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Ongoing and future COVID-19 vaccine clinical trials: challenges and opportunities

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Large-scale deployment of COVID-19 vaccines will seriously affect the ongoing phases 2 and 3 randomised placebo-controlled trials assessing SARS-CoV-2 vaccine candidates. The effect will be particularly acute in high-income countries where the entire adult or older population could be vaccinated by late 2021. Regrettably, only a small proportion of the population in many low-income and middle-income countries will have access to available vaccines. Sponsors of COVID-19 vaccine candidates currently in phase 2 or initiating phase 3 trials in 2021 should consider continuing the research in countries with limited affordability and availability of COVID-19 vaccines. Several ethical principles must be implemented to ensure the equitable, non-exploitative, and respectful conduct of trials in resource-poor settings. Once sufficient knowledge on the immunogenicity response to COVID-19 vaccines is acquired, non-inferiority immunogenicity trials—comparing the immune response of a vaccine candidate to that of an authorised vaccine—would probably be the most common trial design. Until then, placebo-controlled, double-blind, crossover trials will continue to play a role in the development of new vaccine candidates. WHO or the Council for International Organizations of Medical Sciences should define an ethical framework for the requirements and benefits for trial participants and host communities in resource-poor settings that should require commitment from all vaccine candidate sponsors from high-income countries.

Introduction

In late 2020, the scientific community and the media[1,2] discussed the crucial topic of the future of phase 3, efficacy, placebo-controlled, randomised clinical trials (RCTs) of COVID-19 vaccine candidates once one or more vaccines have been authorised and deployed. This topic has three main aspects. Firstly, what investigators should do with placebo recipients of the ongoing vaccine RCTs with the deployed vaccines. Secondly, what the best approach is to ensure the collection of long-term follow-up data to support both vaccine policy recommendations and application for full licensure to regulatory agencies for vaccines that were deployed under a temporary authorisation (eg, emergency use authorisation in the USA, conditional marketing authorisation in the EU, and emergency use listing by WHO). And thirdly, what should happen to ongoing and future trials of other COVID-19 vaccine candidates currently in clinical development.

Investigators, regulators, and bioethicists have provided the scientific, regulatory, and ethical basis for guiding this discussion;[3–9] some have focused on the essential need to collect long-term safety and efficacy data from all phase 3 RCTs,[4–6,8] whereas others addressed the right of placebo recipients to be informed in a timely manner and be vaccinated with a deployed vaccine.[3,7,9] The US Food and Drug Administration Vaccines and Related Biological Products Advisory Committee held three meetings in late 2020,[10–12] which provided public discussions on the unprecedented challenges the world is facing in 2021. A prominent position is that unmasking trial participants and the decision to vaccinate should happen at the time participants meet the eligibility criteria for the priority groups for vaccination, as defined by the health authorities in each setting.[13] This approach fulfils the ethical principles of reciprocity (ie, moral obligation to benefit those who have benefitted us), beneficence (ie, investigators acting in the best interests of participants), and justice (ie, fair distribution of benefits and burdens of research).[13]

However, there has been little discussion on the longer-term challenges of evaluating vaccine candidates that are further behind in their clinical development compared with the candidates that are already, or due to be, temporarily authorised in late 2020 and early 2021. In fact, none of the sources of guidance, such as those issued by WHO or the regulatory agencies, have specifically addressed how the clinical development of COVID-19 vaccine candidates that are currently in phase 2 or 3 trials could be concluded once high-income countries have offered vaccination to all individuals 18 years and older.

The likely effect on Pfizer-BioNTech, Moderna, AstraZeneca, and Janssen vaccine trials

Once one or more of the vaccines that are most likely to be successful (ie, Pfizer-BioNTech [for ≥16-year-olds]; Moderna, AstraZeneca, and Janssen [for ≥18-year-olds]) are deployed in any country, there is general agreement that only two trial designs would provide long-term follow-up data to support the eventual full licensure of the vaccines. The best design is a crossover double-blind trial in which all participants would receive the other intervention that they were not given at the start of the trial (ie, the vaccine or the placebo); as a fallback option, an open-label design could be used, in which all placebo recipients would receive the vaccine that was not administered when randomly assigned.[12–15] All participants should be appropriately informed in a timely manner of the status of vaccine deployment and should re-consent[16]

Lancet Infect Dis 2021

Published Online
May 18, 2021
https://doi.org/10.1016/S1473-3099(21)00263-2

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See Online for appendix

to continue in either of the two types of continuation trials.

However, to date, the crossover placebo-controlled design could only be implemented with the Pfizer-BioNTech phase 3 trial. Unfortunately, this approach is not feasible in the Moderna phase 3 RCT due to the deployment of the Pfizer-BioNTech vaccine and the high proportion of participants belonging to the priority groups eligible for vaccination that have asked to be unblinded and vaccinated.[12] Therefore, in the Moderna trial, the vaccine has been offered to all placebo recipients, and long-term data will be gathered in an open-label method.[12] This approach will also be applied for all Janssen RCTs.[15] Finally, AstraZeneca participants receiving placebo in all trials have been offered one of the authorised vaccines.[17,18]

The temporary authorisation of the four vaccines affects the recruitment and retention of participants in the other trials in adults and older people that are sponsored by Pfizer-BioNTech, Moderna, AstraZeneca, and Janssen (appendix). This, however, will not be the case in the Moderna phase 2 and 3 trial in adolescents (between the ages 12 years and 16 years). Deployment of other vaccines (eg, Bharat [India], Sinovac [China], Sinopharm [China], Sputnik V [Russia]) in early 2021 also affects placebo-controlled RCTs in regions where these authorised vaccines are available.

The likely effect on the fast follower vaccine candidate trials

There is a paucity of discussion about ongoing placebo-controlled RCTs on vaccine candidates that are following behind those of Pfizer-BioNTech, Moderna, AstraZeneca, and Janssen (appendix). The ethical principles of reciprocity, beneficence, and justice dictate that trial participants should not be denied access to any vaccine that is being deployed in their relevant settings, when they themselves become eligible to receive the vaccine based on societal prioritisation and availability.

Serious difficulties will arise with the phase 2 and phase 3 RCTs done with ten other vaccine candidates belonging to five different platforms (DNA: AnGes/Takara and Inovio; protein subunit: Clover, Medigen, Novavax, and Sanofi; RNA: Arcturus and CureVac; virus-like particles: Medicago; and viral vector: Reithera), comprising 16 placebo-controlled RCTs that are at risk of early termination as originally designed or initiated. Sponsors of these trials should therefore consider contingency plans to ensure that the objectives of the clinical development plans can be met. This approach could include the switching of the conduct of their trials to countries where the deployment of COVID-19 vaccines will be in short supply in 2021. Doing large phase 3 efficacy trials in high-income countries will probably not be feasible from mid or late 2021 onwards as the individuals that choose not to be vaccinated with an authorised vaccine are unlikely to be willing to participate in a placebo-controlled RCT with a novel vaccine candidate.

The potential and challenges of doing randomised clinical trials in low-income and middle-income countries

Many low-income and middle-income countries will regrettably have only a small proportion of their population vaccinated against SARS-CoV-2 during 2021–22.[19–21] Placing trials in resource-poor settings could be a reasonable or likely to be the only feasible way forward for the clinical development of many COVID-19 vaccine candidates, which would help to fulfill the legitimate aspiration to having trials run in their territories in low-income and middle-income countries.[22] Inequity will be an ethical challenge as many low-income and middle-income countries are left behind in the access to vaccines, which will clearly contradict what is stated in the Sustainable Development Goals.[23] The wider issue of affordability and availability of vaccines in many low-income and middle-income countries is an important ethical issue, but outside the scope of this Personal View.

When doing trials of COVID-19 vaccine candidates in countries with limited affordability and availability of COVID-19 vaccines, sponsors from high-income countries should seek to allay any concern of ethics dumping[24] or exploitation of the host trial participants and communities. To ensure the equitable, non-exploitative, and respectful conduct of trials in countries with limited affordability and availability of COVID-19 vaccines, sponsors must fulfil the following three principles:[25–29] (1) the research should be responsive to local health needs (ie, should be done in communities with a high burden of COVID-19; (2) both research participants and host communities should benefit from the research; and (3) the COVID-19 vaccine candidates to be tested in countries with limited affordability and availability of COVID-19 vaccines should be those that could eventually be deployed—at an affordable price—in the countries where the trials were done. For instance, vaccine candidates needing ultra-low temperature conditions (–70°C) should not be tested in countries with limited affordability and availability of COVID-19 vaccines without the infrastructure that ensures safe and regular long-term storage and distribution of vaccines under real-life conditions.

The first design to consider could be an efficacy RCT comparing the vaccine candidate with a vaccine authorised in the country with limited affordability and availability of COVID-19 vaccines where the trial will take place.[27,28] However, the large sample size and long follow-up period required could make this design unfeasible. Non-inferiority immunogenicity RCTs, in which immune response to a vaccine candidate is compared with that of an authorised vaccine, would be the next best trial design. Yet, it will not be until mid or late 2021 when enough data will probably be available to establish different immunological measures, and, hopefully, a correlate of protection against disease. Non-inferiority immunogenicity RCTs are scientifically appropriate since the efficacy of a vaccine candidate can be inferred (so-called bridged)

Panel: **Design, ethics, and provisions for the conduct of placebo-controlled randomised clinical trials (RCTs)* to develop COVID-19 vaccine candidates in resource-poor settings in countries with limited affordability and availability to COVID-19 authorised vaccines**

Trial design and benefits for participants and host communities

- The best way to ensure that trial participants and host communities (or specific population groups) benefit from the research is to make the vaccine candidate identified as effective during the trial available
- The best design to fulfill this objective is the crossover double-blind RCT; the crossover period should commence as soon the event-driven primary efficacy outcome of the trial is reached;[14] the RCT should ideally last up to 24 months to assess the durability of the vaccine efficacy and long-term safety
- If host communities (or specific groups) are entitled to be vaccinated with the effective vaccine, the crossover double-blind RCT will allow its deployment to non-trial participants at the time the crossover period has started, and will match the situation that occurred with the Pfizer-BioNTech vaccine in the countries where the placebo-controlled phase 3 RCT is currently being done[11,12]
- If, for whatever reason, the crossover double-blind RCT cannot be done, recipients of placebo should be given the opportunity to receive the vaccine candidate in an open-label method, a similar situation to what had occurred with the Moderna and Janssen trials in the USA and other countries
- The crossover could potentially be started a few months after trial initiation provided the COVID-19 infection rate and identification of COVID-19 cases are similar to that of the Pfizer-BioNTech, Moderna, and Janssen trials
- The trial sponsor should ensure access to adequate treatment for all COVID-19 cases among trial participants

Ethical considerations

- The situation we are considering is that of a resource-poor setting in a country where most citizens will not have access to an authorised COVID-19 vaccine in 2021–22
- Some might argue that a placebo-controlled RCT is unethical since the standard of prevention is the deployed vaccine in the low-income or middle-income country, or even the vaccine with the highest proven efficacy worldwide;[32] however, research not using the standard of prevention as the active control need not be unethical when the vaccine cannot be made available to most of the population, and when the research is scientifically necessary and valuable and of social value to the low-income or middle-income country
- As potential trial participants are unable to access an authorised vaccine, individuals recruited for a crossover placebo-controlled RCT would not be made worse off by trial participation, and indeed, would be better off by having a 66% or 75%† chance of receiving a potentially effective vaccine.[33] Furthermore, if the vaccine candidate is proven to be effective, all volunteers participating in the trial will be vaccinated when the crossover takes place
- In terms of ethical assessment, the placebo-controlled, double-blind, crossover RCT under the mentioned conditions would be ethically acceptable since it complies with the ethical codes provisions[27,28] and the four requirements established by the WHO expert panel, which are:[34] (1) an active-controlled trial is not feasible, (2) the risks of delaying an efficacious vaccine are adequately minimised or mitigated, (3) the use of a placebo control is justified by the potential public health or social value of the research, and (4) the research is responsive to local needs

Other provisions

- If an authorised vaccine becomes available for all or a subset of trial participants before the vaccine candidate assessed in the RCT has shown efficacy, they will be informed, unblinded, and vaccinated with the authorised vaccine
- If the vaccine candidate assessed in the RCT does not prove to be efficacious or safe, the trial sponsor should arrange the provision of any authorised COVID-19 vaccine to trial participants (and to host communities or to specific groups); the vaccine should be provided free-of-charge by the sponsoring company or by international organisations, to ensure equitable sharing of burdens and benefits
- All the provisions outlined—and the management and compensation for serious adverse events—should be stated upfront in the trial protocol to be discussed and agreed with local investigators and approved by research ethics committees and in-country health or regulatory authorities

*Trials done by sponsors based in high-income countries. †66% with a 2:1 (vaccine to placebo ratio) random allocation, similar to trials sponsored by AstraZeneca (NCT04516746) and Novavax (NCT04611802) being done in the USA and other countries, or 75% with a 3:1 random allocation, like in the Sputnik V phase 3 trial (NCT04530396).

by comparing the immune response with that of an authorised vaccine with known clinical efficacy. Bridging estimates of the efficacy of a vaccine candidate could be done irrespective of whether an immune correlate of protection has or has not been well established. However, even clinical immune correlates of protection might not necessarily be applicable to different vaccine constructs, populations, and disease settings,[30,31] particularly over time and with the emergence of novel SARS-CoV-2 variants. Until enough knowledge of immunogenicity responses to COVID-19 vaccines is acquired, placebo-controlled RCTs could be a design for consideration (panel).

In addition to trials in which individuals are randomly assigned to vaccine candidate or placebo, other trial designs (eg, the ring vaccination trial in which participants with increased risk of infection, such as

contact with infected individuals, are recruited first;[35] the stepped-wedge cluster RCT in which initially no participant receives the vaccine but participants of all clusters will receive it at regular intervals or steps)[36] could potentially be appropriate for the clinical development of future COVID-19 vaccine candidates. Yet, RCTs that randomly assign individuals to assess direct effects on individual vaccine protection are more commonly used for regulatory purposes than cluster RCTs in which reduction in transmission of infection (an indirect effect) is also assessed.[30,37]

Finally, controlled human challenge studies of COVID-19 vaccine candidates, provided they fulfill a number of criteria[38] and can be done minimising participants and third party risks,[39] could also be considered to investigate vaccine efficacy and to provide preliminary evidence supporting an immune correlate of protection.[30,31,39,40] These trials have been proposed to be done in high-income countries with previously unvaccinated individuals and due monetary compensation for participation.[41] However, because the number of participants in such trials is small, a trial with a different design and with thousands of participants, and that could only be run in countries with limited affordability and availability of COVID-19 vaccines, would still be needed to gather safety and immunogenicity data.[40]

The widespread circulation of new SARS-CoV-2 variants requires the development of vaccine candidates that could prevent COVID-19 due to these variants. The US Food and Drug Administration guidance[42] requires the conduct of two non-inferiority immunogenicity trials in individuals aged between 18 years and 55 years comparing the neutralising antibody response rates and geometric mean titres elicited by the modified vaccine against the new variant or variants with that of the authorised vaccine. As one of these trials must be done in unvaccinated individuals and individuals who have been previously uninfected with SARS-CoV-2, it is likely that from late 2021 onwards, such trials can only be done in countries with limited affordability and availability of COVID-19 vaccines. The second trial, a booster study, could be carried out in high-income countries as it must be done in previously vaccinated individuals that have received the authorised vaccine according to the authorised dose and dosing regimen.[42] It is probable that both the European Medicines Agency and WHO will be aligned with these requirements. Investigators and health authorities in countries with limited affordability and availability of COVID-19 vaccines should be aware of the presence of SARS-CoV-2 variants. The presence of the B.1.351 variant has been already verified in many countries in sub-Saharan Africa, and P1 variant in Latin America.[43]

Sponsors have the moral obligation of capacity building and providing measures to support the wider needs of managing the COVID-19 pandemic in the host communities. Provision of masks, educational support, and other types of health and social services should be considered.[25–29] A robust and inclusive local community engagement process should be implemented.[44,45] To this end, transparency and open communication will be crucial, and all relevant local stakeholders and community leaders should be extensively briefed on the current situation of COVID-19 vaccines (ie, deployed and under clinical research) in their host country. This approach will be particularly important to understand the perception of the proposed trials, prevent or limit misinformation on the population, and to understand possible reasons for refusal to participate.

Conclusions

Many countries will continue to deploy one or more COVID-19 vaccines under temporary authorisations. Depending on vaccine uptake in different high-income countries within the whole adult or older population, reaching complete vaccination could take 6–12 months. Initiating RCTs in high-income countries will be increasingly difficult as potential participants would be hesitant to receive an experimental vaccine (or placebo) when vaccines are already available. This unprecedented situation could lead sponsors to do their phase 2 and phase 3 trials in low-income and middle-income countries with otherwise limited availability and access to authorised vaccines. This move is an opportunity to promote mutually beneficial partnerships between high-income and low-income and middle-income countries, promoting long-term value for host communities, and to facilitate a sustainable and equitable development.[46] Large-scale international RCTs, such as the one done by the WHO Solidarity Trial Consortium,[47] have shown the appropriateness of involving investigators from Africa, Asia, and Latin America. Furthermore, several low-income and middle-income countries are also participating currently in RCTs with COVID-19 vaccine candidates (appendix).

To help local investigators, research ethics committees, and national health and regulatory authorities in host countries with limited affordability and availability of COVID-19 vaccines where such trials can be done, WHO or the Council for International Organizations of Medical Sciences should define an ethical framework for the minimum requirements and benefits for participants and host communities that sponsors should commit to. Regional institutions, such as the Pan American Health Organization, the Africa Centres for Disease Control and Prevention Consortium for COVID-19 vaccine clinical trials,[22] or networks like the African Vaccine Regulatory Forum, could be involved to adapt this framework to the specific regional context and to coordinate the conduct of local or regional trials. All stakeholders involved in the design and conduct of RCTs in countries with limited affordability and availability of COVID-19 vaccines should ensure that these trials are ethically and scientifically robust. As these trials will be

the foundation for vaccine marketing authorisations worldwide, both the US Food and Drug Administration and European Medicines Agency should partner with the regulators of host countries in inspections to ensure that these studies were done to conform to good clinical practice standards. Discussions and agreement on the most ethical way to do clinical trials and licensure of vaccine candidates in the context of a pandemic deserve further evaluation. Finally, the participants and communities in which such studies are done for the sake of the common good deserve the benefits of such participation.

Contributors
RD-R conceived the idea and wrote the first draft of the manuscript. All authors provided comments and edits throughout the drafting process for important intellectual content. All authors approved the final version of the manuscript and are accountable for all aspects included in this Personal View.

Declaration of interests
VJ reports grants and personal fees from Baxter Healthcare, personal fees from AstraZeneca, grants from NephroPlus, outside the submitted work. GAP is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being done by Merck Research Laboratories, and offers consultative advice on vaccine development to Merck & Co, Medicago, GlaxoSmithKline, Sanofi Pasteur, Emergent Biosolutions, Dynavax, Genentech, Eli Lilly and Company, Janssen Global Services LLC, Kentucky Bioprocessing, AstraZeneca, and Genevant Sciences Inc. GAP holds patents related to vaccinia and measles peptide vaccines, and has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are done in compliance with Mayo Clinic Conflict of Interest policies. All other authors declare no competing interests.

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