether they are sufficient or not. At the same time, if we see that behavior is not in line with the ethical guidelines, then we probably need to make adjustments to the guidelines, make them stricter or make them clearer. These guidelines are indeed always a work in progress. The moment we have approved one set, we basically have to start working on them again, and we always have to make sure that they are up to the challenges of our current times.

If we look at what the Declaration of Helsinki also says, we have to take great care that there is no abuse of these regulations, and if there is, we have to look into them again. We had a few examples today of cases where we would probably have to consider whether certain paragraphs are comprehensive enough or perhaps need to be revisited.

Ulf Schmidt

Professor of Modern History, University of Hamburg, Germany

I fully agree with both of Dr. Ramin Parsa-Parsi and obviously also with Dr. Otmar Kloiber. They are both absolutely right that ultimately if scientists are bent on violating ethical principles none of these guidelines will be enough. It is ultimately the ethical behavior and it's the awareness which is fundamental. Probably all of us here today agree that the Declaration of Helsinki is one of the most important documents having created awareness over the various decades in the scientific community. In a sense, what we may see when we look at it historically as potentially some of the weaknesses of the documents are in fact some of its strengths, because what it requires the international medical community to find consensus, and it is only through this consensus that the document has that reach across the globe.

Where I see the greatest strengths of the document is that doctors and researchers don't want to be seen to be breaching the Declaration of Helsinki. This is not about the extreme cases where someone violates intentionally something. This is more how organizations and research communities wish to be seen. That is an important leverage which this document has and also the organization. It has fulfilled that over the last 50 years with tremendous diplomacy and great skill.

Chieko Kurihara

Specially-appointed Professor, Kanagawa Dental University, Japan

I very much enjoyed Prof. Schmidt's presentation because as Dr. Kloiber said World Medical Association (WMA)'s document is "a little weak on the side of prevention research", but in this historical development, there are many events of the public health issue, as you said, in the issue of the flu and the drug development activity of pharmaceutical company.

I would like to have some comments from the audience. After hearing from some speakers, I would like to ask for comments from Prof. Rihito Kimura, because we are going into historical discussion, and Prof.

Kimura played a very important role in developing the bioethics principles with Beauchamp and Childress [2], and also he participated in the first version of the CIOMS (Council for International Organizations of Medical Sciences) guideline.

Ruth Macklin

Distinguished University Professor Emerita at Albert Einstein College of Medicine in New York City, the United States

I question whether the U.S. FDA (United States Food and Drug Administration) requires placebo-controlled trials. Dr. Peter Lurie mentioned one case in which there were placebo-controlled trials for the mother-to-child transmission and another study that was approved by the FDA that was a non-inferiority study being conducted. My understanding is that it is the pharmaceutical industry that wants to have placebo-controlled trials, partly because they are cheaper to conduct, partly because they can get answers in a shorter period of time and get FDA approval, and, therefore, start making money. On the question whether FDA is driving it, now, it is true that the FDA approves a lot of placebo-controlled trials, but that's not the same as saying that they restrict trials or that they refuse protocols that are not placebo controlled. That's my answer to that.

I did also want to ask Dr. Kloiber who commented that the next version of the Declaration of Helsinki perhaps should make explicit mention of prevention trials. I was wondering what he had in mind and what's needed that the current Declaration of Helsinki does not provide by way of an understanding of prevention trials.

Kloiber Let me respond to two things: about placebo trials and the request by the authorities. I share the view of Prof. Macklin. I would expect just from the logic of the finances and the material problems that it is in the interest of the trial sponsor to reduce the numbers. The numbers you can reduce by having a comparator which gives a very clear result. That is usually is easier with a placebo than with another drug. I would be surprised if the authorities are drivers for placebo arms. Although, there may be compelling reasons to do so, especially with symptomatic treatment. And there may be other good reasons for one or the other question to be answered in a smaller arm, for instance, to test against placebo.

Prof. Macklin, I am not sure that there will be a change in the Declaration of Helsinki. What I would like to see is that we really look into the questions of prevention research. One of the very important questions is the distinction of vulnerable groups and the targeted or concerned groups of prevention research. The current Declaration of Helsinki makes the research in vulnerable groups very difficult, while at the same time, some of the research, especially the prevention research, should target vulnerable groups explicitly. I am not sure that we have to change the Declaration, but we have to discuss it and we have to answer the questions we have been discussing.

Other parts of the Declaration of Helsinki have come under scrutiny with the corona pandemic. One example is the compassionate use of unproven drugs and their extensive use in some countries. Nevertheless, we have to face the questions and we have to discuss it. Will this lead to a change in the declaration? We will find out.

2) Beauchamp TL, Childress JF. Principles of Biomedical Ethics 3rd ed. Oxford University Press, Inc.; 1979.

Peter Lurie

Center for Science in the Public Interest, Washington, DC, the United States

I wanted to respond to Prof. Macklin's excellent point about what the FDA requires. I have seen this from both sides, as an advocate who resisted placebo controls in a certain set of circumstances and as an official who worked at the FDA for a while. Prof. Macklin's description is accurate. It slightly understates what the FDA's preference is. The FDA's preference, of course, depends on the exact situation, but broadly, there is a lot of sympathy for the power of placebo-controlled trials, and certainly some of the people who have resisted the critique of placebo-controlled trials in developing countries have been either present or former FDA officials. But that is not to say that they won't accept something else. They may have a preference, but that does not mean that they won't accept something else. If you were to show up with a non-inferiority trial that without question showed that you were as effective as Moderna or Pfizer, I cannot imagine that the FDA would turn that down in the current context. That seems unlikely to me as long as it was reasonably well designed.

The ethical question for us is not simply to point in the direction of regulatory agencies, but to ask ourselves as individuals, as people who pride ourselves in the ethical conduct of research, what we should be advocating for and to take a stand. There the example that I gave about the situation in Thailand is instructive. I said that there were 16 trials that had been done, one of which did not include a placebo-controlled trial, and we were able to obtain documents about the debate within the National Institutes of Health (NIH) in the United States, which ended up funding the study, in which the NIH repeatedly resisted the idea of a non-inferiority trial. The researchers at Harvard went back to them over and over again and insisted that the use of the placebo would be unethical. There were probably two or three back and forths over this, and Director of the NIH, Dr. Harold Varmus, even testified before Congress that there are different ways of answering the question. That's right. There are different ways, and it's for us to advocate for the most ethical way. Again, strong advocacy can get these authorities who may be rigid to begin with to accept more ethically designed trials.

Rihito Kimura

Professor Emeritus of Bioethics, Waseda University, Japan

Thank you very much for all the speakers' presentations today. I was very much impressed. Prof. Macklin, you mentioned the COVAX Global Initiative. That might be a good example of the accomplishment of some bioethical principles. Do you have any comments relating to bioethical aspects of the COVAX Global Initiative? That is my first question. My second question is to Prof. Schmidt. I appreciated your very clear statement on the issues of clinical research including the ideas on the Nuremberg Code [3] which was implemented by the WMA.

In the case of Japan, I feel very sad to say this, but because of the very negative experience in China and Manchuria, of the experimentation during the war by the special Unit 731, Japan had similar experimentation or even more severe experimentation in humans, particularly against Manchurian and Chinese. These kinds

3) The Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, October 1946-April 1949. Vol. 2, p. 181-2.
https://www.loc.gov/rr/frd/Military_Law/pdf/NT_war-criminals_Vol-II.pdf

of criminal cases by the Japanese Military Medical Corps are not open even for the Japanese. I wrote about the Unit 731 case in the Encyclopedia of Bioethics, which is edited by Warren Reich [4]. That was the first public comment from a bioethical perspective on this human experimentation by the Japanese Military Corps.

Many Japanese medical professionals said this is "*Jintai Jikken*", human experimentation, which can be permitted in critical situations because all of prisoners are going to die anyway, and in their last moments, they could be used as subjects of medical research and so on. I wrote about this issue in the Encyclopedia of Bioethics [4], and then in 1992, CIOMS had this ethics and research project on human subject [5]. This was published in 1993, and I have written the Asian perspective on human experimentation. In this paper, I addressed this very cruel human experimentation on Chinese and Manchurians by the Japanese military. The discussion resulted in 1993 version of the guidelines [6].

Japanese medical experts were not called to the criminal court or the war tribunal like in Nuremberg, because of American intervention, and because American military experts wanted to keep various documents secret and all the Japanese medical experts who had perpetrated these medical crimes were given immunity because of this American intervention. All this medical experimentation data has been transferred to military medical corps in the United States (U.S.). I have found a document in the U.S. National Archives in Maryland that shows that U.S. officials dealt with the Japanese medical criminals in making this secret agreement with the Japanese experts, particularly with the head of this corps led by General Ishii. This was shocking and scandalous. Officially, this was not recognized as a crime by the Japanese government, and many of the Japanese medical experts are saying, it's because of the war that it happened and we have to proceed because science is advancing.

This is one of the great differences between Germany and Japan. I have found a secret note written by an American examiner in Japan at that time using his pencil saying that we are conducting Nuremberg Military Trials against German medical experts and 7 people were sentenced to death by hanging. This examiner in Japan said while Germans are being tried and prosecuted, Japanese are not and maybe in later years, this will cause some big problem.

This is a very big scandal and this is not shared yet officially by many Japanese medical experts. That is one of the most important bioethical issues in Japan, and we need to clarify these issues before doing bioethics. There is no such statement in many bioethics books. Rather recently because of my influence, there has been some textbook writing about this fact and document.

My question to Prof. Schmidt is, you must know of the Japanese case, how did you interpret this kind of treatment with American and Japanese military medical experts and immunity provided to these Japanese by

4) Kimura R. Contemporary Japan, History of Medical Ethics, South and East Asia, pp 1496 ～ 1505. In: Warren T. Reich, ed. Encyclopedia of Bioethics, Revised Edition, Simon & Schuster Macmillan, New York; 1995.

5) Kimura R. Asian perspectives: Experimentation on human subjects in Japan–Bioethical perspectives in a cultural context. In: Bankowski Z, Levine RJ., eds. Ethics and Research on Human Subjects: International Guidelines (Proceedings of the XXVIth CIOMS Conference, Geneva, Switzerland, 5-7 February 1992). p.181~187. (CIOMS, 1993)
https://cioms.ch/publications/product/ethics-and-research-on-human-subjects-international-guidelines/

6) Council for International Organizations of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects. 1993.
https://cioms.ch/publications/product/international-ethical-guidelines-for-biomedical-research-involving-human-subjects/

the Americans. Prof. Schmidt, did you know about this and do you have any comments on this kind of issue. But first, I would like to get short answer from Prof. Macklin about your interpretation of the COVAX Global Initiative, is there any bioethical implications of this organization and how do you think about this?

Macklin　In my understanding, this was one of the first attempts to get some kind of global cooperation in a medical situation. It's very clear this may be one of the first such examples, but it is surely one of the first examples in recent history of a devastating pandemic. There have been other pandemics. There have been milder diseases, or diseases that were more readily controlled, but this is a wakeup call. What's needed now is some kind of new alliance, not just the World Health Organization and these two partner organizations (which I do not mean to criticize). What they have been trying to do does not involve the kind of global cooperation that is needed to do something that might stem the tide of any future pandemic and those are not unheard of.

What I have heard from scientists or read from scientists basically is that this may just be the tip of the iceberg or a wakeup call for the future. We have all those variants out there, and there may be other possibilities. This is not connected to the question of the origins of the current pandemic, and although that is a very controversial issue that goes beyond this webinar, there is now at least slight evidence that something escaped from that laboratory in Wuhan. The WHO effort to try to inquire about that with Chinese cooperation absolutely failed, because the Chinese group that was part of the inquiry was in control of both the inquiry and its results. What is really needed is an indication that there is global cooperation, because there were a lot of Chinese people who died and a pandemic can start anywhere. The need for global cooperation this pandemic is a wakeup call and it needs more than two or three organizations getting together with the WHO.

Schmidt　I would like to thank Prof. Kimura for a very important issue he is raising in this context here. As historians or scholars who are interested in broader political and governmental histories, we are all aware that we always need to contextualize certain events in their particular context, and as you rightly pointed out, the time that we are talking about here is the immediate postwar period in which there was an emerging, as scholars generally call, a Cold War Period, and you are absolutely correct in what you highlighted here that there were very different ways of investigating and prosecuting and also remembering the different war crimes. The war crimes which the German scientists had conducted were quite publicly being presented to the world and they have been discussed and remembered over the years.

That is not the same as with other cases as you highlighted in the case of Japanese, particularly the biological experiments to which you alluded to. Obviously, scholars have also more recently looked into those tests and experiments where I can refer in addition to your own to work to Til Banning Housen who has written a chapter in a book we published in 2007 on the Japanese biological warfare experiments on human subjects in China and more recently Jeanne Guillemin, a scholar from the United States, who has written a book called "Hidden Atrocities" [7] also dealing with the history which was going on in Japan. She actually looked at, as you rightly said, the records for the trials. The records of the Japanese scientists were transferred after the war to the United States. The reason was that the United States wanted to make sure that any potentially relevant or useful data which came out of these experiments could be used during the Cold War. That

7) Guillemin J. Hidden Atrocities: Germ warfare and American obstruction of justice at the Tokyo Trial. Columbia University Press: 2017.

is still the period where the United States military is actively involved in developing a biological weapons potential. That is one of the contextual information which is important to understand why so much in a sense was brought to the United States at the time and also had led possibly to less publicity and also remembering of these experiments to which you quite rightly highlighted.

One other comment I wanted to briefly mention, which Prof. Macklin mentioned earlier in one of the chats, was she asked has there been sanctions for violations of the Declaration of Helsinki, and it's an important point here to raise. This obviously goes beyond an organizational association like the World Medical Association, and when the sanctions do happen in one way or another, they often seem to be happening away from the public eye. I wish to give you one example, namely the example of the Novartis case, which I highlighted in my brief presentation.

What happened was that the actual application which was submitted to the European Medicines Agency (EMA) at the time had to be withdrawn because the EMA began to do an investigation after they were informed that something had not gone quite according to plan and the protocol of that, in a sense all the unethical information about these tests, are hidden away in what's called a withdraw assessment report, which no one would find and read if you wouldn't know about it. You can find it. It's on the EMA website, but it is one of many reports. It's inconspicuous, but once you read it carefully, you realize what actually was going on and why this particular trial was highly unethical and the conclusion which the EMA made was that the Novartis had "failed to provide adequate quality oversight of the study." They detailed that with a number of details, for example, that there had been serious ethical shortcomings including the inclusion of vulnerable populations in the trial, inadequate medical record keeping, changes in the inclusion criteria without appropriate approval by the relevant government authorities and so on.

In a sense you are absolutely right, Prof. Macklin, there are cases, but they are not publicized and hardly known among the global community unless they are being highlighted. I hope that at least is a comment to your important point.

Sandor Kerpel-Fronius

Professor of Clinical Pharmacology, Semmelweis University, Hungary

Chair of Ethics Working Group (2014-2021), IFAPP

I would like to come back to the discussion regarding placebo control and the support by the regulatory authorities, the medical profession, and the pharmaceutical industry. There was a very interesting symposium some years ago about the use of placebo in which medical, industry and regulatory experts came together. It was interesting that the placebo control was supported mostly by the regulatory agencies. The argument was the following, and this is what I want to comment on. The decision of the regulatory authorities will affect millions of people, so their responsibility is much higher than the responsibility of the individual doctors or of the factory experts since if they make a wrong decision because the control was not adequate or because there was no placebo control, this would affect millions of millions of people. I think when we discuss this problem, we should also consider the size of the responsibility of the decision makers. This is a very important point, and this is probably what will explain why the regulatory authorities are much more supportive of placebo control that gives them real safety for their decision.

Dirceu Greco

Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil

First thing is that all documents usually are written and decided by the winners. Nuremberg is a good case, because their decisions and evaluation were directed exclusively to the unethical activities perpetrated by Germans. But I want to remind you that at the same time, from 1932 to 1972, Americans were doing wrong things with their own people and that happened in Tuskegee. At the same time, 1946 to 1948, some of the same Tuskegee people were in Guatemala doing the experiments with the treatment of syphilis and involved vulnerable individuals that lived in Guatemala [8]. People have been using that as a history. It's hard for us, especially for myself being in an underdeveloped country, to have a word, and for us is even worse, because we speak and usually publish in Portuguese. It may be similar for the Japanese. How many speak or can read Japanese outside Japan? If it's not written in English, people just forget about it. That's just a point of provocation for all of us and see how we really face things in a way that should be ethical. It usual depends on who is winning or who has the power.

But I wanted to thank Japanese organizers for this opportunity to have at least 5 minutes in the end and to thank everyone for staying till the end of this first meeting. But I want to comment a bit on Prof. Kurihara's point which I thought was very stimulating. One of my questions was answered about the justice. I hope that we can talk more about that later, about not having a test in Japan, but that's something we can do later. She was very strict. Prof. Macklin, we have a history with many, many years of being together, with Dr. Lurie also. We discussed all of this. It's a "déjà vu". We have been discussing the same thing going over and over again, and in my point of view, this is a dated discussion.

We have been discussing how people must have access, all of us, all of them, to what's coming from research, but I defend that should be not only the post-trial access, for participants who very much secured by being in the research project. But I always liked Prof. Macklin, and I say that to her when we meet, because she is clear, she is objective, and she is very strong in defending her points. I quite agree with the criticism about WHO on the *New England Journal of Medicine* [9] publications. I am now a part of a WHO ACT-A working group on ethics, comprising 12 people. But the publication mentioned where a very capable individuals decided to write a paper on the placebo use in covid-19 vaccine trials as experts, and worst of all, with someone from WHO signing together, it does not seem write, as what is suggested may be considered double standards. Of course, I am completely against what the conclusions were.

On post-trial provisions, Prof. Macklin did not mention that, but especially CIOMS say, "*make provisions*". What does it mean "make provisions" to something? In my opinion it should be "ensure". Make provisions could be anything. That's the thing that we have to think about changing. The patent waiver, we did not talk much about that, but it's something we must discuss all the time, not only for this epidemic, because other epidemics will probably come. We must have a way of making people have the right to access to things that are produced, especially with the vaccines now. Prof. Macklin can say that much clearer than I. And it must be mentioned that the previous U.S. government invested close to $18 billion in the pharma-

8) Reverby SM. "Normal exposure" and inoculation syphis: PHS 'Tuskegee' doctors in Guatemala, 1946-1948 and at Sing Sing prison, Ossining, N York, 1953-1954. May 2, 2010.

9) WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation, Krause PR, Fleming TR, Longini IM, Peto R, Beral V, Bhargava B, Cravioto A, Cramer JP, Ellenberg SS, Figueroa JP, Halloran E, Henao-Restrepo AM, Ryan MJ, Levine MM, Nason M, Nohynek HM, Plotkin S, Rees H, Singh JA, Swaminathan S. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. *N Engl J Med*. 2021 Jan 14;384(2):e2. doi: 10.1056/NEJMp2033538. Epub 2020 Dec 2. PMID: 33264543.

ceutical industry for COVID-19 vaccine research. How can it be possible that industry will have that much profit with the developed vaccines?

With Dr. Lurie, I mentioned that before, we have an intense history in that we published in 2005 in The *Lancet* [10] criticizing FDA's decision to take out the Declaration of Helsinki from their requirement for drug development projects without the Investigational New Drug approval by the U.S. but performed abroad. All these things we have been discussed, but just one thing that I did not quite agree with Dr. Lurie and I mentioned to him in the chat, is the summary in the end. Every time someone says "case to case basis". I get bumps because that you can do things if you do it case by case. I am sure you are not meaning that, but we should be very careful of misinterpretations when you say that.

Prof. Schmidt, of course, we also have a history since 7 years ago, when you decided to write this important book on ethical research [11] and I am very pleased and honored to be part of it, and you said something that I am very concerned about. The first one is that we are living in a post-ethical world. That's true. Everything goes. That's the way things are. People are going to suffer, people are going to die, people are going to be poor, people are going to be vulnerable, and so what can we do? Prof. Macklin and Dr. Lurie now mentioned that most declarations are not binding. No, they are not binding at all. That's what happened in Brazil when the decision was to change some crucial points in the Declaration of Helsinki, namely post-trial access and placebo use in 2008 [12]. Brazil decided that we have specific directives on research ethics. In Brazil, placebo cannot be used unless there is no effective comparator and also the rights for post-trial access are very stringent. It has no time limit, and someone mentioned that the industry is going to have problem by paying that. Can you imagine they spend so much money carrying doctors from place to place in first class trips? For them money is not a problem. So, Brazil decided that and that was a big pressure against it saying that big pharma would quit doing research in Brazil after that. Of course, they are still doing it, because for them, what is important is the size of the market that Brazil represents. Research projects brought to the country are adapted to Brazilian research ethics directs. They are just chameleons.

I hope that in the next week webinar we can discuss a lot on post-trial access, and I will be defending that post-trial access is for all. We must move on from research to discuss post-trial access in public health. In my opinion, everyone has to have access to effective and safe products, and last but not least, I mentioned that in our debates in Japan 2 years before [12]. At that time I had the opportunity to visit Hiroshima and what happened there in the World War Ⅱ was unacceptable. Visit the Hiroshima Peace Memorial Museum and I saw a big board saying that the Americans decided just after the war to open a place where they could receive people that were affected by the bomb. Everyone came, because they thought they are going to be treated, but no, the Americans wanted to follow them to see what the natural history was! That was in 1947. Many other unacceptable situations are happening throughout the world, and we must be very keen and very clear that we have to emancipate ourselves to make sure that unethical situations especially in the prevailing world

10) Lurie P, Greco DB. US exceptionalism comes to research ethics. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1117-9.

11) Schimidt, U, Frewer, A, Sprumont D Ethical Research: *The Declaration of Helsinki, and the Past, Present, and Future of Human Experimentation.* Oxford University Publication; 2020. ISBN: 9780190224172

12) Greco D. Shimoda K, Watanabe H, Organizers. The Past, Present, and Future of Ethics of International Health Research: Research as a stepping-stone to Universal Public Health Care Access. *Clin Eval.* 2020; 48(1): W29-W53. http://cont.o.oo7.jp/48_1/w29-w53.pdf

disparities will no longer be allowed. Disparity is not something that has to be forever. It is very hard to change, but it can change and we must participate in the efforts to change it.

Thanks very much. I congratulate COVID-19 Task Force because most of the work to make these webinars possible for the two bioethical societies (Japanese and Brazilian) was done by your team, and always very pleased to work with you. I wish that next week we are going to have another good debate.

Kurihara　There are many, many things that we wanted to continue the discussion on, but the time is late at night especially in Japan. I thank the Japanese audiences very much for especially staying up till midnight. Thank you very much everyone for your participation. Next week, Friday, June 11, we start next discussion, especially focusing on post-trial access and speakers are mainly from the developing countries. It will be a good opportunity to listen to these speakers' talk and discussion. Thank you very much.

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Opening Remarks of the Day 2 session

Takeo Saio
COVID-19 Task Force, Japan Association for Bioethics
Department of Internal Medicine and Psychiatry, Fuji Toranomon Orthopedic Hospital, Japan

This webinar is co-organized by COVID-19 Task Force of the Japan Association for Bioethics to which I belong and the Brazilian Society of Bioethics, which is chaired by Prof. Dirceu Greco. Prof. Greco is highly respected in his research in infectious diseases and bioethics. The title of this webinar is "Pandemic and Research Ethics: Democracy, Placebo, and Post-Trial Access." Today is the second session following last Friday when we discussed mainly on the ethics of placebo-controlled trial. Today's session is more focused on the ethics of post-trial access inviting Prof. Ames Dhai who established the Steve Biko Center for Bioethics, South Africa, and Dr. Tammam Aloudat who has been engaged in Access Campaign of Médecins Sans Frontières (MSF). Prof. Greco, another organizer, will also make a presentation at the last part.

The world situation is drastically changing to overcome this pandemic. As far as we can foresee, something like the global version of United States' Operation Warp Speed might be thoroughly realized now, global supply of effective vaccines collaborating with COVAX. Human rights, justice, and equity play especially important role among the elements of democracy. Today, we wish to listen to the speakers who have contributed to the establishment of democracy in medicine and research ethics. Not only the last week's session, today also, guests from the World Medical Association (WMA), Dr. Otmar Kloiber and Dr. Ramin Parsa-Parsi are participating again. We wish to congratulate the WMA on receiving the prestigious Golden Arrow Award from the Vienna Congress, representing doctors combatting COVID-19 [1]. Prof. Greco, could you please open today's session.

Dirceu Greco
Chair, Brazilian society of Bioethics
Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil

It's a pleasure to open this second webinar on this important subject. I am very glad to see all these competent individuals sharing their time to discuss subjects that are very dear to all of us, especially in the situation we are all facing now with the COVID-19 continuous spreading. We need to do so many things about it. This discussion about post-trial access has a lot to do with this ongoing epidemic that unfortunately will not be the last. I pass back the word to the Moderators.

1) Duncan N. WMA Wins Prestigious Award; Otmar Kloiber Acceptance Speech; David Barbe Acceptance Speech. *World Medical Journal*. 2021; 67(1): 11-4.

Kyoko Imamura
Japanese Association of Pharmaceutical Medicine (JAPhMed)/Past President, International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)
Project Professor, Social Cooperation Program of IT Healthcare, The Graduate School of Pharmaceutical Sciences, The University of Tokyo, Japan

I am Kyoko Imamura. I am the past president of the IFAPP, International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine, and I am also with Japanese National Member Association, JAPhMed.

Today, I am honored to moderate this seminar, because ethics has been the most important agenda for IFAPP and Prof. Kurihara is the most powerful member of our Ethics Working Group of IFAPP. I found that many of the participants today also attended the last week's session. We have already kicked off and shared most of our concerns and are delighted to have this inspiring discussion.

Today, we are going to have two presentations before we have a short break to go into the second part of our seminar. First, let me invite Prof. Ames Dhai. She is going to touch on the ethics in vaccine allocation in developing countries.

(Published November 15, 2021)

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COVID-19 and bioethics Part 3:
Pandemic and research ethics－Democracy, placebo and post-trial access【Day 2, June 11, 2021】

Ethics in vaccine allocation in developing countries

Ames Dhai [*1]
Professor of Bioethics, University of the Witwatersrand, Johannesburg, South Africa

1. Opening remarks

Good morning, good afternoon, and good evening colleagues. I am Professor Ames Dhai. I established and directed the Steve Biko Centre for Bioethics at the University of Witwatersrand since 2007, and at the end of 2019 retired. I am now Professor of Bioethics and Health Law at the School of Clinical Medicine at Witwatersrand University and Specialist Ethicist in the Office of the President and CEO of the South African Medical Research Council.

I want to thank the organizers of this conference for inviting me to do this presentation today. The topic that I have been given is "Ethics in vaccine allocation in developing countries." I am not going to talk about micro-allocation at individual level or misallocation, but I am going to look at the ethics in macro-allocation decisions for COVID-19 vaccine with particular reference to our developing countries.

2. Presentation outline

By way of outline, I will talk on vaccine nationalism and vaccine equity. I will say a few words on Global Public Good. I will highlight some of the pertinent issues on the African context [1, 2]. I will look at two international documents that call for global vaccine equity and solidarity, which are the Lancet Commission Statement [3] on enhancing global cooperation to end the global COVID-19 pandemic and the UNESCO (United Nations Educational, Scientific and Cultural Organization)'s call in February 2021 [4]. This is its second statement on COVID-19. There is a follow-up one [5] that is being developed, and it is being spearheaded by Prof. Dirceu Greco who is on the panel. I will not discuss that follow-up one and I will leave it to him to bring in if he feels it's necessary.

Subsequently in early May, the world was pleasantly surprised when the United States (US) supported South Africa and India. There was also a flurry of publications on the need for the waiver of the patent. Here

[*1] Founder of the Steve Biko Centre for Bioethics, University of the Witwatersrand, Johannesburg, South Africa; Member and Vice-chair of International Bioethics Committee of United Nations Educational, Scientific and Cultural Organization (UNESCO) (2018-2021)

in this editorial in *Nature*[6], you can see the point is made that a patent waiver is right and fair and wealthier countries must recognize that everyone benefits if vaccine manufacturing is distributed evenly around the world. It also highlights that Africa imports 99% of its vaccines, and African countries lack the preorder purchasing capacity of richer nations. For us to move forward in terms of equitable access to manufacturing vaccines, not only do we have to remove patents, but there has got to be the transfer of knowledge on how to make vaccines and investments in manufacturing capacity.

3. Vaccine equity and vaccine nationalism

When we look at vaccine equity and vaccine nationalism, what exactly are we referring to? It's very simple to understand the issues if we really embrace ethics.

- **Vaccine equity basically affirms human rights.**
- **Vaccine nationalism denies human rights.**
- **Vaccines must be a Global Public Good, accessible and affordable to all.**

Vaccine nationalism degrades the COVID-19 vaccine to a commodity to be sold in the marketplace to the highest bidder. It degrades the COVID-19 vaccine to the bidding and dealing process. This in itself is unconscionable. It's morally reprehensible.

It also erodes the reciprocity and proportionality principles in research ethics by denying those countries from the developing world that participated in the recent trials and contributed to the intervention from accessing the vaccines. Perhaps it is time to push the principle of proportionality whereby if certain countries contributed a certain proportion towards the intervention, then those countries ought to be given first choice for the intervention when available proportional to the contribution made. It's very important when we look at vaccine equity that we must recognize that vaccines must be a Global Public Good and there are many calls for this at international levels, and vaccines must be accessible and affordable to all.

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1) African Union; Africa CDC. Framework for fair, equitable and timely allocation of COVID-19 vaccines in Africa. 31 January 2021.
https://africacdc.org/download/framework-for-fair-equitable-and-timely-allocation-of-covid-19-vaccines-in-africa/

2) Council for Trade-Related Aspects of Intellectual Property Rights. Waiver from certain provisions of the TRIPS Agreement for the prevention, containment and treatment of COVID-19: Communication from India and South Africa. 2 October 2020; IP/C/W/669.
https://docs.wto.org/dol2fe/Pages/SS/directdoc.aspx?filename=q:/IP/C/W669.pdf&Open=True

3) The Lancet COVID-19 Commission. Enhancing global cooperation to end the COVID-19 pandemic. February 2021.
https://covid19commission.org/enhancing-global-cooperation

4) Joint Statement by the UNESCO International Bioethics Committee (IBC) and the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST). UNESCO's ethics commissions' call for global vaccines equity and solidarity joint statement. SHS/BIO/IBC-COMEST/COVID-19 Vaccines. Paris, 24 February 2021.
http://www.sbbioetica.org.br/uploads/repositorio/2021_02_24/Unesco2021GlobalVaccineEquityESolidarityStatement-fev2021.pdf

5) Joint Statement of UNESCO Ethics Commission ensuring equal access for all to vaccines and therapeutic development to confront COVIS-19; Joint statement of the UNESCO International Bioethics Committee (IBC) and UNESCO World Commission for the Ethics of Science and Technology (COMEST). SHS/IBC-COMEST/COVID-19 Vaccines IP Paris, 21 September 2021.
https://unesdoc.unesco.org/ark:/48223/pf0000379042

6) A patent waiver on COVID vaccines is right and fair. *Nature*. 2021 May; 593(7860): 478. doi: 10.1038/d41586-021-01242-1. PMID: 34035532.

4. Understanding Global Public Good

What is a Global Public Good (Table 1)[7]? A Global Public Good impacts spread equitably across the globe without causing division. It is clear in the manner in which the vaccines have been approached that there is a lot of division, and that COVID-19 vaccines as a Global Public Good has not materialized.

A Global Public Good takes into consideration that a price cannot be placed on the benefits of these goods, so the principle of exclusion cannot be applied to it. The use by one individual cannot be allowed to reduce its availability to others. A Global Public Good is not marketable, and the goods and their benefits must be available at negligible or zero cost to all in the global village. We have seen by the many pandemics that we have been having and with COVID-19 which seems to be amongst the worst of all that we are one global village and that a variant can start here today and land up on the other side of the world tomorrow.

Therefore, there are two criteria that determine a public good. It's got to be non-rival in consumption. Consumption by one person must not interfere with the goods being available to others equally. It's got to be non-excludable. Suppliers cannot deny it to those who are unable to pay its market price. Importantly, there are going to be trans-boundary implications with most public goods and in fact there is an ethical imperative for robust international cooperation and action in this context.

5. Cases of vaccine nationalism

Despite the vaccines being a Global Public Good, we saw very early on, in fact soon after the second half of last year (2020), vaccine nationalism and reports and concerns of vaccine nationalism coming through in

Table 1 Understanding Global Public Good

- impacts equitably spread across the globe without causing division.
- price cannot be placed on benefits of these goods:
  - ▷ principle of exclusion cannot be applied to them.
  - ▷ use by one individual cannot be allowed to reduce their availability to others.
- not marketable and the goods and their benefits must be available at negligible or zero cost to all in the global village.
- two criteria that determine a public good:
  - ▷ non-rival in consumption - consumption by one person must not interfere with the goods being available to others equally.
  - ▷ non-excludable - suppliers cannot deny it to those who are unable to pay its market price.
- transboundary implications with most public goods, hence international cooperation and action necessary.

van den Berg RD. Evaluation of the Funding of Global Public Goods Note for the OECD/DAC Evaluation Network – May 27, 2015[7]

7) van den Berg RD. Evaluation of the funding of global public goods-Note for the OECD/DAC Evaluation Network. May 27, 2015. https://www.oecd.org/dac/evaluation/Evaluation-of-Global-Public-Goods-Evalnet-note.pdf

various channels. Amongst the first of these were from Duke University's The Global Health Innovation Center where they published evidence showing that rich countries had gone on a shopping spree for COVID-19 vaccines [8]. This then meant that there would be very few vaccines left for low-income countries.

Many of these countries were going to be able to vaccinate their entire populations several times over again, while low-income countries were at the end of the queue for their turn to purchase vaccines. In fact the data that they put out revealed that several COVAX signatories, including the United Kingdom (UK), the European Union (EU), and Canada were undermining COVAX's pact towards ensuring equitable access of vaccines to all by negotiating side deals with manufacturers for large vaccine shipments resulting in a smaller piece of the pie that would be available to us in the developing world.

6. Countries that have pre-ordered vaccines

Towards the end of last year (2020), the EU was on the top of the list in terms of its preorders followed by US, Japan, and UK, mostly rich countries.

Currently what do we see as of last night? The European Commission orders in terms of the supply agreements on top of the list, but it's good to see that COVAX is catching up, and the African Union has started purchasing as well. It is apparent that while we all see the need for equitable access, if we sit and wait for that equitable access from COVAX, we are never going to get the vaccines. Many of the regions saw it necessary to actually go ahead and get involved in bilateral or multi-lateral agreements.

Currently as of June 9th, we can see the list of countries that have fully vaccinated the share of their populations against COVID-19. These again are mainly the rich countries.

Currently what do we have as of last night again is 17 vaccines that have been approved for use by at least one national regulatory authority. Seven of the vaccines have been authorized by WHO and it is available in its emergency use listing. There are 13.6 billion doses that have been secured globally, and they range in price from $1 to $40. This is clearly highly unaffordable to most of us in the developing world. COVAX has secured 3.86 billion, and it's already shipped 81.9 million doses to 129 countries. Looks good, but it's a drop in the ocean.

7. Who received the first 1 billion vaccines?

Vaccines have developed at a very rapid rate in terms of COVID-19. Already by the end of the April, 1 billion people had been vaccinated only 4 months after the WHO approved a vaccine for emergency use. This was only 16 months after the virus being discovered. Many celebrated this. But, many of us in the developing world looked at such figures, and we said, fine, but who has received the 1 billion vaccines? 75% of these 1 billion went to only 10 countries (Israel: 62.2%, Bhutan: 61.7%, Maldives: 53.4%, United Arab Emirates: 51.4%, United Kingdom: 49.6%, Malta: 48.0%, United States: 41.8%, Chile: 41.6%, Bahrain: 38.8%,

8) Duke Global health Innovation Center. New study shows rich country shopping spree for COVID-19 vaccines could mean fewer vaccinations for billions in low-income countries. November 2, 2020.
https://dukeghic.org/wp-content/uploads/sites/20/2020/11/COVID19-Vax-Press-Release__28Oct2020-1.pdf

Hungary: 37.3%: As of 25 April, 2021, proportion of their populations that have had at least one dose of a COVID-19 vaccine)[9]. You can see in terms of Africa even up to last night, 90% of countries in Africa are going to miss urgent COVID vaccination goals. It's really bad down here.

8. COVID-19 disruptions in Africa and the multilateral approach

Let's consider the ethics of vaccinating people that are not at risk. Vaccinating young adults and moving to vaccinate adolescents while many African healthcare workers have still not received vaccines and many have died is morally reprehensible. Some of us are in the third wave now, so we have concerns of many dying as well. However, high risk populations, those 60 and over have not received the vaccines as yet in Africa while in other parts of the world consideration is being given to and, in some countries, it is being embarked upon to vaccinate the young ones.

The situation of context is, we have had COVID-19 disruptions in Africa (Table 2). You may say, there has been COVID-19 disruptions the world around, but remember, we started off very similar to other developing countries with huge vulnerabilities, huge strains on our health systems, huge economic and social disruptions. These worsened with the pandemic. The gains that we had made on our continent with regard to disease reduction and increase in life expectancy towards reaching our 2030 Sustainable Development Goals (SDGs) have actually gone backwards and that is of concern.

We started off with vulnerabilities, and our vulnerabilities have been heightened by the COVID-19 situation. Early on, our African Union decided to have a multilateral approach to the pandemic response (Fig. 1)[1]. Already in February 2020, it put together the Joint Continental Strategy for COVID-19, and the Africa CDC put together the African Task Force for the Vaccine. The African CDC also together with the African

Table 2 Covid-19 disruptions in Africa

- ▶ Strain on African health systems
  - ▷ PPE shortages
    - ▷ frontline workers ↑ risk → health care workers widespread outbreaks.
    - ▷ Staff shortages.
  - ▷ Disrupted access to non-COVID-19 healthcare services generally.
    - ▷ Disrupted access to essential health services.
    - ▷ infectious disease prevention, routine childhood vaccination, emergency care, and access to life-saving medications.
  - ▷ Disrupted decades of progress - disease reduction and increasing life expectancy.
- ▶ Economic disruptions
  - ▷ socioeconomic status → one of main determinants of health.
- ▶ Social disruptions
  - ▷ Gender, education.
- ▶ ↑ ↑ ↑ ***Vulnerabilities*** *(corruption, displaced persons, refugees, civil war)*

9) Kreier F. 'Unprecedented achievement': who received the first billion COVID vaccinations? *Nature*. 2021 Apr 29. doi: 10.1038/d41586-021-01136-2. Epub ahead of print. PMID: 33927403.

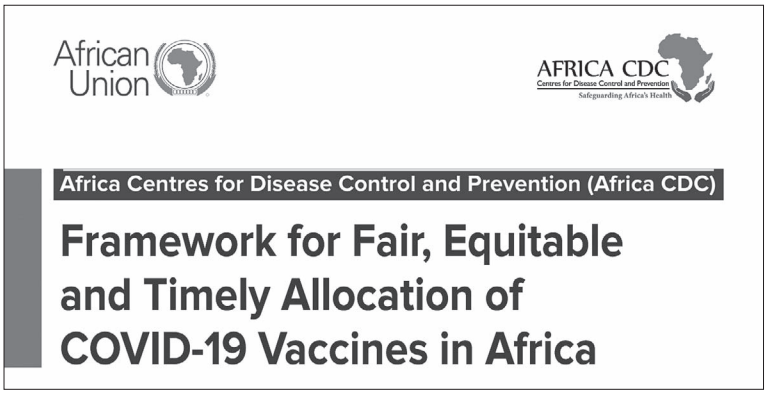
Fig. 1　African Union - multilateral approach to pandemic response

February 2020 – Africa Joint Continental Strategy for COVID-19.

Africa CDC – African Task Force for Coronavirus

Africa CDC – Values Framework

Africa CDC – African Vaccine Deployment Alliance



Source: African Union; Africa CDC. 2021 [1].

Union launched a Values Framework for the Fair, Equitable, and Timely Allocation of COVID-19 Vaccines in Africa.

9. African indigenous values and Umuntu principles

This framework was basically a collaboration between the South African Medical Research Council and the Africa CDC, and it involved a widespread consultation on the African continent. It drew from African indigenous values and Umuntu principles, basically, "***I am because we are, we are therefore I am***" whereby the importance of the community in African indigenous value systems is emphasized and it also emphasized what it means to be a human person (Table 3). We have a saying in Nguni, "***Umuntu Ngumuntu Ngabantu***," "a human being is a human being because of other human beings," and it stresses the inter-dependence and inter-relatedness of humans. We could apply that to the greater good for all while protecting vulnerable individuals and groups.

This would apply both for vaccine access and vaccine hesitancy. We do have a problem with vaccine hesitancy and lack of trust of vaccines, both because of what we have seen at local levels, but also because of us being denied vaccines from the international level. We have an African tradition of lekgotla where all

Table 3　African indigenous values and Ubuntu principles

- "***I am because we are, we are therefore I am***." (Mbiti J): **importance of the community** in African indigenous value systems, and what it means to be a human person.
- "***Umuntu Ngumuntu Ngabantu***" (Nguni saying): a human being is a human being because of other human beings.
  - ▷ **Inter-dependence and inter-relatedness**: greater good for all while protecting vulnerable individuals and groups (for vaccine access and hesitancy).
- African tradition of ***lekgotla*** where all gather under a tree to discuss and exhaust all the options » likened to meaningful **community engagement** in the vaccines discussions.

gather under a tree to discuss and exhaust all options. There are issues to be considered, and we likened this to meaningful community engagement within our vaccine discussions. These are great values and principles. Yes, Africa must take these values seriously and not pay lip service to them. Furthermore, these values could be considered by the world when looking at COVID-19 vaccines as a Global Public Good.

10. Framework for fair, equitable and timely allocation of COVID-19 vaccines

The framework ones drawing from these principles came up with four foundational values:

- **Affirming the humanity of others**
- **Survival of the community**
- **Social solidarity**
- **Meaningful community engagement**

In terms of "**affirming the humanity of others**", allocation decisions must be made such that society at large benefits and the common good is promoted. This could be transposed to the global village where allocation decisions are made such that the global community benefits and common good is promoted throughout the global community.

With "**survival of the communities**", allocation decisions should be based not only the best available evidence, but should look at the greatest risk of severe illness, and other related factors. At a global level, consideration could be given to making allocations to regions with the greatest risk first.

"**Social solidarity**" requires that allocation decisions consider the bonds unifying communities and their interdependence. This could apply to global solidarity when considering the interdependence of countries and our porous borders allowing for ease of movement of variants around the globe.

"**Meaningful community engagement**" will allow for allocation decisions to be trusted. It is such a petty that some of the COVAX donors undermined the COVAX pact such that there emerged distrust of COVAX regarding its ability to deliver in terms of equitable access for all.

11. UNESCO's documents

Article 2 of UNESCO's Statement of the 24th, February this year (2021), stresses that the shortcomings in infrastructure and logistics must be taken into consideration (Table 4) [4]. These shortcomings exacerbate existing divides between the rich and the poor. These shortcomings may restrict the access of the low- and middle-income countries only to certain types of vaccines. It cautions COVAX such that its initiative should not breed discrimination, nor create a situation in which donors would benefit from first-class vaccines and recipients, the lower income countries, receive the second-class vaccines.

UNESCO goes on further to state that for real equity in the global access to vaccines, we need to have a shared ethical recognition of health as a global common good with no territorial limits as well as new global legal instruments for economic and political agreements and treaties (Table 4) [4]. It states that these treaties like the TRIPS were not designed to manage situations like pandemics. It also looks at the issue of the business model of vaccine production. It highlights the responsibility of the pharmaceutical industries to invest in facilities that are able to produce vaccines of the highest possible efficacy, and to facilitate rapid distribu-

Table 4　UNESCO Statement for global vaccines equity and solidarity

2. Ethical concerns for research on vaccines

'Some countries lack adequate infrastructure for such vaccine deployment, which creates an inequality of access, even if the financial bottleneck is resolved through donations. The shortcomings in the infrastructure and logistics needed to ensure equitable vaccine distribution exacerbate the existing divides between the rich and the poor, restricting the access of the low and middle income countries only to certain types of vaccines. The COVID-19 Vaccines Global Access (COVAX) initiative should not breed discrimination, nor create a situation in which donors would benefit from "first-class" vaccines and recipients from "second-class" ones. The unequivocal establishment of efficacy and safety with stringent scientific criteria for all vaccines would alleviate this burden.'

3. Cost, production and distribution: Vaccines as a "global common good"

*'**For real equity in the global access to vaccines**, a shared ethical recognition of health as a **global common good** with no territorial limit is needed, as well as new global legal instruments for economic and political agreements and treaties. The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) and the agreements of the World Trade Organization (WTO) were not designed to manage situations such as pandemics. ....'*

*'Another issue is the business model of the vaccine production. The IBC and COMEST also underline the **responsibility of pharmaceutical industries** to invest in facilities that are able to produce vaccines of the highest possible efficacy and to facilitate rapid distribution to where they are needed. The massive pre-orders by certain national and regional structures such as the European Union and the African Union demonstrate that health must be treated differently from other markets, and require international economic, scientific and ethical frameworks to regulate investments and returns in this essential field, in a way that does not compromise the wellbeing of the marginalized.'*

(Texts in Italic are quotations from original document. Emphases in bold letters are in original documents, underlined emphases are by author.)

Source: UNESCO 2021 [4].

tion to where they are needed. It emphasizes that health must be treated differently from other markers.

12. The Lancet COVID-19 Commission Statement

The Lancet global commission in February 2021 [3] also highlighted the importance of the TRIPS waiver and urged governments from all regions to agree to the TRIPS waiver as proposed by South Africa and India [2] (Table 5). It went to say that additionally, there needed to be accompanying transfer of technical knowledge for the production and manufacturing of vaccines. It emphasized that this would be in line with the globally agreed target of the Sustainable Development Goal 3.8 which calls for 'access to safe, effective, quality, and affordable essential medicines and vaccines for all.'

Subsequently in early May, the world was pleasantly surprised when the US supported South Africa and India. There was also a flurry of publications on the need for the waiver of the patent. Here in this editorial in *Nature* [6], you can see the point is made that a patent waiver is right and fair and wealthier countries must recognize that everyone benefits if vaccine manufacturing is distributed evenly around the world. It also highlights that Africa imports 99% of its vaccines, and African countries lack the preorder purchasing capac-

Table 5 The Lancet COVID-19 Commission Statement Enhancing Global Cooperation to end the COVID-19 Pandemic. February 2021

'Governments from all regions should agree to implement the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) waiver in relation to prevention, containment, or treatment of COVID-19 for the rapid scale-up of production and distribution of vaccine and therapeutics. Additionally, there must be an accompanying transfer of technological knowledge for production and manufacturing of vaccines. This is in line with the globally agreed target of SDG 3.8, calling for "access to safe, effective, quality, and affordable essential medicines and vaccines for all."'

(Texts in Italic are quotations from original document. Underlined emphases are by author.)

Source: The Lancet COVID-19 Commission. 2021 [3].

ity of richer nations. For us to move forward in terms of equitable access to manufacturing vaccines, not only do we have to remove patents, but there has got to be the transfer of knowledge on how to make vaccines and investments in manufacturing capacity.

13. Conclusion

To confront this tragic moral bankruptcy inherent in vaccine nationalism, what is required is a coordinated global response, which is founded on unity and solidarity. The WHO has said no one is safe until everyone is safe. It's very important to remember that this applies both to within and between countries. Remember, national borders are porous. The right to health and, hence, to COVID-19 vaccine as a Global Public Good applies to everyone in the world and not just to people living in the wealthy high-income countries.

Advancing vaccine availability by sharing of intellectual property, allowing for technology transfer, and supporting local manufacturing of generic vaccines in low- and middle-income countries would go a long way in ensuring that the COVID-19 vaccine is truly a public good and not a commodity to be sold in the marketplace through bidding and dealing. That demand outstrip supply even for countries that have purchased in advance is quite clear. We are seeing that now. Therefore, what is the rational way forward? The rational way forward is that we should ensure that supply is rapidly increased, and this can be achieved if manufacturers and rich countries that back them are prepared to share. Sharing, after all, is caring.

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臨床評価　49巻　別冊　2021

COVID-19 and bioethics Part 3:
Pandemic and research ethics－Democracy, placebo and post-trial access【Day 2, June 11, 2021】

Médecins Sans Frontières (MSF) Access Campaign for equitable access in the world

Tammam Aloudat
Managing Director, Global Health Center, Graduate Institute of International Development Studies, Geneva, Switzerland

1. Introduction

In terms of introduction, I am a physician, I come from Syria, and I have worked as a humanitarian worker for the past 20 years with the Red Cross and with MSF, the last of which was in the MSF, Doctors Without Borders (Médecins Sans Frontières) Access Campaign for the 3 years.

I have left MSF and started working in the Graduate Institute of International Development Studies as of last week. Currently, I am the Managing Director of the Global Health Center. I mention that particularly because while the experience and the context that I speak from today is acquired through years of working in the humanitarian sector both as a practitioner, as a medic, and a program manager and an advocate in the Access Campaign. I am not representing the official position of the Access Campaign, which is in a way liberating, because I have spent a lot of time since this invitation trying to understand how do the bioethics affect our conception of access from an angle and point of view not of an ethicist but of a practitioner.

2. COVID-19 as a communal outbreak

What I would like to talk about today is the distribution and availability of COVID-19 technologies, that is, as medicines, diagnostics, and vaccines, but within a framework of having worked in multiple outbreaks and with many infectious diseases in the past ranging from cholera to drug-resistant tuberculosis, hepatitis, polio, meningitis, and others.

While COVID-19 is without a doubt a crisis on a very large proportion, it is no less one that shares much of the characteristics of other outbreaks. It stops being only an issue of biomedical disease affecting a patient and becomes a communal, a collective issue that affects larger groups of people. It becomes an issue that engages not only medicine and the medical evidence, but also the politics and the economics and even the values of our communities. The difference here is COVID-19 has done that on a global scale, and rather than having created new conditions, it has emphasized in many cases conditions that have existed before, conditions of inequity, and lack of justice in distribution and position that we have known to exist for a long time but that have largely been hidden from the public view, especially in western settings.

3. Working in low resource settings

The first thing that we are faced with, and I speak as a physician who has worked in low resource settings, is choices. Rather than having the luxury of working in a hospital where someone else allocates resources, and we are told what to treat or not treat, we are put in a position where we have to make decisions about who gets what treatments because of scarcity. Scarcity creates a largely untenable moral position for physicians who are usually not trained for it. I doubt that anyone is positioned in a place where they decide who lives and who doesn't, but that is a place we are put in regularly in very low resource settings and that we have been put in this pandemic on a global setting.

4. Utilitarian versus untenable ethical frameworks

As a practitioner, there are some ethical frameworks that we can try to understand and use. On the face of it, once we start addressing it, it sounds logical except that it starts creating contradictions and this is where we are today. The immediate sort of blanket assumption underneath public health interventions in epidemics or in any high-burden disease settings is that we have a utilitarian ethics where we are trying to use the available resources to provide the most good for most people, except the moment that starts being practiced in reality, the moment it becomes untenable. It's not applicable in a health setting.

I will give you an example. If we were in MSF to provide only the most efficacious and cheapest intervention, we would end up effectively doing a childhood vaccination and nothing else, but we have made different choices including the treatment of a drug-resistant tuberculosis before the last generation of drugs was available at great cost, and the reason is that we cannot think of the situation as static. Treating drug-resistant tuberculosis has pushed the agenda of the disease further. It has made it available. It has allowed us to speak about it, but it also has addressed people who wouldn't have had any recourse otherwise. It is from a clinician's point of view very difficult to adhere to a purely utilitarian ethics. What else?

5. Justice as a principle of medical ethics

One is the one we are provided with that includes the principles of medical ethics include justice in addition to beneficence and non- maleficence. Justice is the odd one out, because it doesn't talk about the relationship exclusively of a clinician or a patient. It talks about the position of medicine in society and talks about distribution. However, it's never been put to a test at this scale at least in such a public forum, and this is important, because it does not talk about biomedicine only. It doesn't talk about need purely. The need is intersected by economics and by politics, by the position of people in their countries, the position in their class, the position in their gender, and so on.

Then we are faced with situations where we are both put in a position of responsibility vis-a-vis the health of people that are under our care and have been stripped off much of the authority that remains in the hands of sovereign states that on their own have other interests that compete with those of providing best healthcare. This is obvious if we look at some of the statistics. The comical addressing of, for example, the United

States (U.S.) health system whereby the expenditure is nearly double the next country and their position in terms of life expectancy or other health indicators is down in the 20s and 30s. The interest in providing the most efficacious healthcare to the largest number of population is not absolute and is not practiced equally.

6. TRIPS waiver and vaccine distribution inequality

We end up being put in a position where there is an extreme inequality in distribution of whatever available resources and in our case here the one obvious case is the vaccine. We end up having to choose what sort of action constitutes the most ethical one under the circumstances. MSF and many others have rightly chosen to address the issue of WTO (World Trade Organization)-TRIPS (Agreement on Trade-Related Aspects of Intellectual Property Rights) waiver. TRIPS waiver has a merit of addressing an instrument of international norm that restricts access and has a potential to be quite restrictive to the distribution of vaccines. This is a population that has softened as Prof. Ames Dhai mentioned who would have thought that the U.S. administration of all would be one that supports the waiver.

What that means in practice is difficult to anticipate, because it's not only about waiving the intellectual property. It is also about sharing knowledge, about sharing technology, about accepting that we cannot accept an automatic intellectual property on products that have been developed by public funding. It addresses the whole system and the waiver if anything is treatment of a symptom. It is treatment of a symptom of a symptom. As we all know, treating symptoms might be necessary, but it never solves the problem entirely. By that I mean the waiver treats one of the symptoms of intellectual property regime that we are forced to accept, but the intellectual property regime itself along with the imbalance of research and development and the allocation of resources, in themselves symptoms of a world we find ourselves in that accepts the commodification of medicines and hence the commodification of people that live in it except the sovereignty of states as a higher value than the health of people and so on. We are in a situation where we are contented or forced to contend with treating the symptoms of a symptom than the waiver and addressing the consequences of a trade regime that accepts profit on medicines and on people's habit is the one viable route we have.

7. Issues outside of vaccines waiver

But what I will go for now is for the next few minutes try to address some of the issues that we have faced that were outside the immediate vicinity of the waiver and the vaccines that have come up in different context in the lifespan of this pandemic. One of them is the access to healthcare and our ability to accept massive degrees of inequality among different populations and here the availability of healthcare itself. It's no secret the healthcare in North America and Western Europe and as well as other rich countries like Japan, Australia, and New Zealand and so on is by default at an entirely different level than many other poorer countries. Yet we have allowed a course of discussion in the first months of this pandemic to focus on the availability or unavailability of ventilators when we had ventilators necessary to address 2% to 5% of patients in the early stages of the pandemic.

Most of the debate about the management of this pandemic before the vaccines became available or were known to be coming has focused on whether the 2% to 5% of the population in richer countries are going to have optimal care. Not that this is negligible. This is important and this is a massive dilemma, because in the

early stages in Italy, the Association of Anesthetists, for example, issued guidelines about how to take people off ventilators if they had less chances of survival to put people who might survive better. That in itself has implications that are unimaginable to most practitioners in normal times, to take someone off of ventilator and let them effectively perish so someone else can benefit from the same machine.

While at the same time, very little mention was done to the fact that let alone that there aren't ventilators in most of the world, there isn't passive oxygen in most of the world. There aren't ICU beds; there aren't ICU doctors or nurses. That was rarely on the TV except when it was trivialized and characterized like when someone said, "But the Hall of X country in Sub-Saharan Africa has only two ventilators and one of them is booked, is reserved for the President's family." This in itself we could talk about condescending and trivializing discourse rather than argue about why would the country have two ventilators in this day and age. It was made almost a quasi-joke to be put on TV.

That extends to the continuation of that dismissive discourse about countries including Africa doesn't have any cases. The Middle East doesn't have. We don't see them. This is a disease that has affected Europe and the U.S. beyond anyone else, while fully knowing that there are no diagnostics and there are no effective registration systems that would give us a real image. We have contended ourselves with dismissing. It went as far as publications that asked what do we need to learn from Africa and why did they not have – well, they did. The fact that we don't see it doesn't mean it doesn't exist. In my own experience despite the lack of numbers, in my country in Syria, there has been a wave of COVID that has largely unreported because it couldn't be diagnosed, but suddenly you start hearing about relatives who are older who die vaguely from diseases that never affected them that severely before. COVID has ravaged through the rest of the world, but we have managed to dismiss it.

8. Access to medicines and diagnostics

The next one is the access to medicines having suffered this wave of information and misinformation and different evaluation of information, but then also the access to diagnostics. The fact that we have ended up with diagnostic tools that are old. At least the PCR diagnostics aren't ones that are new technologies. The PCRs and machines and cultures have existed before, and we have used them to diagnose drug-resistant tuberculosis among other things. Suddenly, their availability became abundant after years and years of trying to make some of them available for other diseases and this is another contextual issue. We are all proud with how science progressed and made available diagnostic tools and vaccines within months and ignore that same could probably have happened for other diseases and that it didn't.

9. Two regimes of global health

Here I will go back to 10 years to a significant article in my opinion by Andrew Lakoff who talks about two regimes of global health [1]. He talks about a regime of global health that is the global health security that

1) Lakoff A. Two regimes of global health. Humanity: An International Journal of Human Rights, Humanitarianism, and Development. 2010: 1(1): 59-79. DOI: 10.1353/hum.2010.0001

addresses largely diseases that haven't existed yet and aims largely at the protection of western countries, rich countries, from the potential of new diseases. Here the response is aggressive, generous, and rapid. Then there is another global health regime which he calls humanitarian biomedicine, which addresses diseases that are familiar, cheap to address, and yet not addressed like drug-resistant tuberculosis, like neglected tropical disease, leishmaniosis, sleeping sickness, and so on and so on that have needed decades of scarce resources to develop any sort of technologies. In fact, sleeping sickness which still exists in many pockets in South Sudan, Nigeria, Congo, and others didn't get a new diagnostic and treatment until they were developed by non-profit entities like DND*i*, Drugs for Neglected Diseases *Initiative*, which has developed the first non-injectable treatment for sleeping sickness ever.

10. Vaccines as excludable and rivalrous good

Finally, the vaccines. Here is an interesting point, because as Prof. Dhai said, very early in the process there was this talk about vaccines being a global public good. Now there is a point that Prof. Dhai mentioned which is the same countries that proclaimed it a Global Public Good turned away almost instantaneously and started buying vaccines, hoarding vaccines, and we know the statistics, the countries that bought 500% or 300% of what they might need just to guarantee that they will have it early enough.

But the view of Global Public Good as a non-excludable and non-rivalrous, vaccines are excludable and rivalrous. If someone takes a vaccine, someone is not going to take that vaccine. Vaccines are not like clean air or clean water. They have a cost to produce, and when they get consumed, they disappear. It begs the question about whether that has served only as a sort of a sloganistic way of making everybody feel good while the richer countries manage to occupy the market and hoard almost every vaccine where we see the consequences now with nearly full coverage. The United Kingdom yesterday was discussing whether 12 years old at nearly no risks should be vaccinated. It's almost completely justifiable in most western media that this would be a legitimate discussion before healthcare providers have been vaccinated almost anywhere else.

11. Governance for global health

Then, we are left in a place where governance for global health is scattered between sovereign states that are increasingly protective and look inwardly and frames that are put outside as unchallengeable and impossible to change like the fact that medicines and vaccines and diagnostics have to be treated as commodities that go through a market despite all the imperfections and failures of that market which needs public funding and needs IPs to protect, but yet, we are offered no alternative and not allowed to think of any alternative.

A few days ago I read a definition of governance, because supposedly we work on global health governance, but as you all well know, the literature still contests the definition of what global health is and what governance is, so it's a bit difficult, but sociology book from the 60s argues that governance is making people want to do what is needed and failing that making them do what is needed. Governance includes a coercion part implicit to it. There is no requirement of governance to be only democratic or only benevolence, and the problem here is not only making people want to do something but to do what is needed. The decision on what

is needed and what is the global health is taken by a very narrow strata of managerial class, and by philanthropic capitalists and billionaires, and by civil servants who owe their loyalty to their next elections before the health of the people and the rest of the world. That governance, if we do not think that it has left much to be desired under the current pandemic, then we need to reconsider what we think of as success or failure.

12. Global health crisis

This is particularly interesting not only because newer pandemic will come. I have worked in 2005 in Indonesia when the H5N1 was going to be the next pandemic and then in 2009 when actually H5N1 was a pandemic. We have seen Severe Acute Respiratory Syndrome (SARS) happen; we have seen the Middle East Respiratory Syndrome (MARS) happen. We knew a pandemic is going to come, and arguably we haven't been prepared, but not only that we are in a global health crisis that has global implications and yet rather than becoming an equalizer as we were promised in the beginning, it has become another reason for deepening the inequalities that are affecting the people, the inequalities as a result of the COVID itself, but then the others that we haven't yet started exploring that include all the other mortality and morbidity that has happened and is happening in the background and is ignored now, because everybody is paying attention, all the unnecessary child and maternal and infectious disease and non-communicable disease deaths that you have even less access to healthcare.

13. Conclusion

From a position where we as practitioners have to function in this system and still be able to go and have a good night's sleep, hopefully some of the nights at least, there is a difficulty in accepting that there are many days where we have to actually deal with the symptoms of the symptoms. We have to go and pretend the TRIPS waiver will solve everything, and there are days where that stops being enough. I wonder whether we could have an argument one day about an ethical decision that accepts the basis of global health being vertical, run by the west, continues legacies of power and inequality, and owes its allegiances to member states rather than people.

We might need to answer those questions faster than we think because now we are dealing with a single virus with a single potentially vaccine to deal with it and we are struggling to find a solution. In 20 years, we will deal with climate crisis that will make many other diseases differently endemic, we will have no single vaccine to deal with it, and probably be much more expensive and create much more inequality.

I thank you very much for having me because this is a place where we can hear the ethicist guide us. I have very much in my career benefited from listening to people tell us how to think better about the ethics of our practice.

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Discussion (Day 2 No. 1)

Chieko Kurihara
Specially-appointed Professor, Kanagawa Dental University, Japan

Thank you very much Prof. Ames Dhai, Dr. Tammam Aloudat for the very valuable talk about equitable access of many kinds of resources not only vaccine. We Japanese have to recognize shameful government attitude to buy top vaccines for the nation despite the low prevalence comparing Brazil and many other countries like African and European countries. First of all, I would like to invite Dr. Peter Lurie, because he cannot stay until the end. His Citizen's Group is very much engaged in challenging to overcome this kind of inequity in the world.

Peter Lurie
Center for Science in the Public Interest, Washington, DC, the United States

It's very, very difficult to say anything that can add much, certainly not to top what we have just heard from our previous speakers, extraordinarily well put together, beautifully stated, eloquent, and unfortunately mostly unheeded, really a beautiful set of comments. I want to thank you for that.

I only have a couple of things to add because so much has already been said. On a personal note what I found so frustrating about all of this is that this so-called end or ending of the pandemic is exactly the ending that many of us saw coming down the tracks one year ago. This seemed like a virus that was maybe unusually susceptible to vaccination compared to, say, HIV. It seemed that the concerted attention of the scientific establishments around the world would be able to produce something, and indeed within a relatively short period of time it has. But it was equally predictable or perhaps even more so that we would wind up in a situation in which some people who had only limited need for the vaccine would wind up with it and those who clearly would need it would wind up without. That was exactly the situation that was predictable a year ago. It's exactly the situation in which we find ourselves today.

It speaks poorly of humanity as a whole that with all of this concerted attention of almost literally every person around the world knowing about this pandemic going on that we have somehow failed to come up with a solution that is much better than what we have had in the past.

Yes, there have been some signs of progress in COVAX and the recent announcement just yesterday by the Biden Administration of another 500 million doses. Yes, those things are admirable, the endorsement of the TRIPS waiver by the U.S. is also helpful, but at the end of the day, we find ourselves where we usually do, which is with the haves having and have-nots not having. It is just exasperating to see the same play taking place repeatedly.

The second thing is I am not an official ethicist the way some of the people on this call are, but I have taken part in a number of these debates over the years. Sometimes these debates are theoretical. They are about principle. But this one is not merely about that. This is a debate in which literally life and death is at stake,

what we should call a global misallocation of vaccines, a public health malpractice has taken place, and the price is not paid in principle, but it is paid in lives, likely in the hundreds of thousands, probably in the millions. All of these tiny little debates, say, in the United States on whether vaccination should be for 65 year olds or 60 year olds or whether frontline worker should go before healthcare workers are so trivial in comparison to this global misallocation of resources that it's just extraordinary. This is the big debate. This is the true injustice of this epidemic, and it's the same one we have seen taking place for years.

The final thing I will just say is here in the United States, we focus on our so-called newspaper of record which is the New York Times, and it's done a pretty wonderful job of covering this pandemic with a lot of personal stories, very well-done statistical analyses that have run every single day, a section that was devoted to the pandemic running 7-8 pages every single day, and on the weekend a special social piece called "At Home." Just this past week, the New York Times decided to do away with those sections. I am not here to say that that's wrong from a journalistic point of view. At some point, you can't cover a story forever, but I believe that in some western countries, the perception is growing that somehow this pandemic is ending. It's just not so.

In some countries, a number have been mentioned in the Middle East, for example, this pandemic is just beginning. The self-satisfaction of the people in the West about the accomplishments of science, the occasional gestures in favor of vaccine availability just do not take that into account. I suppose that all paths forward begin with a conversation, and I suppose that this is one of them. Let us hope that when the next pandemic comes, because it surely will, we will do better than we did this time.

Ruth Macklin

Distinguished University Professor Emerita at Albert Einstein College of Medicine in New York City, the United States

I want to thank both speakers for their excellent presentations. I started formulating my brief comment and question before I heard Dr. Aloudat's, but now I have to add him to it, because of his seconding and very interesting and thoughtful remarks.

I am in total agreement with the points that both speakers have made. Prof. Dhai's presentation understandably focused on the role of governments and nation states in a global pandemic, including references to international documents and UNESCO. My question, and Dr. Aloudat briefly touched on the issue: what about the private sector? Big pharma in this world stands to make billions and billions in profits. They have already made billions from profits in many other contexts. The next big one coming along is the recent scandal of the U.S. FDA (Food and Drug Administration) having approved a drug for treating Alzheimer's disease that researchers found not to be efficacious. There is lots of money the drug company can make, given all the aging people who already have Alzheimer's and those likely to acquire it in the near future.

Big pharma is a player as a vaccine producer. There is no way to coerce big players in private industry anymore then there is to coerce nation states. But why not call for wealthy, profitable industries--not only pharma, but especially pharma--to contribute to the needs of LMICs (Low- and Middle-income countries) in the COVID pandemic?

Tammam Aloudat

Managing Director, Global Health Center, Graduate Institute of International Development Studies, Geneva, Switzerland

In the same spirit of pragmatism, we cannot wait until every problem is solved, because people's lives are on the scale. One thing is how do we deal with today? There are things that have been informed about and talked about absolutely clearly from the beginning including how can we give billions and billions of dollars and Euros as subsidies to pharmaceutical companies without demanding of them anything but vague promises of access?

In the global south that has meant unaffordable prices because they get to set the prices, but even in the global north this meant that the taxpayers are paying the price twice. They have paid them in subsidies to the pharmaceutical companies and then they are paying them again in prices of vaccines. It's hard for me to conceive, and I don't come from a democracy, but when you are in the democracy, how do those things come to pass and what sort of dogma allows this to be normal? But that's beside the point. There can be conditionality on public money. Their protectionism in the name of we can't sacrifice the economy for the pandemic is too thin to hold that long. That didn't happen, but there were very good cause and the governments should be held accountable for the billions they expended on subsidizing pharmaceutical companies without demanding solid and clear returns in terms of access conditionalities.

The second question for the future at least in my view is, we like market or not, capitalism or not, is it viable for the world to put our collective health and survival in the hands of CEOs whose primary goal is to increase shareholder profitability? Is that a sustainable way to go forward? That is a significant question. I have an opinion that none is probably interested in, but this is a debate that has to be had. We can't just sacrilege the profit and the market to the extent that whoever dies and then we end up with the argument on whether Boris Johnson did say, "let the bodies pile higher", or he didn't exactly say it. Doesn't matter if he did or he didn't, because every other government acted as if they are saying it when they have given almost freehand to the market over the health of their own people.

Ramin Parsa-Parsi

Workgroup Chair of the 2013 revision of the Declaration of Helsinki

German Medical Association

Thank you again Prof. Kurihara for inviting me to participate in this important meeting. This was an interesting and very good and rewarding experience. I would also like to thank our two speakers today, Prof. Dhai and Dr. Aloudat. I appreciated your presentations and agree with you that lifting or waiving patents of vaccines is not enough. It doesn't suffice. We also need a knowledge transfer for vaccine manufacturing. This is probably even more important. That's an opinion I would absolutely share.

I took a lot of notes during the two meetings, especially getting back to our thoughts around the Declaration of Helsinki [1)] and the CIOMS guidelines [2)] and tying back into the discussions we had during the first part of

1) World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research involving Human Subjects. Adopted Jun 1964, last amended in Oct 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

2) Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-related Research Involving Humans. 2016.
https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

the event. Prof. Macklin highlighted the differences between the CIOMS and Declaration of Helsinki guidelines with regard to this specific paragraph on post-trial access. Prof. Kurihara, we also took note of your proposal that communities should probably also be included in this process, not just the individual trial participants. Post-trial access is a matter of extreme importance and has to be considered before research begins.

The issue of community engagement before the beginning of a trial should be discussed. This should involve all the different stakeholders, meaning sponsors, big pharma industry, developers, investigators, the trial subjects, but also governments. It should involve all these parties in order to get to a fair and good outcome and to ensure the success of the trial, also after it has been completed. This is all something we will need to confer about and discuss again once we revisit the documents focused on clinical trials. I am referring here primarily to the WMA (World Medical Association) Declaration of Helsinki (DoH) because that's the document that will most likely be reviewed again soon. It was helpful to have the differences between the DoH and the CIOMS guidelines highlighted again. The meeting provided valuable feedback which we will certainly consider, and I will also forward this feedback to the WMA Medical Ethics Committee for consideration.

I took a lot of good thoughts from these discussions. Thank you.

Ames Dhai

Professor of Bioethics, University of the Witwatersrand, Johannesburg, South Africa

Thank you so much for the comments, Dr. Parsa-Parsi and Prof. Macklin. To go back to Prof. Macklin in terms of big pharma not being given emphasis, the Article 3 of the UNESCO document [3] that I presented does emphasize the need to look at that business model. There has to be change to that business model. It also emphasizes the responsibilities of pharma that have to materialize meaningfully into action as well. Yes, while presenting a general overview, pharma was included into the discussions. You can't leave out big pharma in terms of the culprits they are as well. What we have seen with the vaccines, more especially vaccine nationalism and the bilateral agreements is that there are concerns all round to include high income countries, their governments, and pharma. Perhaps it's time for countries' governments in the developing world to say to big pharma, we are not going to allow you to do any clinical trial here unless there is that promise or that undertaking that we will have access to the interventions, not only for those that were involved in the study, but also to our populations that participated in some way or the other, and this needs to come from our government levels so we need commitment at that level as well.

Kurihara There are many things to discuss. Especially we have to collaborate with pharmaceutical companies, and we wish to change the previous policy of companies after experiencing of this COVID-19 situation.

(Published November 15, 2021)

3) Joint Statement by the UNESCO International Bioethics Committee (IBC) and the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST). UNESCO's ethics commissions' call for global vaccines equity and solidarity joint statement. SHS/BIO/IBC-COMEST/COVID-19 Vaccines. Paris, 24 February 2021.
http://www.sbbioetica.org.br/uploads/repositorio/2021_02_24/Unesco2021GlobalVaccineEquityESolidarityStatement-fev2021.pdf

COVID-19 and bioethics Part 3:
Pandemic and research ethics－Democracy, placebo and post-trial access【Day 2, June 11, 2021】

Post-Trial Access for All: Perspective of achieving universal access to adequate public health*1

Dirceu Greco*2
Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil

1. Opening remarks

Let me start by thanking again the Japanese partners of this very interesting seminar, Japan Association for Bioethics. The Brazilian Society of Bioethics is proud to be with you, and this event is very important for all of us.

What I am going to talk now is a continuation of what Prof. Ames Dhai said very well and what Prof. Ruth Macklin last week and Dr. Peter Lurie spoke about today. We are facing just a tip of an iceberg that affects us all, but I am going to try to make it clear when I start talking. First of all I have no conflict of interest to be declared in this presentation.

2. Two hypotheses

I have some hypothesis (Table 1).

Research has to be relevant with social value. We need to have international ethical guidelines to be followed. In clinical trials, access to proven preventive, diagnostic, and therapeutics must be provided without

*1 Previous lectures and papers on related topics published in *Clinical Evaluation* can be seen from the following, especially the reference No. 1:
- Presidential Symposium in the 40th Annual Scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics, 2019 International Collaborative Research and New Trends of Research Ethics /
The 120th Pharmaceutical Study Group Meeting Ethics of international collaborative research: Perspectives from Brazil
http://cont.o.oo7.jp/48_1/48_1contents_e.html
- COVID-19 and bioethics: Part1 Ethical Challenges and COVID-19
The Recommendation No. 01/2020 of the Brazilian Society of Bioethics (SBB)
http://cont.o.oo7.jp/48_3/p661-84.pdf

*2 Chair of the Brazilian Society of Bioethics, 2019-2021; Member and Vice-chair of International Bioethics Committee of United Nations Educational, Scientific and Cultural Organization, 2018-2021

1) Greco D. Shimoda K, Watanabe H, Organizers. The Past, Present, and Future of Ethics of International Health Research: Research as a stepping-stone to Universal Public Health Care Access. *Clin Eval.* 2020; 48(1): W29-W53.
http://cont.o.oo7.jp/48_1/w29-w53.pdf

Table 1 Hypothesis

- Research with human subjects must be relevant, with social value.
- International ethical guidelines for research are also necessary.
- In clinical trials access to best proven preventive, diagnostic and therapeutic must be provided, without double standards, including post-trial.
- Results of human research must be translated into public health access.
- Access is even more important and urgent in public health emergencies – e.g., patent exemption for COVID-19 products must be issued.

Hypothesis 2: Access post-trial as a right

The obligation to guarantee post-trial access to products (and care) if these are shown to be effective (and safe) is based on the following ethical principles:

- The principle of beneficence requires that the welfare of participants be actively promoted.
- The principle of non-maleficence requires that the welfare of participants is not negatively affected due to the interruption of non-access to efficacious products.
- The principle of justice:

As **reciprocity** calls for providing something in return to participants who have volunteered their time, been inconvenienced or experienced discomfort by enrolling in the trial.

And also as **distributive justice**, a notion pertinent to situations that call for the fair allocation of benefits.

double standards including post-trial. Results of human research must be translated into public health access. That is going to be my motto today. Access is even more important, not exclusively, and urgent in public health emergencies, for example, patent exemption for COVID-19 products must be issued.

My second hypothesis is access post-trial as a right (Table 1). I argue that obligation to post-trial access to products and care is based on many ethical principles; "beneficence" requires that the welfare of the participants be actively promoted, "non-maleficence" requires that the welfare of participants is not negatively affected due to the interruptions or non-access to efficacious products, and maybe the most important is the principle of "justice", being "reciprocity" as part of it and more importantly "distributive justice" as a notion pertinent to situation that call for fair allocation of benefits.

These are two hypotheses I am going to detail now.

3. What is owed following a clinical trial?

I was trying not to make so much about discussing the post-trial access after trials, as my main point, and I am going to put myself forward as a physician, an infectious disease expert. I have been dealing directly with the effects of pandemics. I have been very much involved with at least two of them. The first one was HIV-AIDS that hit all of us and still hitting the whole world and now COVID-19. My emphasis is much more in the public health system than on the usually very controlled clinical trial. And I am going to show you what some selected documents have established. Prof. Ruth Macklin mentioned some of them.

I will start with CIOMS 2016 [2], one in relation to clinical trials. It's on Guideline 1, Guideline 2, and Guideline 6.

UNESCO [3, 4] has a lot of items and they were already mentioned by Prof. Ames Dhai. One of them is Sharing of Benefits, Article 15.

The 2007 UNAIDS/WHO Guidance document [5] that Prof. Macklin and I participated very strongly on its establishment, but which unfortunately, has been succeeded by a very much lax document which was just released [6].

The 2010 WHO Guidance on Ethics of Tuberculosis [7] is a very good document, and it addresses a lot about public health access.

The 2013 Declaration of Helsinki [8] Paragraph 34 on post-trial access is lax in this subject.

I am going to talk a little bit about a developing country position imbedded in the 2012 Brazilian Research Ethics Commission, resolutions 404 and 466 [9], on post-trial access.

My argument is that the right to post-trial access in a clinical trial is a dated discussion, because the main focus of all of us should be to ensure access to the benefits of trials in public health to all, not only in the COVID-19 pandemic.

4. CIOMS 2016 – Guideline 2 and Guideline 6

The CIOMS 2016 [2] Guideline 2 is bit lax about post-trial access, because it says that "***as part of their obligation, sponsors, and researchers must also***" and I don't like this following wording "***make every effort***". It doesn't mean anything to say "***...in cooperation***", "***to make available...***". To make ***every effort*** and ***to make available***, it is not very clear what we are saying about post-trial access. That is the first point.

Guideline 2 does not specifically mention post-trial access, but in Commentary of Guideline 6, it says, "***As***

2) Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-related Research Involving Humans. 2016.
https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/

3) United Nations Educational, Scientific and Cultural Organization. Universal Declaration on Bioethics and Human Rights. 19 October 2005.
https://en.unesco.org/themes/ethics-science-and-technology/bioethics-and-human-rights

4) Joint Statement by the UNESCO International Bioethics Committee (IBC) and the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST). UNESCO's ethics commissions' call for global vaccines equity and solidarity joint statement. SHS/BIO/IBC-COMEST/COVID-19 Vaccines. Paris, 24 February 2021.
http://www.sbbioetica.org.br/uploads/repositorio/2021_02_24/Unesco2021GlobalVaccineEquityESolidarityStatement-fev2021.pdf

5) Joint United Nations Programme on HIV/AIDS (UNAIDS) 2007. Ethical considerations in biomedical HIV prevention trials: UNAIDS/WHO guidance document. 2007.
http://data.unaids.org/pub/manual/2007/jc1349_ethics_2_11_07_en.pdf

6) Joint United Nations Programme on HIV/AIDS and World Health Organization; 2021. Ethical considerations in HIV prevention trials. Geneva; 2021. Licence: CC BY-NC-SA 3.0 IGO.
https://www.unaids.org/sites/default/files/media_asset/ethical-considerations-hiv-prevention-trials_en.pdf

7) World Health Organization. Guidance on ethics of tuberculosis prevention, care and control. 2010.
https://apps.who.int/iris/bitstream/handle/10665/44452/9789241500531_eng.pdf;jsessionid=A807FA85616DD9B062232400AD281696?sequence=1

8) World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research involving Human Subjects. Adopted Jun 1964, last amended in Oct 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

9) Brazilian Research Ethics Commission Resolution 466/2012, which succeeded Resolution 404/2008.

part of their obligation to transition to care after research, researchers and sponsors may have," again the verbs employed all the time are not "must", nor "have to", but it is "may have", and "make every effort". This is not a strong position related to post-trial access.

On the other hand, CIOMS 2016 Guideline 1 may be understood as an added protection for post-trial access, because it says and that is the strongest stance that they make: that "***Scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment or injustice.***" We must keep an eye on this, specifically on avoiding ***injustice***.

The CIOMS Guideline 6, but again I am not going to go through all this very busy slide. In commentary, it states again, "***may have to provide continued access to interventions***", but also that sponsors and researchers may no longer have an obligation to provide continued access to a study intervention that has demonstrated benefit when it becomes available in the public health system. Worse than that, it says that "***sponsors, researchers, and community members may agree before a trial starts that any intervention that has demonstrated significant benefit will be provided for a predetermined period of time***". It makes everything very easy to make a case for not providing exactly what people believe are going to get.

5. UNESCO 2005 Universal Declaration on Bioethics and Human Rights

UNESCO 2005 document [3] is a document I consider very important as it was approved by 1996 countries, but it still lax in relation to post-trial access, because it says, in the item 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***." That's very good, but unfortunately, it says that "***benefits may take <u>any</u>*** (Emphasis by underline is added by author. The same applies hereinafter.) ***of the following forms***". "*Any*" of course means "any of them". One of them is very good: "(c)***provision of new diagnostic and therapeutic modalities of products stemming from research***" and "***(e)access to scientific and technological knowledge***". But if may interpret the possibilities in different ways, you may choose one, two or three of mentioned forms. You may, for instance, chose *capacity building* or *support for health service*. My opinion is it should include all (and not any) of the listed possibilities or at least that some of them must be always included. In my opinion, one of these should be "***provision of new diagnostic and therapeutic modalities of products stemming from research***".

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

The UNAIDS/WHO 2007 document [5], unfortunately, this has been succeeded by a revised one [6]. This is an important document, because it speaks very strongly for benefits for people that are participating, and in the end, it says that "***some of the activities related to the conduct of biomedical HIV prevention trials which <u>may</u> benefit those who participate <u>may</u> actually be rights***". That's a good point, but I consider that instead of "may" it should be "must". This document has been updated in 2021 [6] but in my opinion the new position on this point is weaker than in the 2007 Guidance Document.

7. Declaration of Helsinki: Post-trial access

We now come to Declaration of Helsinki [8] and I have very many criticisms (Table 2). I have spoken about that many times. In 2000, I participated in the approval of important changes in the Declaration (Edinburgh, United Kingdom). In 2008, I was also in Seoul, South Korea, for another revision of the Declaration. I did not manage to participate in the General Assembly that approved the current version (Fortaleza, Brazil). It is worth emphasizing that in 2000, for the first time, the right to post-trial access was very clear: "***Every patient entering a study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study***".

This was changed in 2008 and again in 2013. Now it says that "***in advance of a clinical trial***", those people "***should make provisions for post-trial access for all participants who still need an intervention identified as beneficial***"; "***This information must also be disclosed***." The difference you see here, "should make provisions" in the 2013 version is very different from "should be assured". This is weaker than in the 2000 version, and there was a fierce discussion on the subject between 2000 and 2013. I hope that the WMA (World Medical Association) after considering all arguments in favor of the right to post-trial access, and especially with what's happening with COVID, may consider again a stronger language for the coming version, basing in then Declaration of the 2000 version.

8. WHO 2010 – Guidance on ethics of TB prevention, care and control

This is a very important document. It's from 2010 and again from WHO [7]. It's on ethics of tuberculosis

Table 2　The WMA Declaration of Helsinki: Post-trial access

Edinburg 2000
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
Seoul 2008
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
Fortaleza 2013
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.

prevention, care, and control, and it's very strong in the defense of participants and also on access in public health (Table 3). Prof. Dhai mentioned when should we permit trials to be done in our countries. This Guidance provides a list of sine qua non prerequisites for permitting a clinical trial. I wish to highlight two circumstances in which biomedical trials should not be performed: "***When agreements have not been reached among all research stakeholders on access to medical care and treatment***"; and "***when agreements have not been reached on responsibilities and plans to make trial products (drugs, other treatments, or preventive measures) that prove to be safe and effective, available to communities and countries where they have been tested, at an affordable price***." Although this is a WHO document I think it is not followed as it should.

This Guidance goes on and detail the rights to access to TB care for all, and the obligations to provide TB services. They use questions to elaborate on: "***Do governments have an ethical obligation to provide universal access to TB care?***" "***Yes***". Many important documents are mentioned such as WHO Constitution and

Table 3 WHO 2010 Guidance on ethics of TB prevention, care and control: Access to care for all

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

Does this obligation mean that tb care should be provided for free?

- **Yes.** "Anti-TB drugs should be available free of charge to all TB patients, both because many patients are poor and may find them difficult to afford, and because treatment has benefits that extend to society as a whole (cure prevents transmission to others)" - *Stop TB Strategy*

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.

2. The obligation to provide access to TB services

Do governments have an ethical obligation to provide universal access to tb care?
Yes. Provision of universal access to TB care is grounded in their duty to fulfill the human right to health.

As stated in **the WHO Constitution,** "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".

Similarly, the **International Covenant on Economic, Social and Cultural Rights** recognizes "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health" and specifically calls on State Parties to take steps necessary for "the prevention, treatment and control of epidemic, endemic, occupational and other diseases".

(emphasis added)

Source: WHO 2010 [7]. Table is reproduced from *Clin Eval*. 48(1) [1].

the International Covenant on Economic, Social, and Cultural Rights from UN, and in these it is based the argument that universal access to the TB care is grounded in their duty to fulfill the human right to health. It can be applied also to the COVID-19 pandemic.

In the same document, another question: does this "obligation" means that TB care should be provided for free? Yes. That is specific for anti-TB drugs, but why not for other drugs, for other diseases that are also prevalent throughout the world. I want to elaborate on this. The COVID-19 pandemic came not as a substitution for the other problems that we have. It's an add-on. If it disappears, we are going to have a lot of things to take care of and I hope we can another three, four, five meetings like this to discuss how to tackle them.

The document mentions that research results should lead to technology transfer. That's exactly what I have been saying about COVID-19, and the research protocol must provide attention to how findings will be translated into public health policies. What we have been discussing in South Africa, Brazil, in many other developing countries, and undeveloped countries especially in relation to the waiving of patents is part of the solution. It has been difficult because of the pressure from the big pharma, the money that is involved, which makes it very hard for people to counteract. But we must be part of this counteracting.

9. Brazilian Research Ethics Guideline

I am going to tell you a developing country position regarding research ethics. This is a case study that I consider is very interesting, and it is about the Brazilian Research Ethics Guidelines and the Unified Health System, which has as its acronym SUS (*Sistema Único de Saúde* -Unified Health System). SUS in Brazil is completely public, financed by taxpayer's money, and provides access to health to all 210 million Brazilians. I am going to remember just one specific date, that is 1st of August 2008, and this is just two months before the 59th WMA General Assembly that changed the 2000 Declaration of Helsinki.

Brazilian anticipated the results of this GA especially in two specific items. First, Brazil was proposing to cancel the two notes of clarification approved by the WMA, related to flexibilization on the use of placebo and on post-trial access. Those weakened the rights of the volunteers, and the Brazilian Health Council approved Resolution 404/2008 [9] keeping what was stated in the 2000 version of the Declaration of Helsinki. I am not going to read the terms of Res. 404 which are in this slide, but will call you attention especially in relation to access to healthcare: it says that participants at the conclusion of the study will be provided with the best proven prophylactic, diagnostic, and therapeutic methods identified by the study.

It is worth emphasizing, and everyone knows, the Declaration of Helsinki is not binding. It's a very good document, very important, very respected, but the countries, if they can make it even more strict, the better. That's exactly what Brazil did at that time. In this resolution, it was also included the proposition to further discussion on access to health and to the products that have showed efficacy, not only in a clinical trial, but to all who need them, in public health.

Of course, these points were later embedded in the newer resolution 466/2012, that succeeded the original research ethics guidelines (res. 196/96) (Table 4). It explicitly defines that at the end of the study, the sponsor must ensure to all participants access free of charge and for all the needed time the best prophylactic, diagnostic, and therapeutic methods identified by the study. And it goes on stating that there is no time limit. If it shows to be safe and effective, it must be provided, independently of the products getting to the public health

Table 4 Brazilian Research Ethics Commission Resolution 466/2012*

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:
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.

(emphasis added)
Table is reproduced from *Clin Eval*. 48(1) [1].

system or not.

Brazil is, to my knowledge, the only country with such a strict and protective position. When this resolution was issued, many people said that big pharma would not do research in Brazil anymore. But this has not happened. What actually happened is that they adapt their clinical trials to the Brazilian Guidelines. This may be explained, at least partially, because for them the drug market in Brazil is one of the largest in the world. Thus, if they have to give up a tiny part of their enormous profits, they will still make a lot of money. Thus, the Brazilian example could be used by many other countries, but this has not happened... And of course, big pharma continues to pressure the Brazilian authorities to make these two items more flexible.

10. Brazil's Universal Public Health System (SUS)

The Universal Public Health System is of paramount importance, because that is what we expect globally. Dr. Lurie or someone else has mentioned that the public health system in the United States is amazingly bad and exclude many people from care. Brazil, a country with an enormous disparity, which makes me ashamed, has public health system that includes everybody - 210 million people can have access to it. The exemplary response to the AIDS epidemic, providing care and antiretrovirals free-of-charge to all, is a good case study and it happened only because we have this system. Of course, the system is under-financed and has been overwhelmed now by the COVID-19 pandemic, but the appalling situation with the current pandemic would be even worse without the SUS. It is worth noting that although everyone has the right to access the public health system, less than a 4th of the population also have private insurance.

We can give an idea of the magnitude of the public health system in Brazil in terms of numbers. Its dimension is really amazing. It has the world's largest human milk bank. Organ transplantation is also one of the world's largest. It funds 90% of preventive vaccines, 80% of treatments in oncology. All antiretroviral drugs and the still very expensive antiviral drugs (for hepatitis C) are exclusively funded by the system. I must emphasize that everything is funded exclusively by municipal, state, and federal taxes. All this is in danger

to be lost with the neo-liberal/right wing policies in place in Brazil today.

As mentioned before, it is a successful example. I will show a summary of what Brazil put in place to confront HIV/AIDS. This is 2009, but it is very similar in 2020: Brazil has the same HIV prevalence as in North America and Europe, that is, 0.4% for the general population, and this was due in part by the issuing in 1996 of a law giving the right to all people living with HIV/AIDS to receive the needed antiretroviral treatment. And in Brazil has available 21 antiretrovirals to everyone who needs it and close to half of them by local public laboratories. This is a very interesting example that if there is political will and ample participation of the whole society, things can be done even in situations of disparity as we have in this country. And of note, just once, Brazil issued a compulsory license for one drug (efavirenz) from Merck. The price decreased from $1.45 per tablet to $0.6 and it is produced in Brazil since then. The next slide gives an idea of the magnitude of the public health system in Brazil in terms of numbers at is just an example, a sample.

11. COVID-19 pandemic in Brazil

As you all know, Brazil is a big country. I live in Belo Horizonte, which roughly 400 km inland, both from Rio and San Paulo and we are almost 20,000 km away from Japan! But what I wanted to show you is that as of June 2021 Brazil has 17 million cases of COVID-19, with an unacceptable death toll (biweekly deaths per million was 77, compared to 1.36 in Japan, as of middle October) almost 500,000 people who have died from COVID-19 and these numbers could be a lot lower if irresponsible federal government had acted sooner. But they have negated the seriousness of the epidemic. It took them a long time to decide to buy vaccines, to join the COVAX Initiative and to establish proper nonpharmacological preventive measures, such as use of masks and social distancing. As Dr. Lurie mentioned, a few countries are saying that in very little time they are going to have epidemic under control, but that will certainly not happen anytime soon globally. What is happening now is some industrializes/developed countries which have most of the world's wealth are buying most of the COVID-19 vaccines available. Currently Brazil has only 14.6% of the population fully vaccinated, even producing two of the vaccines locally. And will follow discussing the need for expanding worldwide production of patent-free vaccines and other products for COVID.

12. WTO (World Trade Organization)

The Brazilian SUS is shown again as it is an important tool to guarantee sustainability. This is about HIV, but it is very similar to COVID and other infectious diseases. There is a need for technology transfer. We may start using the flexibilities allowed by WTO (World Trade Organization) - TRIPS Agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights) defined by the WTO Doha Declaration. However, it is not enough to use the Doha Declaration on TRIPS. As mentioned above, Brazil just once used a compulsory license [10], but now we are in another situation that relates to post-trial access for all, globally. This slide

10) Greco D, Invited lecturer. Kimura R, Special guest. Victoria Perottino M, Guest Discussant. Saio T, Kurihara C, Organizers & Discussants. Ethics of international collaborative research: Perspectives from Brazil: Part 1 Selected notes on Paulo Freire: Part 2 Access, Compulsory license, Case Study. *Clin Eval*. 2020; 48(1): W95-W123.
http://cont.o.oo7.jp/48_1/w95-w123.pdf

shows the approval of TRIPS Agreement in 1995 and also the following Doha Declaration, but even if it is possible to use Doha Declaration for compulsory licensing, it is almost impossible to do that in an urgent situation and globally, not only because of red-tapping, but also the difficulty to use all the tools and knowledge that is needed to the actual producing of needed products: vaccines, drugs, other devices. Big pharma usually does not open all needed knowledge for the production of these goods.

Thus, it was really a good thing that in 2020 South Africa and India spearheaded a proposal to the WTO to waive product patents to control COVID-19 globally. These two countries belong to the BRICS (Brazil, Russia, India, China, South Africa). Unfortunately, Brazil in the beginning did not join them. Recently in part due to the United States decision to back this proposal, the Brazilian government agreed only to participate in the discussion of the proposal. South Africa and India's initial proposal, now backed up by over 130 countries, was very comprehensive, that is they ask for the temporary suspension of several provisions, including copyright, industrial designs, patents, and undisclosed information. With that, it will be feasible to many countries that have well-prepared, well-equipped laboratories and researchers, to start producing very soon. It is worth emphasizing that over 10 countries are qualified by WHO to produce human vaccines. The other thing that should be worth fighting for after or concomitantly with the discussion of this temporary suspension, is a revision of the TRIPS Agreement itself which today impedes the access to many other needed products for other illnesses. It is really just that intellectual property rights should be equally applied both for consumer goods and health products? I don't think it should, so maybe if the waiver is approved it could be a good start.

If the waiver is applied for COVID-19 products, this could also happen post-pandemic for all diseases that affect many people worldwide. In Brazil, several health, Bioethics institutions have backed the WTO proposal: a statement was issued in February 2021 by the Brazilian Society of Bioethics, the Brazilian Association of Collective Health, the Brazilian Center of Health Studies and United Network supporting the not patenting of products developed to confront COVID-19 [11]. In addition to the document issued in February, 2021 [4], as Prof. Dhai mentioned another document on the need for international solidarity in relation to access to vaccines for all is to be approved by UNESCO [12]. There is a lot of discussion on this issue. A new draft is being discussed as a joint statement by UNESCO's ethics committees (IBC and COMEST) with the objective of ensuring equal access of vaccines for all and agreeing with the proposal to suspend patents of vaccines and related products developed to confront COVID-19. It is not still consensual among the committees' members (approved after this webinar). I hope it will become consensual, because with so many people, so many individuals, so many governments, backing that up, UNESCO should be in the same boat in this situation.

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11) Position of the Brazilian Society of Bioethics (SBB), the Brazilian Association of Collective Health (ABRASCO), the Brazilian Center for Health Studies (CEBES) and the United Network (Rede Unida) for the not patenting of products developed to confront COVID-19. February 27th, 2021.
http://www.sbbioetica.org.br/uploads/repositorio/2021_03_24/SBBEEntidades-on-Patents-10Mar21-english1.pdf

12) Joint Statement of UNESCO Ethics Commission ensuring equal access for all to vaccines and therapeutic development to confront COVIS-19; Joint statement of the UNESCO International Bioethics Committee (IBC) and UNESCO World Commission for the Ethics of Science and Technology (COMEST). SHS/IBC-COMEST/COVID-19 Vaccines IP Paris, 21 September 2021.
https://unesdoc.unesco.org/ark:/48223/pf0000379042
(Approved after this webinar.)

13. Conclusion

I always liked this 1964 quote from Norberto Bobbio, an Italian philosopher. He said that "***the greatest problems of our time in relation to the human rights, is not any more to set its foundations but to protect them***". What is it saying is that we have everything in our hands to do what we need to do. When we say we, I am being a bit too immodest, because there are many hurdles, but the tools are there. We must make pressures so that the available tools can be used throughout the world, especially in situations that we are seeing in many diseases.

The first conclusion is that is true that we need better preventative methods, more efficacious and less expensive drugs and many more efficacious vaccines. Clinical trials with these objectives can be performed where vulnerability is lower. We are arguing that if it proves effective, it has to be distributed throughout the world. All stakeholders should participate in all the stages of the study, from the developing to the application, and it's crucial to develop universally acceptable ethical principles. If ethical standards are lowered, it will certainly be difficult to eventually raise them. This is the kind of criticism to what happens with some of the documents that I mentioned before - some of them were very strict and protective, and now they are laxer, maybe wrongly adapting according to the new times and the prevailing neoliberalism.

Decisions about post-trial access should be based on the principles of justice. Volunteers must have access to drugs, vaccines, prevention strategies, and any other study benefits. In my opinion, the discussion on access to care and treatment in research may be considered dated. The endless debates about the rights of participants to post-trial access must be substituted with a broader and more difficult objective of providing access to all efficacious products of research in public health. It is not my phrase, the next one, but I want to emphasize that the *status quo* of inequality must not be an immutable fact and that we must fight for universal access to health, which must be truly recognized as a human right and not as an economic commodity.

Just to remind you all, what I said in the beginning, I am repeating in the end, is that COVID is not just one but more epidemics we have to face. If you look at diseases listed here, at least 20 of them are included among what is called Neglected Tropical Diseases (https://www.who.int/teams/control-of-neglected-tropical-diseases/overview). I agree with many that they should be called diseases that disproportionally affect neglected populations. It is more appropriate to consider like that, because many of these diseases we have in Brazil, but I am not affected by them, because I am not part of the neglected population. Three other diseases are not included in this list, AIDS, Tuberculosis, and Syphilis, because there are specific programs to tackle them. In 2013, the World Health Assembly adopted a Resolution calling for a world decision to prevent, control, eliminate and eradicate these diseases. In 2015, they released a new document with a kind of roadmap for this end. As mentioned before there are many documents, and there are tools to be used to eliminate, to prevent or to control most of these diseases. I add that there is money to do it, but unfortunately there is the need to have political will, plus our participation as concerned citizens, together with civil society to demand actions to make it clear that these diseases must be controlled.

I am going to conclude with two quotes and a tribute. I hope it applies to us here: Thucydides writing on the Peloponesian War mentioned that "***Justice will prevail when those who are not subjected to injustice are as indignant as those who are***." I may be considered as part of this indignant group, because I'm not directly

subject to injustice: I am a physician, I am white, I can work and I have a salary, but of course I am an exception compared to most people in the world. On the other hand, I dare to say that "***justice will prevail when those affected by injustice are able or emancipate themselves to fight for their rights***". Of course, we should take part in fighting for that. In Portuguese, many people use "empowerment" for Thucydides quote. I prefer to use emancipation instead of empowering people. This is a sense frequently used by the late Brazilian educator Paulo Freire. People can be empowered, but I understand that we cannot empower people as people can emancipate themselves.

One more quote is from Cuban Jose Marti when he says that "***my country is humanity***". Maybe that's a way that we now together in this international discussion may also consider. If everyone is not saved, no one will be saved. And my tribute is to London 2012 Summer Olympics in their opening ceremony. They honored the United Kingdom National Health System, and the people that were part of this opening ceremony were NHS (National Health System) nurses. That's a very interesting and direct way of saying that it is essential to have a national health system. And very recently, during the COVID-19 pandemic, an airplane from a company from United Kingdom had this phrase on its fuselage, "Thank you very much National Health System." I finish now saying again, thank you to all of you.

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COVID-19 and bioethics Part 3:
Pandemic and research ethics－Democracy, placebo and post-trial access【Day 2, June 11, 2021】

Learnings for ethics from Covid-19

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1. Learnings from Covid-19 and our past approaches to ethics in research

Since the beginnings of bioethics as a discipline in the 1950's, perhaps nothing has challenged the international ethics community more than the present Covid-19 pandemic. Where did our rights-based ethics find itself within the science, politics, and economics of biomedical research during this global public health crisis? As a community of ethicists were we sufficiently prepared to address the urgency of medical research and public health measures during a time when we were perhaps most needed? Did we resolutely and in solidarity with one another critically evaluate our own role in health-related research and the structures of ethics in our international organizations, national frameworks, and institutional practices? Were we as ethicists and members of this international teachers' and researchers' community in ethics sufficiently self-critical? To these questions, unfortunately, we must respond emphatically, No.

Ethics has enjoyed a long presence in the debates on what is morally acceptable in biomedical research based largely on widely influential international guidances going back to the *Nuremburg Code* (1947)[1)], the *Declaration of Helsinki* (1964-2013)[2)], the CIOMS *International Ethical Guidelines for Health-related Research Involving Humans* (1982-2016)[3)], the UNAIDS *Ethical Considerations in HIV Preventive Vaccine Research* (2000)[4)], the WHO *Operational Guidelines for Ethics Committees Reviewing Biomedical Research* (2000)[5)], and the WHO *Handbook on Good Clinical Practice* (2005)[6)]. We have, however, failed during this

1) Nuremburg_code.pdf. (n.d.). Retrieved 8 February 2021.
https://www.fhi360.org/sites/all/libraries/webpages/fhi-retc2/Resources/nuremburg_code.pdf.
2) World Medical Association. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 2013. (n.d.-a). Retrieved 8 February 2021.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
3) Council for International Organizations of Medical Sciences. International ethical guidelines for health-related research involving humans. 2016.
https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf
4) UNAIDS. Ethical Considerations in HIV Preventive Vaccine Research: A UNAIDS Guidance Document. 2000.
https://data.unaids.org/publications/irc-pub01/jc072-ethicalcons_en.pdf
5) World Health Organization. Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participant. 2011.
https://apps.who.int/iris/bitstream/handle/10665/44783/9789241502948_eng.pdf?sequence=1&isAllowed=y
6) World Health Organization. Effective Media Communication during Public Health Emergencies: WHO handbook and field guide. 2005.
https://www.who.int/csr/resources/publications/WHO_CDS_2005_31/en/

most critical time for individuals, communities, and public health generally to provide a critical reflection on the way medicines are being developed and public health measures are taken.

2. The Covid-19 challenge

Already in September 2020, the Secretary General of the United Nations, António Guterres warned us:

> The pandemic is a clear test of international cooperation — a test we have essentially failed . . . . [due to] a lack of global preparedness, cooperation, unity and solidarity [7].

Early in the pandemic the international community promised to share its learnings, to share the evidence of the findings of its research, to share the data, and to share the fruits of the research that was driven by public funding. Now in June 2021, as already in September 2020, the international community, as well as those responsible inside nations, failed to measure up to the needs for solidarity in a global health crisis. Rather, as Secretary General Guterres pointed out, and tried to warn us, we have been utterly failing in our preparedness, cooperation, and sharing of scientific and economic resources during this pandemic. No amount of tinkering with international guidelines can make up for this failure. Ethics needs to recognize (not undermine) the central place of human dignity in biomedical research while providing a critical response to human experimentation and public health measures that undercut the fundamental values sought for informed consent, ethics review, and respect for persons.

Covid-19 has been identified in nearly all countries. There are currently 173 million reported cases and 3.73 million deaths worldwide (as of June 2021). We have seen an enormous impact from this virus on health: physical health, emotional health, psychological health, and (outwardly) economic health. The response from ethics to Covid-19 research and public health measures has been lacking. We have excluded people, we have excluded voices, and we have downplayed the work that was critical. We have entered into our own silos, and we have gone back to what is comfortable with regards to ethics and with regard to the discussions that we have had in ethics rather than to move forward and look at the situation as it is today, not the situation when with UNAIDS began this discussion in 1997 or when the World Medial Association picked it up in1999 and 2000 or it was later followed by CIOMS. This cannot be strictly an historical discussion on who said what when and where. We can say looking back over the course of this discussion on placebo-controlled trials and post-trial access to the “best-proven” intervention that we have failed to place ethics, and to prepare ethics, for playing a significant role in health-related research. The failure has been extraordinary.

3. Placebos and post-trial access to medicines during Covid-19

During this pandemic, a number of ethicists have again confronted the discussion on the role of placebos in clinical trials on medicines addressing Covid-19 [8] as well as the question of post-trial access to medicines by individuals and populations [9]. As in the past, standard of care and the rights of trial participants and their

7) United Nations. Secretary-General Highlights ‘Essential’ Failure of International Cooperation, in Address to Security Council Meeting on Post-Coronavirus Global Governance. 24 Sep 2020.
https://www.un.org/press/en/2020/sc14312.doc.htm

communities absorb the focus of this discussion. Fair questions. However, the inability of the ethics community to come to terms with what is at stake in placebo-controlled clinical trials and post-trial access to medicines, including in regions where they have had less familiarity, may lie in a certain intransience in posing the question:

> The dominant bioethical position . . . . ensured that inequalities of power and resources were perpetuated, not remedied, by the AZT debates [10].

Since the early 1980's azidothymidine (AZT) had been studied in clinical trials using placebos in patients infected with the human immunodeficiency virus (HIV) and experiencing the resulting acquired immunodeficiency syndrome (AIDS). While the AZT trials raised safety concerns, the drug was shown to have significant efficacy [11]. The United States Food and Drug Administration (FDA) approved AZT for AIDS Related Complex (ARC) in March 1987 [12].

In response to concerns raised by ethicists and scientists regarding the use of AZT in these placebo-controlled studies, the US NIH issued the following statement:

> It is an unfortunate fact that the current standard of perinatal care for the HIV-infected pregnant women in the sites of the studies does not include any HIV prophylactic intervention at all. Nor does the standard of care for these HIV-infected women include the combination therapies recommended and used for some HIV-infected women in the U.S. However, the inclusion of this regrettable, but real, performance-site standard in the form of placebo controls provides the direct comparison of standard and new intervention that is needed to form the basis for rational policy decisions and will result in the most rapid, accurate, and reliable answer to the question of the value of the intervention being studied compared to the local standard of care [13].

In 1997, Marcie Angell (then Editor of the *New England Journal of Medicine*), published a highly cited editorial [14] questioning "the placebo-controlled trial orthodoxy" and the apparent "slavish adherence to the

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8) Ortiz-Millán G. Placebo-controlled trials of Covid-19 vaccines - Are they still ethical? *Indian J Med Ethics*. 2021 Apr-Jun; VI(2): 1-8. doi: 10.20529/IJME.2021.015. PMID: 33908358.

9) Moodley, Keymanthri, and Theresa Rossouw. South African COVID-19 vaccine trials hold key lessons for future partnerships. The Conversation. 9 Feb 2021.
https://theconversation.com/south-african-covid-19-vaccine-trials-hold-key-lessons-for-future-partnerships-154676

10) Wendland, Claire L. "Research, Therapy, and Bioethical Hegemony: The Controversy over Perinatal AZT Trials in Africa." African Studies Review, vol. 51, no. 3, Cambridge University Press, 2008, pp. 1-23.
http://www.jstor.org/stable/27667377.

11) Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, Leedom JM, Groopman JE, Mildvan D, Schooley RT, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med*. 1987 Jul 23; 317(4): 185-91. doi: 10.1056/NEJM198707233170401. PMID: 3299089.

12) Brook I. Approval of Zidovudine (AZT) for Acquired Immunodeficiency Syndrome: A Challenge to the Medical and Pharmaceutical Communities. *JAMA*. 1987; 258(11): 1517. doi:10.1001/jama.1987.03400110099035.

13) The Conduct of Clinical Trials of Maternal-Infant Transmission of HIV Supported by the United States Department of Health in Developing Countries: A Summary of the Needs of Developing Countries, the Scientific Applications, and the Ethical Considerations Assessed by the National Institutes of Health and the Centers for Disease Control and Prevention 1994-1997. July 1997.
http://www.columbia.edu/cu/musher/AIDS_case/nimh_cdc_review.htm

14) Angell M. The ethics of clinical research in the Third World. *N Engl J Med*. 1997 Sep 18; 337(12): 847-9. doi: 10.1056/NEJM199709183371209. PMID: 9295243.

tenets of clinical trials" in the context of AZT trials carried out in Côte d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic. She considered that up to 16 studies funded by the US Centers for Disease Control (CDC) and National Institutes of Health (NIH) as well as by UNAIDS, 15 of which involved the use of placebos against AZT. Nevertheless, her editorial board supported the publication of such trials in "the *Journal*" (prophylaxis vs placebo study against tuberculosis in the same issue of the *NEJM*) after having cited the Declaration of Helsinki, which clarifies the requirements that "the goals of the research are always secondary to the well-being of the participants."

Now in the midst of a crisis of public health, science, and ethics during this Covid-19 pandemic, in stark contrast to the Declaration of Helsinki, bioethicists from the National Institutes of Health in the United States argued that the obligations researchers have

> . . . to their participants are distinct from the obligations that clinicians have to their patients . . . . The differences between the ethics of clinical research and clinical care are reflected in the consensus that it can be ethically appropriate to invite research participants to accept some risks to collect socially valuable data [15].

These government ethicists, however, provide no references to their assertion of a "consensus" that individuals should take risks for "socially valuable data." They argue that – based on urgency, informed consent, and ethics review – placebo-controlled studies for the Pfizer and Moderna Covid-19 vaccines, even after they have been shown to be 95% and 94.5% effective:

> [Others] argue . . . that researchers conducting clinical trials are obligated to treat participants consistent with their clinical interests and conclude that it is unethical to give participants a placebo once a safe and efficacious vaccine has been identified. We disagree. This view fails to recognize that the obligations researchers have to their participants are distinct from the obligations that clinicians have to their patients.

When researchers, who are also clinicians, fail to consider the obligations we have toward their patients' health as patients (even when they are also research participants) in favor of some perceived urgency, contribution to their perceived needs of science, the public good, or "data," then we have returned to the kind of government research of the 1950's and 1960's where ethics was essentially consider "for others, not for us" [16].

A near same position was then taken by the WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation [17], who also argued that placebo-controlled trials were justified:

> [We] believe it is ethically appropriate to continue blinded follow-up of placebo recipients in existing trials and to randomly assign new participants to vaccine or placebo. Moreover, under these conditions, we believe that trial sponsors are not ethically obligated to unblind treatment assign-

15) Wendler D, Ochoa J, Millum J, Grady C, Taylor HA. COVID-19 vaccine trial ethics once we have efficacious vaccines. *Science*. 2020 Dec 11;370(6522):1277-1279. doi: 10.1126/science.abf5084. Epub 2020 Dec 3. PMID: 33273060.

16) Baker R. The human radiation experiments: final report of the President's Advisory Committee on Human Radiation Experiments. *Med Hist*. 1997;41(2):256-257.
https://www.osti.gov/opennet/servlets/purl/129478/129478.pdf

17) WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation, Krause PR, Fleming TR, Longini IM, Peto R, Beral V, Bhargava B, Cravioto A, Cramer JP, Ellenberg SS, Figueroa JP, Halloran E, Henao-Restrepo AM, Ryan MJ, Levine MM, Nason M, Nohynek HM, Plotkin S, Rees H, Singh JA, Swaminathan S. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. *N Engl J Med*. 2021 Jan 14;384(2):e2. doi: 10.1056/NEJMp2033538. Epub 2020 Dec 2. PMID: 33264543.

> ments for participants who desire to obtain a different investigational vaccine. People who enroll in clinical trials for altruistic reasons would probably understand the value of gathering data . . . .

Again, the same argument as that from the NIH appears in the WHO: the idea that the research participant's own health should somehow default to exigencies of science. We return now with the WHO to the place where the NIH was in July 1997:

> Countries with limited or no access to a known effective vaccine could thus ethically permit placebo-controlled trials of vaccines of potential relevance to them even if effective vaccines were already being marketed elsewhere.

In a world where we have been repeatedly been told that there are Covid-19 vaccines that are highly safe and highly effective, where we have been promised solidarity and equity, our leading public health institutions are using ethics to argue for the hegemony of political and financial interests in research on human subjects.

4. Vaccine nationalism and vaccine diplomacy

One of the failures here is in the very title of the United Nations. We speak about "vaccine nationalism," but what we have failed to discuss during this webinar is "vaccine diplomacy."[18] We now see the international community, often with the support of international ethics bodies, using those terms differently for different countries. One is as derogatory as the other depending on the context in which one or the other is used, but both are present around the world, in high-income countries, in middle-income countries, and in low-income countries. The solution to this nationalism that has so inhibited our ability to move beyond our own specific interests, including in ethics, is not more nationalism. That is not the solution. Neither is the solution more "internationalism," a solution that inherently is nationalistic in its approach. Ethics should look to provide a corridor for critical reflection that amounts to more than scientific, political, and economic considerations in health-related research and public health measures during this Covid-19 pandemic. Why did it not do so?

What have we seen at the patient level? Let us consider people, individuals and communities. Let us consider their interests, their needs, and their ambitions. This is the place where ethics should be. We have seen a reluctance for patients to come to hospitals for scheduled clinical trial visits[19]. We have seen a reluctance for patients not just to come to hospitals for clinic trial visits but also for care: for cancer treatment and care, for cardiac treatment, for rare diseases, and a whole host of normal healthcare care[20]. We have seen a sig-

18) Gruszcanysk, L., & WU, C. (2021). Between the High Ideals and Reality: Managing COVID-19 Vaccine Nationalism. European Journal of Risk Regulation, 12(3), 711-719. doi:10.1017/err.2021.9. See also: Iftekhar EN, Priesemann V, Balling R, Bauer S, Beutels P, Calero Valdez A, Cuschieri S, Czypionka T, Dumpis U, Glaab E, Grill E, Hanson C, Hotulainen P, Klimek P, Kretzschmar M, Krüger T, Krutzinna J, Low N, Machado H, Martins C, McKee M, Mohr SB, Nassehi A, Perc M, Petelos E, Pickersgill M, Prainsack B, Rocklöv J, Schernhammer E, Staines A, Szczurek E, Tsiodras S, Van Gucht S, Willeit P. A look into the future of the COVID-19 pandemic in Europe: an expert consultation. *Lancet Reg Health Eur*. 2021 Sep; 8: 100185. doi: 10.1016/j.lanepe.2021.100185. Epub 2021 Jul 30. PMID: 34345876; PMCID: PMC8321710.

19) Sathian B, Asim M, Banerjee I, et al. Impact of COVID-19 on clinical trials and clinical research: A systematic review. *Nepal J Epidemiol*. 2020; 10(3): 878-887. Published 2020 Sep 30. doi: 10.3126/nje.v10i3.31622.

20) Rosenbaum L. The Untold Toll - The Pandemic's Effects on Patients without Covid-19. *N Engl J Med*. 2020 Jun 11; 382(24): 2368-2371. doi: 10.1056/NEJMms2009984. Epub 2020 Apr 17. PMID: 32302076.

nificant delay in patients presenting for diagnosis and treatment across the board, including Covid-19, but in many other diseases. And we saw a dramatic shift in the pharmaceutical industry and in the public health community towards its response to Covid-19 and away from non-Covid-19 clinical research [21]. Our entire healthcare systems became Covid-19 focused, completely dominating all other healthcare provision, including our mental health provisions.

5. Poor selection of trial cohorts

One of the things that we have seen with regard to Covid-19 is a poor selection of trial cohorts. *Lancet Global Health* reported in May 2021 that the global collective clinical trial response to Covid-19 has occurred with inadequate collaboration between researchers [22]. Inconclusive research findings from many clinical trials have re-emphasized the importance of high-quality clinical trial research [23]. Our science has slipped. It has not become better because of Covid-19. It's become more politicized [24], more nationalized, less cooperative - less cooperative in the field of science, less cooperative in the field of data, and less cooperative in the field of ethics.

The medical research response to Covid-19 has been inefficient and wasteful. The pharmaceutical industry is at fault, but not only this industry, these researchers. The report indicates that we have seen this across the medical world, across researchers and not only in first-world countries. We have seen an overwhelmingly large number of clinical trials having been registered and done with questionable methodological quality. The Covid-19 pandemic has highlighted the need for more coordination and collaboration, but how we are to achieve this coordination and collaboration, that we still do not know.

6. Lack of preparedness

Fundamentally, what this pandemic shows us is that there has been a lack of preparedness, a lack that we cannot limit to only this pandemic or potential future public health emergencies. Fundamentally, we have failed to recognize that this radical disruption in our societies was caused not only by a virus, but even more so by our responses to it. This calls for basic changes in how we carry out research and in how we perform

21) Iftekhar EN, Priesemann V, Balling R, Bauer S, Beutels P, Calero Valdez A, Cuschieri S, Czypionka T, Dumpis U, Glaab E, Grill E, Hanson C, Hotulainen P, Klimek P, Kretzschmar M, Krüger T, Krutzinna J, Low N, Machado H, Martins C, McKee M, Mohr SB, Nassehi A, Perc M, Petelos E, Pickersgill M, Prainsack B, Rocklöv J, Schernhammer E, Staines A, Szczurek E, Tsiodras S, Van Gucht S, Willeit P. A look into the future of the COVID-19 pandemic in Europe: an expert consultation. *Lancet Reg Health Eur*. 2021 Sep;8:100185. doi: 10.1016/j.lanepe.2021.100185. Epub 2021 Jul 30. PMID: 34345876; PMCID: PMC8321710.

22) Park JJH, Mogg R, Smith GE, Nakimuli-Mpungu E, Jehan F, Rayner CR, Condo J, Decloedt EH, Nachega JB, Reis G, Mills EJ. How COVID-19 has fundamentally changed clinical research in global health. *Lancet Glob Health*. 2021 May; 9(5): e711-e720. doi: 10.1016/S2214-109X(20)30542-8. PMID: 33865476; PMCID: PMC8049590.

23) Rodgers, F., Pepperrell, T., Keestra, S. et al. Missing clinical trial data: the evidence gap in primary data for potential COVID-19 drugs. *Trials*. 2021; 22(59). https://doi.org/10.1186/s13063-021-05024-y.

24) Crabu S, Giardullo P, Sciandra A, Neresini F (2021) Politics overwhelms science in the Covid-19 pandemic: Evidence from the whole coverage of the Italian quality newspapers. *PLoS ONE*. 16(5): e0252034. https://doi.org/10.1371/journal.pone.0252034.

public health interventions. We need to implement research and public health measures based on true evidence carried out in scientific frameworks that allow us to evaluate those interventions.

Here in Belgium, we see every night on television and nearly every hour on the radio how imperative vaccines are. We are told about which percentage of our population has been vaccinated. We are told about how scary it is to go out on the street without a mask. What we do not hear on our news is that our emergency rooms at night are full: they are not, however, filled with Covid-19 patients; they are filled with acute mental illness patients. We do not see on the news that in Belgium there is no room in a hospital for patients with mental illness, that critical operations are delayed, or that there is no room in care homes for patients with mental illness. We never had this situation before.

7. Ethics found marginalized in the Covid-19 response

Did ethics play a role in the Covid-19 response? Ethics appears to have played no role at all. Ethics was and has been for all practical purposes marginalized. “Ethicists” lent their support to insufficiently prepared research and public health measures not based on evidence. They lent their voices to decisions largely taken on political, economic, and investment bases.

Probably the role of investment has played the largest role in this public health response to the Covid-19 pandemic. It is not just about high-income countries and low-income countries. We have poor people in Belgium. We have people in Belgium who have no access to any kind of healthcare. We have poor people around the world. Through our response to Covid-19, we are increasing the amount of poor people in the world, and we are increasing wealth of the wealthiest. “Philanthropists” who have carried great influence in our international organizations, our national responses, and media reports in directing the Covid-19 response have at the same time increased their grotesque fortunes. Governments too have acted largely in the interests of the powerful, including those holding influential positions in agencies and academia. It is not just the pharmaceutical industry that should give ethics pause for reflection during this pandemic.

> Pandemics, like natural disasters and austerity, reveal that we are not all in it together. There is instead an uneven capacity to act and react for some while opportunities abound for profiteering by others [25].

Further, we need to appreciate that preparedness in ethics is not just for this pandemic and potential future public health emergencies, but it is fundamentally about recognizing that the radical disruption caused by a virus (or another unexpected health emergency) and our response to it brings with it a requirement for basic changes to how ethics and the community of ethicists comport themselves to society, governments, and powerful international public health and economic organizations.

8. Why ethics failed?

Ethics failed because of the structures of power in our communities, in our societies; ethics failed because

25) Klaus Dodds, Vanesa Castan Broto, Klaus Detterbeck, Martin Jones, Virginie Mamadouh, Maano Ramutsindela, Monica Varsanyi, David Wachsmuth & Chih Yuan Woon (2020) The COVID-19 pandemic: territorial, political and governance dimensions of the crisis, Territory, Politics, Governance, 8: 3, 289-298, DOI: 10.1080/21622671.2020.1771022.

it sought a place of power in politics, science, and public health rather than critiquing the cost of using a pandemic to pursue power and wealth. Ethics also failed because of the scientific and public health communities, a dramatic failure of science and public health during this pandemic. Ethics failed principally because of the ethicists themselves: because ethicists failed to have the courage to critique public health decision making and move beyond the comfort of a staid discourse on guidelines and equity. There has been no place for ethics in the public-health decision-making and there still is no place for ethics in public-health decision-making. It is not that ethics suddenly took a backseat.

> Without global solidarity, this virus cannot be defeated. It spreads when we don't cooperate and when we look inwards instead of outwards and trying to help each other.
>
> Tedros Adhanom Ghebreyesus, Director-General, World Health Organization (February 2021)[26)]

The WHO Director-General is correct: science and public health fail when they fail to follow their own evidence, their own maxims. Ethics too needs to heed this warning. Ethicists themselves have not stepped back and asked with true reflection: What is ethics about? Why is ethics important to the discussion? What role should ethics play? Ethics failed because it wanted so hard to measure up to the science, a science that lent its support to decisions largely taken on political, economic, and investment bases. Ethics failed to measure the science against its own principles and maxims. This failure bears with it monstrous impacts for individuals, communities, and our global society.

Acknowledgement: Learning in the margins

(November recognitions just prior to publication. Lest we forget the pathways that brought us to this interim in time.)

I wish to express my appreciation to those who most helped me examine and appreciate the role of ethics these past 18 months as the world comes to terms with a health and science crisis. As the COVID-19 pandemic unfolded in early 2020, a global group of ethicists, public health professionals, scientists, and socially engaged persons came together under the heading 'Preparedness Planning for Clinical Research During Public Health Emergencies (PREP)' to share their knowledge, experiences, and questions in order to learn, perform better in their institutions, and write and teach with greater understanding and sensitivity. It was the largest and most inclusive grassroots gathering during this period. Facilitated by the Good Clinical Practice Alliance – Europe (GCPA), the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), and the MRCT Center of Brigham and Women's Hospital and Harvard University, the group met weekly for a year on an open virtual platform that welcomed participants from every continent having more than 50 countries represented. We had the opportunity to receive reports from, and discuss with, experts from the WHO, WHO-AFRO, PAHO, CIOMS, UNESCO, the US OHRP, the EU EMA, the UK MHRA, FPM-RCP, Nuffield Council on Bioethics, INSERM, DNDi, Drug Regulatory Authority of Pakistan (DRAP), Ghana Food and Drugs Authority, AVEREF, Research Data Alliance (RDA), FERCAP, FERCI, GO FAIR, the Cochrane Group, Epidemic Ethics, COVID-19 Clinical Research Coalition, The Pan-African Clinical Trials Database, Union of the Help and Support for Patients (Russian Federation), Center for iPS Cell Research and Application Kyoto University, Japan, and others. In the context of the emerging and often confusing global health security crisis, we examined clinical trials on vaccines and therapeutics, pediatrics research

26) WHO chief calls for global cooperation, solidarity to tackle COVID-19 pandemic. Xinhua. 2 Feb 2021. http://www.xinhuanet.com/english/2021-02/20/c_139753261.htm

and care, databases and data sharing, observational research, research on recent epidemics, oral health research, research in the social sciences and anthropology, and current developments in ethics review, informed consent, vaccine passports, and the political, economic, social, and ethics structures that were so determinative for global, regional, national, and local heath in times of a crisis. The group delved into the effects of COVID-19 on diseases of poverty, rare diseases, cancer, and general access to healthcare. The ethics review systems on every continent were discussed, with specific attention given to assisting countries in reviewing, evaluating, and adjusting their ethics review structures and procedures. Several research projects were carried out by the group, including into the attitudes of healthcare workers, a global survey of ethics review practices and interests, and the drafting of global guidance to support ethics committees during this challenging time. The role of the Declaration of Helsinki, the CIOMS guidelines, regulatory decisions, and the International Health Regulations were weighed in the framework of decisions being taken by governments and international organizations as we considered national and local impacts. This was an exercise of ethics in the margins: respectful listening to voices from diverse backgrounds and perspectives, and the building of friendships across divides. The learnings provided in the remarks above are deeply indebted to those voices who animated that open and transformative discussion. Global Friends of PREP continues to meet monthly facilitated by the GE2P2 Global Foundation. All are welcome to attend. Contact: David R. Curry (david.r.curry@ge2p2global.org).

A special thank you is due here to the organizers and editorial teams, who did an extraordinary job in conceiving this discussion, bringing the experts together, and editing and translating the proceedings for these reflections on ‘COVID-19 and bioethics: Pandemic and research ethics－Democracy, placebo and post-trial access’.

(Published November 15, 2021)

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Discussion (Day 2 No. 2)

Chieko Kurihara

Specially-appointed Professor, Kanagawa Dental University, Japan

Thank you very much Prof. Dirceu Greco for your powerful presentation. We learnt so much from Brazilian experience to battle with the difficult situations. We learned there are many things that bioethics can do. Japanese don't have such kind of experience, but we have to make such efforts. Thank you, Dr. Francis Crawley, for your excellent comment and analysis on how ethics can do in this difficult situation.

Ruth Macklin

Distinguished University Professor Emerita at Albert Einstein College of Medicine in New York City, the United States

Prof. Greco made an excellent overview of these many international documents, bringing in more than I had even remembered. Also, I liked the point about the weakened wording in some of these documents from one iteration to another. Of course, none of the provisions of these various guidelines are binding on anyone, but many countries do state their adherence to the provisions.

My question is, basically: are there too many guidance documents? Which ones should anybody - any government or any individuals - adhere to? People can pick and choose which ones they prefer or agree with more than others.

I note for the audience (if they are not familiar with it) that many years ago, the U.S. FDA (Food and Drug Administration) stated its adherence to the Declaration of Helsinki, but once a revised version of Declaration of Helsinki came out with specific wording on placebos (1996 and 2000 versions), the FDA didn't like that because the FDA loves placebos, and so the FDA pulled out and no longer adhered to the Declaration of Helsinki [1]. With all this picking and choosing, how valuable are these international documents, which say many good things but that very few people pay attention to?

Dirceu Greco

Professor Emeritus, Infectious Diseases and Bioethics, Federal University of Minas Gerais, Brazil

We have been together many times discussing these documents and I quite agree with Prof. Macklin's positions. The plethora of documents is a reason for mentioning Bobbio's saying about the fundamentals of human rights. What can one do? Just choose one or the other? We may say, I do not like the contents of this one, so I am going to get another one.

I am going to take this opportunity to say two things. The last discussion of the UNAIDS/WHO Guidance

1) Food and Drug Administration. Human subject protection; foreign clinical studies not conducted under an investigational new drug application. *Fed Reg*. 2004; 69; June 10, 2004: 32467-75.
http://edocket.access.gpo.gov/2004/04-13063.htm

Document[2] was just before the beginning of this pandemic. It was in Switzerland. Prof. Macklin, Dr. Otmar Kloiber and I were there, and I was very uncomfortable when someone presented in that meeting one guideline from the U.S. National Institutes of Health. We were discussing international UN (United Nations), WHO (World Health Organization) documents and a particular guideline from National Institutes of Health was included. What I mean is that there are so many guidelines and one way out to protect ethics and human rights is to have one specific for the country, including all what is needed for their protection.

But that's very difficult, because in many places, and I am going to go back to the National Institutes of Health again, most of these projects are international. And several are financed by them. They may put whatever they want. It's very hard to go against. We have this opportunity here. We have now here 46 people. I hope that we come together, think about that, and see what we can do as a group in all the venues that we participate naming to have one international document which could be binding. That could be from the United Nations/WHO as they had so many others. Maybe they still are not that much respected, but they could be binding for people to follow them. That's the first thing.

I am going to show you one thing that Prof. Macklin mentioned. In 2006, the FDA decided to take the Declaration of Helsinki out[1], out of foreign studies not conducted under an investigational new drug application (IND) because apparently, they were afraid that a new version was going to be very strict to them – their proposal was opened up for people to make comments. Of course, I made comments, Dr. Lurie made comments[3]. Prof. Ruth Macklin, of course, made comments. They didn't care. They just decided that "*later this year, the US Food and Drug Administration will adopt new standards of human ethical clinical trials conducted without its advance sign-off in foreign countries*." This took out the Declaration of Helsinki and they recommended that just the Good Clinical Practice document be followed. The GCP is not an ethical document.

Dr. Lurie and I published a paper in the *Lancet*[3] where we said that "*the Declaration of Helsinki is the standard bearer for international research ethics. It would be tragic if the US tendency to arrogantly flout international mores claimed the declaration as another victim*". I reckon it was a good paper, but no repercussions. But just a little bit later, there was an editorial in *Nature*[4]. It was very interesting because it was very much against FDA position. But they did not care. They do whatever they want, because again they have the power, they have the money. We have to keep fighting.

Ulf Schmidt

Professor of Modern History, University of Hamburg, Germany

I still think this is the absolute amazing meeting here and the debate we had over the last 2 weeks I can only commend you for having brought all these experts and played this together.

Let me just comment on some of the things which was said in the last two papers. Prof. Macklin is obviously absolutely right about the number of different codes and guidelines which the world has today. In the mid-1990s, Professor Troiler from Basel once looked at the number of codes which existed at the time, and

2) Joint United Nations Programme on HIV/AIDS and World Health Organization; 2021. Ethical considerations in HIV prevention trials. Geneva; 2021. Licence: CC BY-NC-SA 3.0 IGO.
https://www.unaids.org/sites/default/files/media_asset/ethical-considerations-hiv-prevention-trials_en.pdf

3) Lurie P, Greco DB. US exceptionalism comes to research ethics. *Lancet*. 2005 Mar 26-Apr 1; 365(9465): 1117-9.

4) Trials on trial. *Nature*. 2008 May 22;453(7194): 427-8. doi: 10.1038/453427b.

he counted something like 300 medical ethics codes in different fields of expertise. You can probably gather from even that the problems for scientists and experts to navigate that mass of documents and know which one was relevant for them. One of the results of that was obviously that the Declaration of Helsinki has become an increasingly a point of orientation because of that confusion in the field. That's a very important point being raised.

The other point which came through very well and I commend Dr. Francis Crawley for bringing up the issue of ethics and the failure of ethics in the current public health crisis. What is interesting in the current situation is that we have a discrepancy here between bioethics on the one hand which is historically largely and has been shaped by a western perspective, the discipline itself as it evolves from a post-war period, and was established in universities and as a field of professional activity on the one hand and the lack of development of something what one could call public health ethics. That is an area which is underdeveloped conceptually and historically, and what Dr. Crawley was highlighting here is the lack of recognition that ethics need to play a part in public health to a greater extent as how ethicists have ever really conceptualized that and engaged with.

Finally, a very important point he made, in relation to international cooperation which was obviously a very, very great importance after the Second World War and the whole creation of international institution and organizations from the WHO to the WMA and others are testament to that cooperation, we are obviously seeing a major failure in cooperation and collaboration and one may obviously ask whether this is only due to populist politicians and that we could say, the world has just had bad luck. At the moment when the pandemic struck, we were given a bad hand so to speak, as far as the international politicians are concerned, but the reality is slightly more complex than that.

What I want to highlight is perceptions of different communities, how they see themselves. Dr. Crawley highlighted that there was a failure of science. Before joining today's discussion, I was in a workshop with top scientists, top virologist, and the perception is a complete different one. It is literally one of complete success. Scientists think that they have achieved the greatest success in this pandemic by collaborating and developing vaccine so quickly. What I want to highlight is that there seems to be very different ways of perceiving this pandemic in different communities, and this meeting has very much highlighted the issues which are of fundamental importance at various levels of our debate.

Otmar Kloiber

Secretary General, World Medical Association

First, let me thank you for bringing this together as the previous speakers did. It's a very interesting and very important discussion we have here. I would like to quote an American writer, Damien Barr, who has written a poem about the Corona pandemic. Let me give you some of his lines which are so important. He wrote, "I heard that we are in the same boat but it's not that. We are in the same storm, but not in the same boat". Later on, he said, "some are on super yachts and some have just one oar, and I may add, some are sitting on the sundeck and some are about to drown." What this pandemic revealed is just the ongoing inequity which we are seeing in this world It is nothing new. Aren't there some fundamental things that we have to change and that we have to address?

Some are just bashing the pharmaceutical industry, all the richness and profits they have made and praising some of the healthcare systems. But it's not that easy. Yes, there is a failure that is going on for many years

for instance, that our international cooperation is based on agreements that favour money-making but not the people.

We have agreements like TRIPS (Agreement on Trade-Related Aspects of Intellectual Property Rights) and GATT (General Agreement on Tariffs and Trade) which are arranged around economic systems with the idea, that if you allow more profit, more trade, more business, then everything else will follow and there will be more justice and there will be more wealth for everybody. We have learnt that it is not that easy and there is no guaranty that more economic cooperation improves the situation of the people. However, that doesn't mean that we shouldn't cooperate. It doesn't mean that we shouldn't trade, but the question is whether the ideas on which we have based all those cooperations are the right ones. Whether the primacy has to be on we are doing business and then everything will follow or whether we should ask, what people need and how do we do this in a fair, in a just way. But those questions have never been asked. If you look at the very recent past on treaties that have been negotiated again, those treaties are not favouring the poor of this world or even a fair dealing with those. It's still this mentality of us against the rest of the world which is prevailing.

Is there hope to think that politicians alone will do this? Let's be serious. What we have seen during the last 18 months has not been a hallmark of political achievements - in nearly no country of this world. Yes, some have been better prepared but those are now falling back quite obviously because they have missed the opportunity to engage in vaccination and in doing the next steps. In most other countries, politics has failed. The Secretary General of the United Nations Mr Guterres is completely right. It has failed. Is that only to blame politicians? No. We have nice papers at the World Medical Association that described exactly the situation that would come up with a pandemic. We have asked for pandemic preparedness, but what have we done? We have not insisted. We were not standing on the feet of our politicians saying you have to change that.

Prof. Ames Dhai quite rightfully spoke about moral bankruptcy. That is a very strong term and it is correct. But on the other hand, is there a different behaviour in those countries which are in need? Look at the situation in Africa? A lot of governments seem to be more interested in engaging in the next war with their neighbours than providing healthcare to their people.

The underlying problems are those of inequity. Those we have to address. We are not getting a quick fix for this pandemic. That will not be possible, but we will have to focus on what we do next and how to continue. There is a strong role for civil society and for scientists to remind our politicians that we need different treaties, that we need a different system for intellectual properties. Just waving our patents does not make a big difference. We need a new system of how we deal with intellectual property and what we think is the common good and what is not. Thus, there is a role for civil society to engage more, a role for all of us, whether you are a scientist or activist or you are providing humanitarian help. We all must push much harder on our politicians, to remind them that inequity has to be fought. That's not easy.

Let me just tell you coming from a rich country, from a country which on an international scale has done pretty well with the vaccinations. What the people demand and what they charge my health minister for in Germany is not that he is considering providing more vaccines to other countries. They are lamenting that he has not bought enough vaccines for Germany. That is what they are excusing him of as a failure, not the concerns about third countries. He indeed may tell you that he has sworn an oath to protect his country, not to protect other countries. In the thinking of global health and global inequity, we have to advance the

political system a big step forward. We must get better prepared, but the preparedness has to be on all levels, and it has to be with the engagement of all of us, not only of the industry, not only of the politicians. If we don't all engage, it will not change.

Tammam Aloudat

Managing Director, Global Health Center, Graduate Institute of International Development Studies, Geneva, Switzerland

There is obviously a pragmatic point that comes from a civil society organization like MSF which historically working on access to medicines comes from the fact that we have patients that we cannot afford to treat, even as a western relatively rich organization that comes from the HIV pandemic and the exploitative way the early days of anti-retrovirals were. But that obviously is one part of it and we have engaged over the years with many access issues and faced the consequences of the inequities that have been addressed, and there have been directions that debate the necessity for the exploitative intellectual property regime which allows by design and by definition a highly manipulative system to recreate and reinvest and reinvent medicines that are by definition created to be profitable before being anything else, the exploitation of public resource and so on, and then the demand of poorer countries to work against their own populations by making them enforce IP regimes that aren't of their interest. But it also extends to research and development. It extends to the fact that many of the medicines that get patented are developed publicly and so on.

But then if I take my ex-MSF hat aside for a second and I try to follow up on Dr. Crawley and Dr. Kloiber's comments, Dr. Crawley talks about the position of ethics. Again, like much of the academic disciplines, there are first way too many directions to be followed usefully in an applicable way for a practitioner and an advocate to do. I will just give an example of where the starting position of an ethical argument has been fairly disappointing. A few years back, there was an article in the *Lancet* by Persad and Emanuel [5] argued that in the interest of coverage and from an ethical point of view, we should promote the use of second-line, less efficacious more toxic medicines in sub-Saharan Africa.

In that position, the ethical stand was to give worst medicines because they are poor, and we have tried to answer that. The fact that this ignores what makes people poor and how is this becoming a double punishment. For their poverty, they get worse healthcare by design, not by necessity, and that is dressed as an ethical position. It takes me back to that it's the starting point that matters. Dr. Kloiber has talked about equity, and he made the point of the waste and conflicts in Sub-Saharan African and African countries that are wasting money. That is probably technically true, except that reflects a point that ignores the historical context that has put them there and the fact that they don't buy weapons from outer space. They buy them from liberal democracies that continue to do that - this dismembering one inequity issue from the political and from the geopolitical context and allowing this invention of innocence of liberal democracies. In the World Health Assembly 2 years ago, it was liberal democracy, Canada, Norway, Germany, UK, who opposed a resolution in transparency. The same countries opposed the waiver today. There is a consistent acceptance of the imbalance as the norm from which we start our moral positions. That is unchallengeable.

It is troubling that this is where we are now, because if we are going to talk about beyond waiving IP (intel-

5) Persad GC, Emanuel EJ. The ethics of expanding access to cheaper, less effective treatments. *Lancet*. 2016 Aug 27; 388(10047): 932-4. doi: 10.1016/S0140-6736(15)01025-9. Epub 2016 Apr 20. PMID: 27108231.

lectual property) issues at pharma, then at least as someone who has no leg to stand on among ethicists like yourself, I need something that takes me beyond just it's not only the job of politicians and pharmaceutical companies. It's all of our jobs. When something becomes everybody's responsibility, it becomes nobody's responsibility, and that is very difficult to deal with in any practical manner. Until we have that, forgive us if the obvious targets are pharmaceutical companies and politicians who are the direct harm, who are the ones who are linking aid to trade, who are the ones who are putting profit above all, and who are the ones who are doing it with very little shame and cover when things hit the fan.

Greco Yes, I want to second Dr. Aloudat, but I want to stress against something that have been said before. Much of the ethics is not involved in all of these. Maybe the ethics as an institute, but all of us are people that are working ethically trying to make a difference. I can say and I am repeating what I have already said what has happened in Brazil in the last 40 years, when it was decided to face frontally the AIDS epidemic - different from what Dr. Aloudat said, we decided to provide drugs for everyone. We have a problem that many of you have difficulty in accessing what we publish because we speak a language that most do not understand. If we publish in Portuguese, you don't read. Many things that happen in countries like mine are not as publicized as for instance what comes from South Africa, as they publish in English. Repeating again Brazil has been at a time a very good case study example of how to face things with the participation of civil society, as it happened in the confrontation of the AIDS pandemic.

I am going to quote Dr. Kloiber but in a different way. We are here in the same storm, but pharma is in another boat and maybe this is the worse part of the problem. As Dr. Aloudat said, it is very easy, and I do that all the time in Brazil, to blame the government for everything that is happening there. Of course, they are a substantial part of a problem, but we are part of the solution. The problem is that we are in a small boat. We have to join together to make the emancipation that we have been saying all the time to happen. I am going to use the example again when in 1988 Brazil decided to establish one only public health system for everyone. And the Brazilian Unified Health System (SUS) was created. Is it fantastic? Of course, it is not, but it's amazing to think that currently over 200 million people have access to one public health system for everyone. That's a good start. I must use all those examples from developing countries to say that it's possible and I agree with Dr. Aloudat. Our biggest target now this moment is pharma industry. It's not the only one. It's not going to be the solution even if we succeed. Even if we find a way of suspending or much altering the TRIPS agreement for health products, it will not make a big difference now, but it will be a good start. It will certainly be a significant step forward, something that we can do as people together, and this debate is an example. We have people from many places in the world, but even if we don't have tha power to do that at once we together will make a difference. And this movement can sow the necessary seeds.

For instance, when Prof. Kurihara and myself, one in Japan, another in Brazil, decide to do things like that together, it's a small plant that we have to keep growing, keep watering to see what can happen aiming at changing the status quo. I am not naïve on that. It's not going to be easy. It's going to take time, and maybe the COVID pandemic could be another stepping stone, because people all over the world are talking about unacceptable situations that were pre-COVID, all the inequity, the lack of access, the neglected disease, they were there before, and COVID just put it on stage, in the spotlight. We have to use that now to see that the end of this pandemic will not mean just returning to what we had before.

Francis P. Crawley
Good Clinical Practice Alliance – Europe (GCPA)
Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), Leuven, Belgium

I thank the participants for the excellent conversation this webinar has realized. It has been timely and important. The webinar has shown that the first place to look when you look for failure is to look to yourself. We have had the courage to do here.

Rihito Kimura
Professor Emeritus of Bioethics, Waseda University, Japan

Thank you very much indeed for the wonderful symposium for 2 days since last week. We really appreciate all the speakers' very important comments. We are not having open conversations like this in Japan yet. I really enjoyed the event and we seriously considered what is the basic starting point of bioethics after the war. I had an impression that we have to go back to the fundamentals, we have to go back to the roots of the ideas, of the new medical ethics since the time of the Nuremberg Code, 1947 [6].

Last week, I talked about my thesis on the experience in Japan, and I think Dr. Schmidt has read this book. I have written on issues of the Japanese bioethical experience during wartime which has had a very negative impact to all the Japanese medical people, and I recommend one of the very important books in thinking of this bioethical development since after the war is this book, "Against Relativism" written by Prof. Macklin [7]. Bioethicist nowadays must read this very important book based on very good analysis of cultural elements. She mentioned the cultural diversity and the search for ethical universals in medicine. In this time of COVID 19, we need to see through the fundamental issues after the war and we have to review all the development of bioethics regarding time of this COVID-19 to find out new ways to proceed. I have received many interesting pieces of advice and suggestions during this conversation, and I really appreciate all people's participation with very good analysis, insight, and energy.

I really appreciated as a Japanese bioethicist to have this very important contribution from people from all over the world.

Greco It has been a pleasure to be with Prof. Kimura, Prof. Kurihara, Dr. Saio, Prof. Imamura, to meet all the Japanese group and other international colleagues. For me it has been great to participate in the continuation of our debate in 2019 in Tokyo. Even if the Brazilian Society of Bioethics was a part of it, it was a work spearheaded together, with a great input from Japan.

Let's hope that we can keep fighting against inequity, keep fighting for the people, even if we are not in the same small boat as most vulnerable people are. But we have a reason to keep the indignation together so that we can do even more than we have been doing. I thank you all and give the word back to you to say the last farewell. Thank you very much.

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6) The Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, October 1946-April 1949. Vol. 2, p. 181-2.

7) Macklin R. *Against Relativism: Cultural diversity and the search for ethical universals in medicine*. Oxford University Press; 1999.