Public Policy and Law

CLINICAL ETHICS

How to continue COVID-19 vaccine clinical trials? The ethics of vaccine research in a time of pandemic

Clinical Ethics
2022, Vol. 17(1) 32–40
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/14777509211052467
journals.sagepub.com/home/cet
SAGE

Silvia Ceruti[1], Marco Cosentino[1] and Mario Picozzi[2]

Abstract

Between December 2020 and March 2021, the US Food and Drug Administration and the European Medicines Agency issued Emergency Use Authorizations and Conditional Marketing Authorizations for the distribution of the first COVID-19 vaccines. Although these vaccines were thoroughly assessed before their approval, regulators required companies to continue ongoing placebo-controlled clinical trials in order to gather further reliable scientific information on their safety and efficacy, as well as to start new studies to evaluate additional candidates. The aim of this paper is to present and discuss the ethical issues raised by the tension between the need to continue these types of clinical trials and the obligations related to the protection of the rights and well-being of research participants. Specifically, we question whether—how, and to what extent—fundamental principles governing research involving human beings can be applied to the current pandemic situation. We argue that continuing ongoing placebo-controlled clinical trials can be considered ethically justifiable only if all participants are adequately informed of any developments that may affect their willingness to remain enrolled, including the current situation of resource scarcity and the prioritization criteria established for vaccination. However, we also argue that currently approved vaccines, which are considered safe and effective enough to be administered to millions of people as part of the vaccination campaign, necessarily represent the "best proven intervention" currently available and, therefore, should be used as comparators in future studies instead of placebo.

Keywords

COVID 19, vaccine, clinical equipoise, research ethics, clinical trials

Introduction

In December 2020, the US Food and Drug Administration (FDA) issued Emergency Use Authorizations (EUAs) for the first vaccine candidates for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), developed by Pfizer-BioNTech[1] and Moderna.[2] Between December 2020 and January 2021, also the European Medicines Agency (EMA) recommended granting Conditional Marketing Authorizations (CMAs) for the same candidates,[3,4] as well as for a third candidate, produced by AstraZeneca.[5] Finally, between the end of February and the beginning of March, both regulatory authorities used the same procedures to authorize a fourth vaccine candidate, manufactured by Janssen Biotech Inc., a Janssen Pharmaceutical Company of Johnson & Johnson.[6,7] These vaccines started being distributed and their increasing availability currently represents an important step forward in overcoming the global health emergency which is causing a large number of hospitalizations and deaths.

Although both the FDA and EMA thoroughly assessed the information on the quality and safety of these candidates, and although companies provided evidence on their efficacy in preventing COVID-19 symptoms, they are still considered to be investigational and, in order to obtain full licensing approval, regulators require companies to continue to collect information on their long-term safety and efficacy until December 2022.

Furthermore, in order to meet current medical needs, regulatory authorities, international organizations, and the

[1]Department of Medicine and Surgery, University of Insubria, Italy
[2]Department of Biotechnologies and Life Sciences, University of Insubria, Italy

Corresponding author:
Silvia Ceruti, University of Insubria, Varese, Lombardia, Italy.
Email: cerutisilvia@gmail.com

scientific community in general have often stressed on the need to also start new studies to evaluate additional candidates.

However, continuing ongoing clinical trials and starting others require consideration of the ethical issues arising from the tension between the need of gathering further information (and preserving collected data), which can benefit both the scientific community and the world population, and obligations related to the protection of the rights and well-being of research participants.

An unprecedented scenario?

To answer ethical questions related to vaccine research in this time of pandemic, it may be important to ask whether the pandemic actually represents a situation that is not only extraordinary but unique and, if so, to what extent the exceptional nature of the situation may influence how these issues are—or should be—addressed.

In dealing with the current pandemic, an important role was played by nonstandard tools used to evaluate, approve, and authorize the distribution of the first vaccines; as anticipated, in fact, both the FDA and the EMA granted emergency/conditional authorizations in order to ensure timely distribution and administration of these frontrunner vaccines.

In general, in the event of a public health emergency—as a pandemic certainly is—the US FDA can authorize the use of medical countermeasures (MCMs) "to protect the US from [chemical, biological, radiological, and nuclear (CBRN) threats, and] emerging infectious diseases."[8] MCMs include biologic products, drugs, and devices. MCMs may be *medical products* that have already been approved by the FDA, but in some cases, at the time of a public health emergency, it may be deemed essential to introduce a new MCM that has not yet been approved. In these situations, the FDA can then use the EUA to allow the use of such MCM. In other words, with the EUA, it is possible to authorize the use of a medical product not yet approved during a declared emergency.

Similarly—while not totally overlapping—the EMA's CMA is a tool that allows for the fast and pragmatic approval of a *medicine* that addresses urgent unmet medical needs on the basis of less comprehensive data than normally required.[9] More specifically, regarding the development, evaluation, approval, and monitoring of COVID-19 vaccines, according to the EMA "A conditional marketing authorisation guarantees that the approved vaccine: meets rigorous EU standards for safety, efficacy and quality; is manufactured and controlled in approved, certified facilities in line with high pharmaceutical standards that are compatible with large-scale commercialization."[10]

The EUA and CMA programs were established in 2004 and 2006, respectively. Based on available data, the FDA issued ~200 EUAs between 2005 and 2019[11] while more than 380 EUAs were issued since the start of the pandemic just for medical products used to diagnose, prevent, protect, or treat conditions associated with COVID-19.[12] Similarly, according to the "Report on ten years of experience at the European Medicines Agency," the EMA granted 30 CMAs for medicines between 2006 and 2016,[13] whereas since the start of the pandemic, and only for the prevention and treatment of conditions associated with COVID-19, CMAs were issued for four vaccines (Comirnaty, COVID-19 Vaccine Moderna, COVID-19 Vaccine AstraZeneca, and COVID-19 Vaccine Janssen) and one treatment (Veklury—Remdesivir).[14]

Thus, although this type of authorization had already been granted in the past (even for vaccines: e.g. CMAs have been issued for Arepanrix—Pandemic influenza vaccine (H1N1)[15] and Humenza—Pandemic influenza vaccine (H1N1),[16] both currently withdrawn, and for the Pandemic influenza vaccine H5N1 AstraZeneca (previously Pandemic influenza vaccine H5N1 Medimmune)[17] still licensed in Europe), prior to 2020 these tools had never been used so widely with reference to a single disease and, most importantly, neither the FDA nor the EMA had ever issued an emergency/conditional authorization for a vaccine intended for large-scale distribution.

What seems to be different in the case of the current pandemic is that, compared to the past, it is not just a matter of responding urgently to a health emergency or unmet medical needs, but of dealing with a global health crisis that also has important and unprecedented political, social, and economic implications.

Based on these considerations, it is therefore necessary to ask whether even the ethical issues related to vaccine research should be interpreted differently, or whether traditional principles can be applied to this unprecedented scenario.

Providing information about current vaccines: open issues

Informed decision about remaining in a vaccine clinical trial, as well as in general about being vaccinated, requires full understanding of the so far documented efficacy and safety of available vaccines.

Regarding vaccine efficacy, a series of commentaries recently published in the British Medical Journal,[18,19] extensively discussed the actual scope and limitations of the currently available evidence supporting the efficacy claims of the Pfizer-BioNTech and Moderna vaccines.

First, it should be noted that the primary endpoint of both phase III trials was the occurrence of COVID-19 of any severity, not the ability of vaccines to prevent infections. Indeed, regarding severity, most cases of COVID-19 recorded throughout the trials were mild, and the few

severe do not allow to conclude anything about any specific protection. Moreover, the claims about the 95% efficacy regard the relative risk reduction. For instance, 176 confirmed COVID-19 cases were reported so far in the Pfizer-BioNTech trial, 8 in the vaccine group, and 168 in the placebo group, which gives a 95.5% risk reduction to develop symptomatic COVID-19. Since the number of subjects in each group was however higher than 17.000, the absolute reduction of the risk—that is, the difference in the frequency of COVID-19 between vaccine and control group—is $[(168/17.511) - (8/17.411)] \times 100 = 0.92\% - 0.05\% = 0.9\%$. In lay terms, the reported 95% efficacy of the current vaccines does not mean that 95% of the population would be protected. Rather, it means that the unprotected individuals have a 0.95% probability to develop symptomatic COVID-19, in comparison to the 0.05% probability after vaccine.

Moreover, as no information has been gathered so far in any trial on asymptomatic infections with SARS-CoV-2, no evidence exists regarding the ability of vaccines to prevent the infection. Remarkably, the recently reported interim results of a study brought about in the United Kingdom (UK) and which regularly tested thousands of healthcare workers showed that people who had previously been infected with COVID-19 are likely to be protected against reinfection for several months, but could still carry the virus in their nose and throat and transmit it to others.[20] Accordingly, the England's deputy chief medical officer recently warned that people who received a COVID-19 vaccine could still pass the virus on to others and should continue following lockdown rules.[21]

Additional uncertainties about vaccine efficacy are: (a) no definite information about long term protection, as efficacy refers just to a few weeks after completion of the vaccination protocol, and (b) no evidence about specific subgroups at risk, such as the frail elderly.

Another way to look at the efficacy is to calculate the number needed to treat (NNT) for COVID-19 vaccines, that is, the average number of subjects who need to be vaccinated to prevent one additional COVID-19 case. Using the numbers discussed above for the Pfizer-BioNTech vaccine, the NNT would be 114, that is, 114 subjects should receive the vaccine in order to prevent one case of COVID-19. The NNT can be useful for physicians in particular when it is used in conjunction with the number needed to harm (NNH), which indicates how many persons need to be exposed to a risk factor to cause harm in one person who would not otherwise have been harmed.

Data on safety are still limited to results reported in phase III studies and eventually to initial experience with adverse event monitoring during ongoing national vaccination campaigns. In the Pfizer-BioNTech study, the most serious adverse event reported was Bell's palsy, with four cases in the vaccine group versus 0 cases in the control group.[22] Bell's palsy consists of an acute, unilateral, partial, or complete paralysis of the face, which spontaneously recovers within 1 month, even if up to 30% show delayed or incomplete recovery, with long-term impact on quality of life and self-esteem.[23] The NNH for Bell's palsy is 4.348, that is one case every 4.348 people receiving the vaccine. Accordingly, the summary of product characteristics issued by EMA for the Pfizer-BioNTech vaccine reports the expected frequency of Bell's palsy in the range 1/1.000–1/10.000.[24]

The two most serious adverse events reported in national vaccination campaigns are allergic reactions and death. Allergic reactions can be directly linked to the vaccines due to their usually immediate onset after vaccine injections. Their frequency with COVID-19 vaccines is currently not entirely determined, even if the UK Medicines and Healthcare products Regulatory Agency initially issued a warning for anyone with a previous history of allergic reactions, which was later retracted,[25] and in California a batch of COVID-19 vaccine from Moderna was provisionally suspended due to possible allergic reactions.[26] On 28 January 2021, the EMA released the "COVID-19 Vaccine Safety Update" regarding the Pfizer-BioNTech vaccine, in which the Pharmacovigilance Risk Assessment Committee (PRAC) noted that a recent analysis in the United States estimated the frequency of anaphylaxis to be around 11 cases per million doses of Pfizer-BioNTech vaccine administered. As an estimate of this frequency could not yet be determined in the EU, PRAC asked the marketing authorization holder to continue to review all cases of anaphylaxis for further evaluation by the committee.[27]

Regarding the risk of death, concerns were recently raised in Norway, where up to 29 deaths were observed after administration of the first dose of the vaccine in elderly people with serious underlying health conditions.[28] After thorough investigation, the Norwegian Medicines Agency concluded that the role of even relatively mild side effects of the vaccine cannot be completely ruled out in at least 13 cases occurred in the frailest patients.[29] Since at the tile of the initial report about 42.000 people had been vaccinated in Norway, a hypothetic NNH for death would be a quite dramatic 1.449, taking into account all the 29 reports, or just 3.226, considering only the 13 reports selected after scrutiny. It should be nonetheless considered that 42.000 includes all the population and not just the frail elderly. These subjects are of particular concern, considering also that vaccine efficacy in this subgroup is still largely undefined.

Based on these considerations, it can be argued that, on the one hand, the decision to administer the vaccine to subjects at particularly high risk—such as people with a history of allergic reactions or the elderly with serious underlying health conditions—should be carefully evaluated on a case-by-case basis through a careful risk-benefit assessment; on the other hand, as also expressly requested by the regulatory agencies, both ongoing trials and new

studies will need to provide information regarding active surveillance of vulnerable populations (such as pregnant women and elderly vaccinees).

The ethics of continuing COVID-19 vaccines placebo-controlled clinical trials

Traditionally, it is stated that the ethics of research involving human beings requires *clinical equipoise*, a state of genuine uncertainty within the expert medical community regarding the comparative therapeutic merits of each arm in a trial[30]: Until there is clear evidence regarding which of the compared treatments is the best, random assignment to the test or control is considered ethically justified, whereas once the equipoise is solved participants should no longer be randomized to the treatment known to be inferior to the best proven intervention.

The concept of equipoise is widespread in clinical research, although it has been controversial since its first formulation.[31]

According to the principle of equipoise, if a vaccine candidate is found to be effective continuing ongoing studies without changing treatment and starting new blinded placebo-controlled trials on other candidates should be considered ethically unjust.

Some commentators argue that: "The most general problem with equipoise is that it conflates the ethics of clinical research with the ethics of medical care"[32]: Given that subjects involved in COVID-19 vaccine clinical trials are not patients but healthy volunteers, "the obligation researchers have to their participants are distinct from the obligations that clinicians have to their patients."[33]

These statements do not seem to be totally convincing. Although participants are healthy at the time of enrollment, those enrolled in the placebo arm run the same risk of contracting COVID-19 as all non-participants but, unlike the latter, would not have the opportunity to access a preventive treatment considered by regulators to be sufficiently (safe and) effective to be distributed globally. Allowing access to an effective vaccine is part of preventive medicine, which should be guaranteed to all individuals. Continuing to use placebo as a control instead of one of the already approved vaccines would violate the right of participants to receive what should currently be considered "the best proven intervention," even if only with reference to its ability to prevent the occurrence of COVID-19 symptoms.

In this sense, what seems to be crucial is not the fact that participants are not patients but healthy volunteers, but rather the requirement to provide participants enrolled in the control arm with what is considered "the best proven intervention." Consequently, in the current scenario, the key question appears to be whether, in fact, there is still a state of clinical equipoise between distributed vaccines and placebos that ethically justifies continuing to use the same study design instead of unblind participants in ongoing trials and starting new studies using approved vaccines as controls.

A state of uncertainty clearly existed when the first COVID-19 vaccine clinical trials were planned at the beginning of 2020. However, now that some vaccines have received EUAs and CMAs, it could be argued that the state of clinical equipoise no longer exists.

As stated by some authors, certainly the equipoise is solved with regard the prevention of COVID-19 symptoms in the short term but for what concerns other crucial outcomes (e.g. long-term safety and efficacy, the efficacy in different population, the infectivity of vaccinated subjects) equipoise remains.[34]

According to the WHO Ad Hoc Group on the Next Steps for Covid-19 Vaccine Evaluation: "While it is still feasible and ethical, ongoing studies and others that are about to start should continue to collect high-quality information using directly randomized comparisons against placebo to address as many as data requirements as possible."[35] In this view, to collect further reliable data on still investigational vaccines or new candidates, researchers and sponsors should continue blinded, placebo-controlled trials even when the efficacy of one or more of them appears to be high, and even after they are approved and become available—as indeed they are. On the contrary, modifying the design of the ongoing trials unblinding volunteers and/or start new studies without a direct control against placebo could cause a considerable loss of data and affect the elaboration of the final results.[36]

Although these concerns may be considered well founded given the risk of biases in observational studies,[37] according to the Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects: "8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects."[38] Besides, drugs long-term safety, rare side effects, quality of life and cost-effectiveness are usually investigated in phase IV clinical trials, which involve thousands of people in observational studies.

Similarly, the American Medical Association's Code of Medical Ethics states: "To ensure that the interests of human participants are protected, physician-researchers and those who serve on oversight bodies should give careful attention to issues of methodological rigor, informed consent, characteristics of the medical condition under study, and safety and monitoring, in keeping with the following guidelines: [….] c) Design studies to minimize the amount of time participants are on placebo without compromising the scientific integrity of the study or the value of study data."[39]

Based on these assumptions, it can be argued that the undeniable need to acquire further data through additional

studies should be carefully balanced with the due protection of research participants and that, as some authors have argued, "A more fine-grained analysis of clinical equipoise is needed to account for cases in which uncertainty in the medical community exists for some outcomes and not for others and to understand how priorities and interests differ across participants and researchers."[34]

Ongoing studies

As mentioned, Pfizer-BioNTech and Moderna COVID-19 vaccines, while adhering to the rigorous standards for safety, effectiveness, and manufacturing quality needed to obtain EUAs and CMAs, are not full licensed for marketing distribution because there remain uncertainties about their long-term safety and efficacy. Moreover, according to both the FDA and the EMA, additional data are required in order to: (a) complete the characterization of the active substance and finished product; (b) enhance the control strategy, including the active substance and finished product specifications; (c) confirm the consistency of the finished product manufacturing process; (d) confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, in particular for the excipients ALC-0315 and ALC-0159, which are the key components of the lipid mixtures used to prepare vaccines.

As mentioned, since these are placebo-controlled trials, a potential conflict can be identified between the societal and scientific value of continuing to collect consistent information on vaccines and the obligation of researchers and sponsors to safeguard the health and well-being of research participants. Similar concerns arise with regard to ongoing studies of other vaccine candidates. In all of these cases, it would be necessary to determine whether these studies should be unbundled to allow volunteers who received the placebo to have access to the vaccines currently available.

The authorization of one or more vaccines is an element that could strongly affect the willingness of individuals to continue participating in a clinical trial. Moreover, as in any other clinical trial, all volunteers have the right to withdraw at any time and for any reason.

Both Pfizer-BioNTech and Moderna companies stated they have an ethical obligation to unblind all research subjects allowing them to know whether they received vaccine or placebo and choose whether to continue their participation in the trial or to get vaccinated. This is not unusual: in many clinical trials, if the investigational drug is proven effective, the process of unblinding and then offering the drug before full license approval to the placebo participants is common.

In order to balance the conflicting needs of continuing to collect reliable data and protecting research participants, the World Health Organization (WHO) Ad Hoc Group on the Next Steps for COVID-19 Vaccine Evaluation recommended to design "large, simple trial to evaluate serious safety outcomes, in which many participants (even hundreds of thousands) are randomly assigned to vaccine or placebo and those who receive placebo are vaccinated only about 2 months later."[35] Similarly, some experts suggested to change the design of the ongoing studies to allow all participants who received the placebo to also get the effective vaccine: They proposed a blinded crossover study that guarantees that all volunteers receive the vaccine, while remaining unaware of the time they received it.[40,41]

The feasibility of these proposals is however challenged by serious doubts casted on the occurrence of inadvertent unblinding in both the Pfizer-BioNTech and Moderna trials. Indeed, in both trials a normal saline placebo was used and it has been proposed that differences in post-injection side-effects between vaccine and placebo may have allowed for educated guessing.[18] In several cases, unblinding is confirmed by trial participant who share their experiences on the web, either based on side-effects or even because some of them after vaccination checked for serum antibodies.[42]

These changes to the design of the ongoing studies could also raise ethical issues related to vaccine allocation and distribution. In fact, the suggested crossover procedure would involve the administration of a considerable quantity of vaccines to volunteers who may not belong to categories considered at risk by regulatory authorities, to the detriment of individuals for which priority in vaccination has been established. Under the current condition of vaccine scarcity, offering the active vaccines to all volunteers who received placebo in Pfizer-BioNTech and Moderna clinical trials would mean denying vaccination to a considerable number of individuals who are considered most in need and for whom vaccination prioritization has been established.

Some commentators also claimed that research subjects who received placebos in the first clinical trials should be first in line to be vaccinated to thank them for their sacrifice.

However, even in this case there may be reasons to disagree. First, participation in a clinical trial is grounded on voluntary and altruistic bases and participants do not have to expect any remuneration for their "sacrifice." Ensuring vaccination priority in this case could set a dangerous precedent by creating wrong expectations for next trials. Moreover, the attribution of this type of priority may not respect the criterion of equity. According to regulatory authorities, the vaccine should be given first to those who need it most: healthcare personnel and other essential workers, adults with high-risk medical conditions, and adults aged 65 years or older.[43] Finally, in a situation of short-term resource scarcity, social merit *per se* should not be a criterion for assigning priority; even if this were the case, other individuals who, in different ways, made

great efforts during the pandemic should also be considered worthy of recognition.

For these reasons, in this pandemic scenario in which vaccines currently approved for administration should be considered scarce resources, it seems reasonable to assume that researchers and sponsors should not be considered ethically obligated to unblind all volunteers, but they should inform all research subjects about developments that might affect their willingness to remain in a clinical trial. This information should cover both the data relating to the efficacy and safety of the vaccines that have been approved, and the current situation of vaccine scarcity and the priority criteria established for vaccinations. In this way, only research subjects who are eligible for vaccination outside the trials would have a real interest to be unblinded, while participants who are not eligible yet could reasonably choose to continue their participation because it would not entail any additional risk for them.[44]

Finally, it must be always kept in mind that, for all currently available vaccines, data on efficacy and safety refer to short time periods, usually no more than a few weeks from completion of the treatment administration. In other words, it remains to be established whether vaccines would confirm, eventually increase or possibly even decrease their efficacy on the long term. Bringing ongoing studies to completion over the originally planned durations (usually, at least 2 years) would allow full assessment of vaccine efficacy and safety profile. Should current studies be stopped due to drop out of subjects from the placebo arms, then the possibility to assess such vaccines would be irreparably compromised.

New candidate COVID-19 vaccines

As anticipated, in addition to continuing ongoing trials, starting new studies to evaluate new candidates could lead to other important benefits. Other vaccines may be found to be safer or more effective or effective in different populations, may be developed at lower cost and/or on a larger scale, or may be more easily stored and administered.

Some authors argue that even once a vaccine becomes available for public distribution, clinical trials of new candidates can be designed maintaining control against placebo when the subjects involved are fully informed about the availability of the licensed drug and express their willingness to participate by voluntarily delaying vaccination for altruistic reasons.[32] However, according to the Declaration of Helsinki: "9. […] The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent."[38] In other words, even if informed consent is an essential condition for participating in a clinical trial and represents an expression of respect for patient autonomy, it is not sufficient for ethical clinical research[45]: Researchers and sponsors must always be held responsible for assessing the risk-benefit profile for each participant.

Consequently, it must be questioned whether these trials can still be designed using placebo as a control even now that some vaccines—considered safe and effective enough to be administered to millions of people—are available. The Declaration of Helsinki also states: "33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo […] 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."[38] Likewise, the International Ethical Guidelines for Health-Related Research Involving Humans, issued by the Council for International Organizations of Medical Sciences (CIOMS), states that: "When there is an established effective intervention, placebo may be used as a comparator without providing the established effective intervention to participants only if: If there are compelling scientific reasons for using placebo; and if 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."[46]

Again, the question is whether the currently approved vaccines can be considered the best proven intervention. Although these vaccines are still largely investigational, based on the available data, at the present time they clearly represent a more effective intervention than placebo in preventing the occurrence of symptomatic COVID-19. For this reason, it can be argued that researchers should consider using them as controls in future clinical trials if there is no other "compelling scientific reason to use placebo."

Conclusion

The arguments presented above suggest that, in this unprecedented pandemic scenario, the need to continue ongoing clinical trials—as well as to start new studies—in order to collect further reliable scientific information on safety, efficacy and duration of protection of COVID-19 vaccine candidates, should be more carefully balanced with the equally fundamental need to ensure the protection of the rights and well-being of research participants.

In particular, although the continuation of placebo-controlled clinical trials is widely recommended, we believe that it is not ethically justifiable—as well as reasonably plausible—to assume that currently approved vaccines are safe and effective enough to be administered to millions of people as part of the global vaccination campaign but, at the same time, not safe and effective enough to be considered "the best proven intervention." As first vaccines provided clear evidence that they may be effective, at least in preventing COVID-19 symptoms in the short term, and gained EMAs and CMAs, we argue that to choose how to proceed with current clinical trials and how to design those that follow it should be taken into account: (a) the current global situation of vaccine scarcity; (b) the priority established for the access to vaccination on the basis of the risk of contracting the disease or developing it in a severe form; (c) the obligation to provide information to all participants—current and prospective—on all aspects that might affect their willingness to remain/be enrolled in vaccine clinical trials; (d) the possibility of using alternative study designs that allow the collection of consistent additional information while providing the best possible protection for research subjects.

Based on these considerations, it therefore seems reasonable to assume that there is no ethical obligation to unblind all volunteers enrolled in ongoing placebo-controlled clinical trials, but only an obligation to fully inform them, because only research subjects who are eligible for vaccination outside the trials would have a real interest in withdrawing, while participants who are not yet eligible could reasonably choose to continue their participation as it would not pose any additional risk to them. However, given that currently approved vaccines are clearly more effective than placebo in at least preventing the occurrence of symptomatic COVID-19, we argue that they should be used as controls in future studies, unless there are "compelling scientific reasons to use placebo" which should be clearly identified and documented.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Silvia Ceruti https://orcid.org/0000-0002-0535-4022
Mario Picozzi https://orcid.org/0000-0001-5327-4441

References

1. Food and Drug Administration. FDA takes key action in fight against COVID-19 by issuing emergency use authorization for first COVID-19 vaccine, https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19 (2020), accessed 14 March 2021).
2. Food and Drug Administration. Moderna COVID-19 vaccine, https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine (2020, accessed 14 March 2021).
3. European Medicine Agency. EMA recommends first COVID-19 vaccine for authorisation in the EU, https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu (2020, accessed 14 March 2021).
4. European Medicine Agency. EMA recommends COVID-19 vaccine moderna for authorisation in the EU, https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu (2021, accessed 14 March 2021).
5. European Medicine Agency. EMA recommends COVID-19 vaccine AstraZeneca for authorisation in the EU, https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-astrazeneca-authorisation-eu (2021, accessed 14 March 2021).
6. Food and Drug Administration. Janssen COVID-19 vaccine, https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine (2021, accessed 14 March 2021).
7. European Medicine Agency. EMA recommends COVID-19 vaccine Janssen for authorisation in the EU, https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-janssen-authorisation-eu (2021, accessed 14 March 2021).
8. Food and Drug Administration. MCM Issues. FDA works to address numerous issues related to public health security. Find information on MCM-related emergency preparedness and response topics, https://www.fda.gov/emergency-preparedness-and-response/medical-countermeasures-initiative-mcmi/mcm-issues (2020, accessed 14 March 2021).
9. European Medicine Agency. Conditional marketing authorisation, https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (2020, accessed 14 March 2021).
10. European Medicine Agency. COVID-19 vaccines: development, evaluation, approval and monitoring, https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring#scientific-evaluation-and-approval-section (2020, accessed 14 March 2021).
11. Food and Drug Administration. Medical countermeasures, https://www.fda.gov/media/134232/download (2020, accessed 14 March 2021).
12. Food and Drug Administration. Emergency use authorization, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs (2021, accessed 14 March 2021).
13. European Medicine Agency. Conditional marketing authorization. Report on ten years of experience at the European Medicines Agency, https://www.ema.europa.eu/en/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf (2017, accessed 14 March 2021).
14. European Medicine Agency. COVID-19 treatments: authorized, https://www.ema.europa.eu/en/human-regulatory/overview/

public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-covid-19/covid-19-treatments-authorised (2020, accessed 14 March 2021).
15. European Medicine Agency. Arepanrix, https://www.ema.europa.eu/en/medicines/human/EPAR/arepanrix (2011, accessed 14 March 2021).
16. European Medicine Agency. Humenza, https://www.ema.europa.eu/en/medicines/human/EPAR/humenza (2011, accessed 14 March 2021).
17. European Medicine Agency. Pandemic influenza vaccine H5N1 AstraZeneca (previously pandemic influenza vaccine H5N1 medimmune), https://www.ema.europa.eu/en/medicines/human/EPAR/pandemic-influenza-vaccine-h5n1-astrazeneca-previously-pandemic-influenza-vaccine-h5n1-medimmune (2017, accessed 14 March 2021).
18. Doshi P. Pfizer and Moderna's "95% effective" vaccines—let's be cautious and first see the full data, https://blogs.bmj.com/bmj/2020/11/26/peter-doshi-pfizer-and-modernas-95-effective-vaccines-lets-be-cautious-and-first-see-the-full-data/ (2020, accessed 14 March 2021).
19. Doshi P. Pfizer and Moderna's "95% effective" vaccines—we need more details and the raw data, https://blogs.bmj.com/bmj/2021/01/04/peter-doshi-pfizer-and-modernas-95-effective-vaccines-we-need-more-details-and-the-raw-data/ (2021, accessed 14 March 2021).
20. Mahase E. Covid-19Past infection provides 83% protection for five months but may stop transmission, study fins. *Br Med J* 2021; **372**: n124.
21. BBC. Covid: Vaccinated people may spread virus, says Van-Tam, https://www.bbc.com/news/uk-55784199 (2021, accessed 14 March 2021).
22. Food and Drug Administration. Pfizer-BioNTech COVID-19 vaccine, https://www.fda.gov/media/144245/download (2020, accessed 14 March 2021).
23. Holland NJ and Bernstein JM. Bell's palsy. *BMJ Clin Evid* 2014; **2014**: 1204.
24. European Medicine Agency. Comirnaty, INN-COVID-19 mRNA vaccine (nucleoside-modified, https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf (2020; accessed 14 March 2021).
25. GOV.UK. Confirmation of guidance to vaccination centres on managing allergic reactions following covid-19 vaccination with the Pfizer/Biontech vaccine, https://www.gov.uk/government/news/confirmation-of-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination-with-the-pfizer-biontech-vaccine (2020, accessed 14 March 2021).
26. Reuters. California resumes Moderna COVID-19 vaccine usage after pause, https://www.reuters.com/article/us-health-coronavirus-california-moderna/california-resumes-moderna-covid-19-vaccine-usage-after-pause-idUSKBN29Q0MK (2021, accessed 14 March 2021).
27. European Medicine Agency. COVID-19 vaccine safety update, https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-comirnaty-january-2021_en.pdf (2021, accessed 14 March 2021).
28. Taraldsen l.e. Norway raises concern over vaccine jabs for the elderly, https://www.bloombergquint.com/politics/norway-vaccine-fatalities-among-people-75-and-older-rise-to-29 (2021, accessed 14 March 2021).
29. Norwegian Medicines Agency, Weekly report on suspected adverse drug reactions to coronavirus vaccines, https://legemiddelverket.no/Documents/English/Covid-19/Adverse%20drug%20reactions%20covid-19%20vaccines%20as%20of%20January%2014%202021.pdf (2021, accessed 14 March 2021).
30. Freedman B. Equipoise and the ethics of clinical research. *New Engl J Med* 1987; **317**: 141–145.
31. Hey SP, London AJ, Weijer C, *et al.* Is the concept of clinical equipoise still relevant to research? *Br Med J* 2017; **359**: j5787.
32. Miller FG. Ethics of placebo-controls in coronavirus vaccine trails. Online referencing, https://www.thehastingscenter.org/ethics-of-placebo-controls-in-coronavirus-vaccine-trials/ (2020, accessed 14 March 2021).
33. Wendler D, Ochoa J, Millum J, *et al.* COVID-19 vaccine trial ethics once we have efficacious vaccines. *Science* 2020; **370**: 1277–1279.
34. Friesen P, Caplan AL and Miller JE. COVID-19 vaccine research and the trouble with clinical equipoise. *Lancet* 2021; **397**: 576.
35. WHO Ad Hoc expert group on the next steps for covid-19 vaccine evaluation. Placebo-controlled trials of covid-19 vaccines—why we still need them. *N Engl J Med* 2021 Jan 14; **384**: e2.
36. Lenzer J. Covid-19: should vaccine trials be unblinded? *Br Med J* 2020; **371**: m4956.
37. Lipsitch M, Jha A and Simonsen L. Observational studies and the difficult quest for causality: lessons from vaccine effectiveness and impact studies. *Int J Epidemiol* 2016; **45**: 2060–2074.
38. World Medical Association, Declaration of Helsinki - ethical principles for medical research involving human subjects, 8th ed. Online referencing, https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (2013, accessed 14 March 2021).
39. AMA. Ethical use of placebo controls in research.https://www.ama-assn.org/delivering-care/ethics/ethical-use-placebo-controls-research (2021, accessed 14 March 2021).
40. Food and Drug Administration. Vaccines and related biological products advisory committee meeting December 10, 2020, https://www.fda.gov/media/144245/download (2020, accessed 14 March 2021).
41. Food and Drug Administration. Vaccines and related biological products advisory committee meeting December 17, 2020, https://www.fda.gov/media/144434/download (2020, accessed 14 March 2021).
42. Williams G. Pfizer vaccine trial participants share experience, https://www.wect.com/2020/12/16/participants-pfizer-covid-vaccine-trial-share-experiences/ (2020, accessed 14 March 2021).
43. Bell BP, Romero JR and Lee GM. Scientific and ethical principles underlying recommendations from the advisory committee on immunization practices for COVID-19 vaccination implementation. *JAMA* 2020; **324**: 2025–2026.

44. Rid A, Lipsitch M and Miller FG. The ethics of continuing placebo in SARS-CoV-2 vaccine trials. *JAMA* 2021; **325**(3): 219–220. doi:10.1001/jama.2020.25053
45. Emanuel EJ, Wendler D and Grady C. What makes clinical research ethical? *JAMA* 2000; **238**: 2701–2711.
46. Council for International Organizations of Medical Sciences (CIOMS). "Internation al ethical guidelines for health-related research involving humans" (Report, CIOMS, 2016): 15. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf (2016, accessed 14 March 2021).