Placebo control group in COVID-19 vaccine trials: context and timing matters

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The debate about when placebo comparators in COVID-19 vaccine trials will no longer be acceptable goes on. A number of recent articles have argued that placebo-controlled randomized clinical trials (RCTs) are becoming infeasible and not ethically acceptable anymore [1–5]. The main ethical objection relies on the non-fulfillment of the clinical equipoise principle [6], once temporarily authorized COVID-19 vaccines are available (e.g., emergency use authorization in the USA, conditional marketing authorization in the EU, emergency use listing by WHO). Clinical equipoise requires that participants will be allocated to an intervention that is not inferior to any available alternative: so, placebo-controlled RCTs must not be allowed anymore when assessing novel COVID-19 vaccine candidates. Yet, context matters greatly. This approach is acceptable if we limit this contention to countries with adequate access to temporarily authorized COVID-19 vaccines, i.e., to high-income countries.

Today, regrettably, hundreds of millions of individuals that live in low- and middle-income countries lack access to temporarily authorized COVID-19 vaccines due to limited vaccine availability and will do so well into 2023 [7]. However, in these territories, and until sufficient knowledge on immunogenicity, safety and efficacy of multiple COVID-19 vaccines is gathered, especially with the widespread of different SARS-CoV-2 variants of concern, double-blind placebo-controlled trials can and should be considered in the clinical development of new COVID-19 vaccine candidates [8–10]. In these trials, participants should only be included

with fully informed consent and the best possible standard of COVID-19 care must be available to all participants. As soon as the safety and efficacy of the vaccine candidate is demonstrated, participants should have the chance to be unblinded immediately and placebo recipients immunized with the vaccine candidate. Participants should be allowed to unblind and access a known effective vaccine should one become available to them. In addition, and in particular, the research should respond to local needs (placebo-controlled trials should be done in regions impacted with high burden of COVID-19), both participants and communities should benefit from the trial, and the vaccine candidate to be tested, if proved to be efficacious and safe, should be made available in the country where the trial is conducted [8]. To this end and from the very beginning, transparency should be the fundamental guiding principle in the cooperation between the sponsor and local stakeholders with full community partnership and engagement throughout. The commitment of local investigators, research ethics committees, and health authorities as well as of local community leaders is a must to ensure a fruitful community engagement and participation.

Placebo-controlled RCTs in current COVID-19 vaccine candidates' development

A review of the WHO databases [11, 12] showed that a number of phase 3 placebo-controlled RCTs in naïve healthy adults are currently being conducted (or should be started soon) in low- and middle-income countries with limited access to temporarily authorized COVID-19 vaccines. The main features of this type of trial and the percentage of the population that have been, at least, partially vaccinated in participating countries, as a proxy of availability of temporarily authorized COVID-19 vaccines, are shown in Table 1.

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Table 1 Large phase 3 randomized placebo-controlled trials in healthy naïve ≥ 18-year-old individuals assessing COVID-19 vaccine candidates: trials to be started after 1 April 2021^a (data captured from the registries as of 16 November 2021)

Trial	Sponsor	Vaccine candidate type	Study start date	N	Last update	Participating countries (%) ^b
Trials already started						
IRCT20210303050558N1 ^c	Pasture Institute (Iran)	Protein subunit, conjugated ^d	25 April 2021	24,000	7 November 2021	Iran (65)
NCT04904549 PACTR202106588702901	Sanofi Pasteur (France)	Adjuvanted recombinant protein: monovalent and bivalent	26 May 2021	21,046 ^e	8 October 2021	Colombia (64), Ghana (7), Honduras (39), India (54), Japan ^f (79), Kenya (7), Nepal (29), USA ^f (68)
NCT04922788	Nanogen (Vietnam)	Protein subunit	7 June 2021	13,000	11 June 2021	Vietnam (66)
NCT04904471 PACTR202103845381761	WestVac (China)	Recombinant (Sf9 cells)	18 June 2021	40,000	2 November 2021	Indonesia (47), Kenya (7), Mexico (58), Philippines (30)
PACTR202105817814362	South African Medical Research Council	mRNA ^g	13 July 2021	14,000	3 November 2021	Botswana (32), Kenya (7), Malawi (5), South Africa (27), Swaziland (NP), Uganda (8), Zambia (2), Zimbabwe (23)
NCT05005559 IRCT20150303021315N24	CinnaGen (Iran)	Protein subunit	7 August 2021	16,876	5 October 2021	Iran (65)
NCT05096845 PACTR202107562417077	Livzon (China)	Fusion protein	25 August 2021	22,500	27 October 2021	Philippines (30)
NCT04847102	Walvax Biotechnology (China)	mRNA	27 August 2021 [16]	28,000	17 May 2021	Indonesia [16] (47), Mexico [16] (58), Nepal (29) [16]
Trials to be started						
NCT04852705	Shenzhen Kangtai Biologicals (China)	Inactivated (Vero cell)	May 2021 (estimated)	28,000	22 April 2021	Malaysia [17] (78), Philippines [17] (30), Ukraine [17] (28)
NCT04984408 ^h	International Vaccine Institute (UNDP)	Inactivated (Vero cell) ⁱ	1 October 2021 (estimated)	8,825	16 August 2021	Mozambique (15)
NCT05096832	Livzon (China)	Fusion protein	31 October 2021 (estimated)	10,722	29 October 2021	Pakistan (35)

NP, not provided; UNDP, United Nations Development Programme (Seoul, South Korea)

^aCOVAX delivered the first COVID-19 vaccines on 24 February 2021, and as of 8 April, more than 38 million doses have been delivered to 100 economies [13], whereas China had exported over 115 million doses by 1 April [14]

^bPercentage of the population that were at least partially vaccinated as of 16 November 2021 [15]

^cData from Iranian Registry of Clinical Trials

^dThis is the Soberana 02 (Cuba) vaccine

^eThe trial aimed to recruit 37,430 participants when it was started in the USA

^fAll American and Japanese sites have stopped recruitment, but are active

^gThis is the Moderna (USA) vaccine

^hThe control group will receive Flu quadrivalent vaccine instead of inert placebo

ⁱThis is a BBIBP-CorV (Sinopharm, China) vaccine

Only placebo-controlled RCTs that started after 1 April 2021 are described. These are trials that were likely started after, at least, some participating countries had the opportunity to access to a certain number of authorized COVID-19 vaccine doses. These trials are sponsored by local or foreign companies or organizations and are placed in four continents. Of these RCTs, two of them deserve a reflection.

First, the one to be conducted in eight Sub-Saharan countries is aimed to assess SARS-CoV-2 variants of concern (PACTR202105817814362). The trial has been approved by 12 local research committees in five participating countries and by the UCSF Human Research Protection Program institutional review board since the trial is sponsored by the US NIAID. The approved protocol states that, at the first set of vaccinations, 7,000 participants will be allocated to receive the two vaccine doses, whereas the other 7,000 will receive two placebo injections; some 2 to 4 months later, in a double-blind fashion, participants will be crossed over to receive two placebo injections or two vaccine doses. The protocol states that if an authorized vaccine becomes available, participants will have the option of being unblinded and receive the authorized vaccine. Unblinding is not reported in the information posted on the registries for the other trials mentioned in Table 1, except for the one to be discussed below.

Second, the trial sponsored by Sanofi Pasteur (NCT04904549) was started in the USA in June 2021. This trial should have not been approved neither by American institutional review boards nor by Japanese research ethics committees (RECs), since clinical equipoise was not present at the time the trial protocol was reviewed in these countries [18]. All US sites have stopped recruitment eight weeks after the trial was started, as did the Japanese centers shortly after. As happened in the Sub-Saharan trial mentioned above, participants can request unblinding. This trial has a number of recruiting sites in Africa, Asia, and Latin America. The conduct of this trial in Colombia raises ethical concerns, since with 64% of the population being at least partially vaccinated [15] and with an adult population of 69% of the total [19], it might have enough doses to vaccinate all adults.

All trials that are being sponsored by Chinese companies are being (or will be) conducted outside China. Having 82% of all Chinese population at least partially vaccinated [15], and being adults about 77% of the population [19], it is almost certain that any Chinese adult could have access to any available COVID-19 vaccine. So, no new placebo-controlled RCTs should be conducted in healthy naïve adults in China. All participating countries of these trials have a limited percentage of their populations partially vaccinated against SARS-CoV-2, so the conduct of these placebo-controlled RCTs is ethically sound. However, there are two exceptions. Thus, sites from Malaysia and Mexico should not participate since, with 78% and 58% of their populations partially or fully vaccinated [15], so no adult should have

difficulty getting vaccinated with a temporarily authorized COVID-19 vaccine. Recruitment to these trials should be stopped and participants should have the option of being unblinded and receiving a vaccine out of study something that is uncertain since there is no information available about it.

The same approach should be applied to local companies from Iran and Vietnam that are conducting placebo-controlled RCTs in their countries where 65% and 66% of their populations have been partially or fully vaccinated.

Finally, WHO-sponsored Solidarity Vaccine Trial (ISRCTN15779782) is an adaptive RCT [20] that was started in September 2021 with three COVID-19 vaccine candidates to be assessed vs placebo. These are Codagenix and Serum Institute of India live-attenuated virus vaccine (Covi-Vac); Medigen, Dynamax, and NIAID protein subunit vaccine (MVC-COV1901); and Arcturus mRNA vaccine (ARCT-154) [11].

Comparative immunogenicity RCTs in current COVID-19 vaccine candidates' development

Currently, there is a window of opportunity to conduct placebo-controlled RCTs in settings with limited access to authorized COVID-19 vaccines before immunogenicity trials are widely implemented. And this will happen once correlates of protection are accepted by the scientific community and regulatory agencies, something that has not happened yet although several preliminary reports on correlates of protection to a few vaccines have been published [21–25]. An important concern that has been recently flagged is that immunogenicity RCTs comparing a novel vaccine candidate with an authorized vaccine might find the issue of not having these latter available for the conduct of comparative RCTs, since the use of available temporarily authorized COVID-19 vaccines are restricted to fulfill public health needs [26]. Yet currently, there are three phase 3 immunogenicity RCTs assessing vaccine candidates vs the AstraZeneca vaccine in healthy adults: Valneva's inactivated virus vaccine (France, NCT04864561, $n=4,019$, started in April); SK Bioscience's protein subunit vaccine (South Korea, NCT05007951, $n=3,990$, started in August); and Medigen's protein subunit vaccine (Taiwan, NCT05011526, $n=1,020$, not yet recruiting). In addition, in September, one immunogenicity RCT (CTRI/2021/08/036074; $n=2,140$) started in India assessing Biological E's protein subunit vaccine (Corbevax) vs Covishield (the AstraZeneca vaccine manufactured by Serum Institute of India), whereas one month later, a RCT (NCT05077176; $n=7,300$) was started to assess Health Institutes of Turkey inactivated virus vaccine (Turkovac) vs Coronavac (Sinopharm inactivated vaccine).

Conclusion

The lack of enough available temporarily authorized COVID-19 vaccines to immunize all their naïve healthy adult populations is the main problem of many low- and middle-income countries regarding the COVID-19 pandemic. Until this huge public health issue is solved and unto the scientific and regulatory acceptance of correlates of protection for temporarily authorized COVID-19 vaccines, denying the conduct of ethically and scientifically sound placebo-controlled RCTs with novel vaccine candidates in countries with limited access to authorized COVID-19 vaccines prevents both having these countries involved in a type of research that is of high social value for their communities and building capabilities in vaccine development that could be critical in future pandemics.

Declarations

Conflict of interest The author declares no competing interests.

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