Opening Remarks of the Day 1 session

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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.

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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

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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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Prof. Kazutaka Shimoda

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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
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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

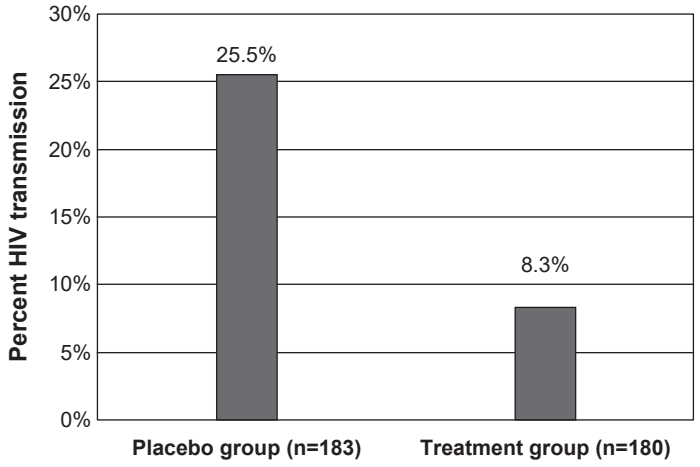
I will start off with a review of other fairly well-known cases. If we start with the perinatal case, we are looking at a placebo-controlled trial that was done with HIV positive pregnant women in the early 1990s using the drug (Fig. 1) [3] zidovudine or AZT with an object of preventing HIV transmission 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].

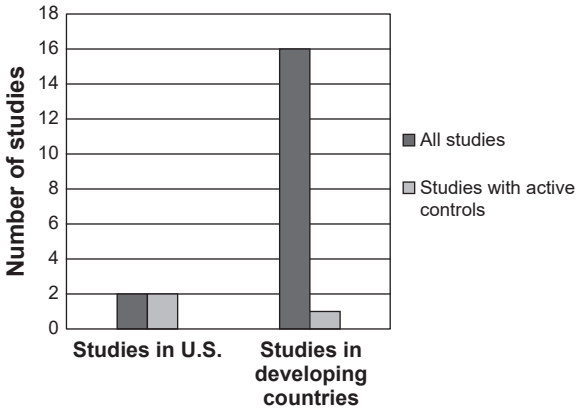
sion and so the use of a placebo was ethical, and this is the result was reported in *New England Journal of Medicine*[3].

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,

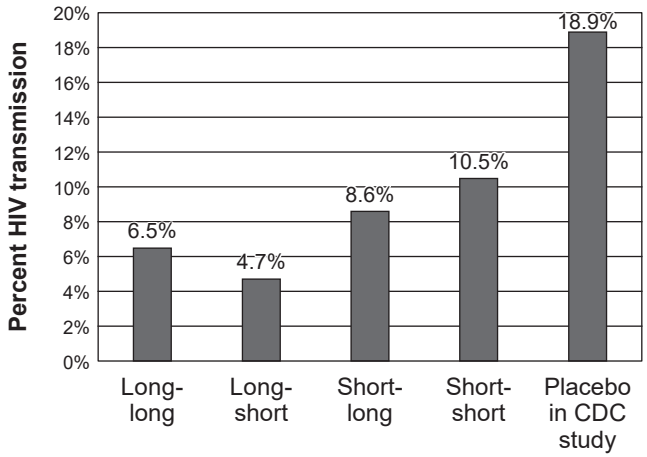
and in those two trials in each case, active controls were being used. No placebo was being used in two out of two. In the developing world, however, there were 16 trials and in 15 out of 16, a placebo or some other intervention not known to be effective was being employed. This is the double standard 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.

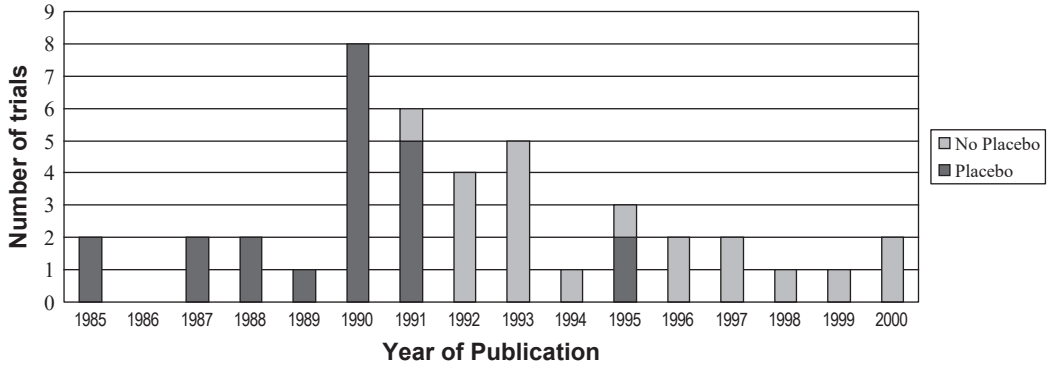
The product was called Surfaxin which is one of a series of surfactants, which are products instilled into the lungs of neonates and which can help the lung inflate if they have a condition called respiratory distress syndrome, which has a very high mortality. At the time of this study, which was in 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.

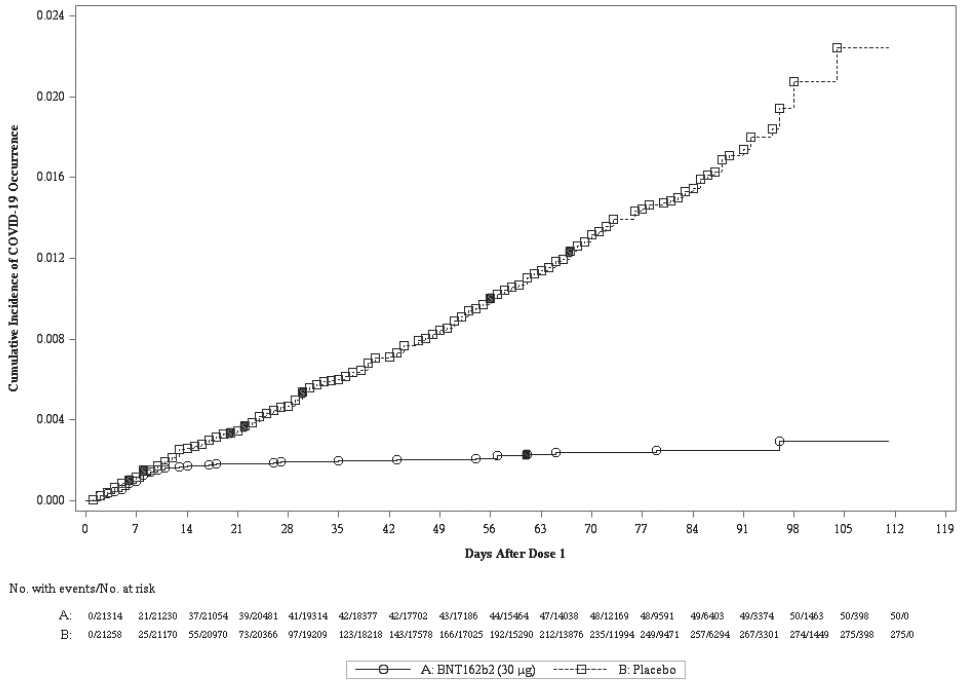
There are 17 vaccines that are now authorized in at least one country. A fair number of them are authorized only in their home country. There are eight of them that have substantial presence in the international market in that they have been authorized in at least 10 countries. There are over 100 countries 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.

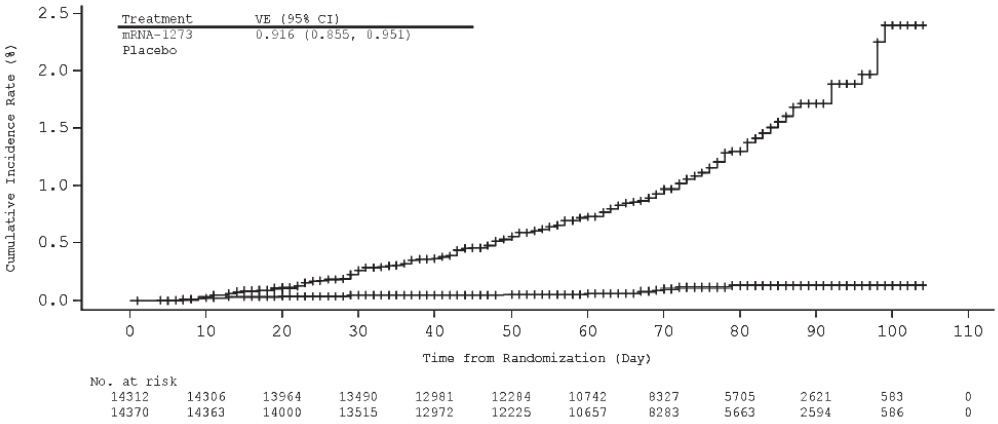
As of June 4, 2021, there was clear evidence of widespread disparities in vaccination rates. The per capita rate of vaccination is highest in North America, Chile, Uruguay, Europe, China, Mongolia, and some countries here in the Middle East, but very few countries with nothing. In places like Brazil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

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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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