Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Current COVID-19 vaccine trials in high-income countries: are placebo-controlled trials ethical?

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Is it ethical to have a placebo arm in any COVID-19 vaccine trial at this point in time in high-income countries like the USA and those in Europe, where all adults have access to temporarily authorized COVID-19 vaccines? This has recently happened in the USA and might happen in other countries. Thus, on 1 June 2021, Sanofi reported that a placebo-controlled randomized clinical trial (RCT) assessing their new COVID-19 vaccine candidate had initiated recruitment in the USA (Table 1: A and B). How could investigational review boards (IRBs), the equivalent of research ethics committees (RECs) in Europe, have accepted as ethical starting a placebo-controlled RCT with widespread vaccination under emergency use authorization (EUA) ongoing? What should be taken into consideration when assessing whether a placebo-controlled RCT on a novel COVID-19 vaccine candidate is ethically appropriate in countries with no access limitation to temporarily authorized vaccines? Are there now other placebo-controlled RCTs running in these countries that could be ethically acceptable? We will discuss the Sanofi trial as an example in the discussion of this type of RCT.

The Declaration of Helsinki states that a new intervention must be tested against the best proven intervention(s); it allows the use of placebo "where no proven intervention exists" [5]. This is not the case with regards to temporarily authorized COVID-19 vaccines in the USA and Europe, where there are available vaccine doses for all adults willing to be vaccinated. The American Medical Association's Code of Medical Ethics states that where there are accepted interventions, the use of placebo arm requires "thoughtful ethical justification" [6]. The willingness of participants to having the chance of being on placebo for several months is irrelevant (Table 1: C).

The Sanofi trial protocol includes a section devoted to the "Rationale for placebo" stating that the use of a placebo group is ethically acceptable provided the trial is conducted "in settings where vaccine supplies are limited, where vaccines remain investigational and/or where public health recommendations for use of these vaccines have not been made" [1]. The appropriateness of a placebo group in any of these three situations was supported by a WHO expert group [7]. It could be argued that countries with limited access to COVID-19 vaccines fulfil the first of these three circumstances [8]. However, could any of these conditions apply in the USA and Europe? Sufficient temporarily authorized COVID-19 vaccine doses are currently available in both regions for the target population of the trial, i.e. adults and elderly. Furthermore, the Advisory Committee on Immunization Practices (ACIP) and the Centers for Disease and Prevention (CDC) in the USA, and public health authorities of all European countries, have strongly recommended the immunization of all adults and elderly in their jurisdictions. So, the only situation that might support the approval of the placebo-controlled RCT of the Sanofi COVID-19 vaccine candidates, is to consider them as 'investigational' and, as such, not 'proven' interventions [5] or 'accepted interventions' [6].

But, these temporarily authorized vaccines have become the standard of prevention against COVID-19. Currently, hundreds of millions of individuals have been vaccinated in the world, which is allowing their safety profile to be established at an unprecedented fast pace. And, furthermore, these vaccines have been shown to be highly effective in the real world [9–11]. The fact that from the regulatory perspective these temporarily COVID-19 vaccines are technically considered 'investigational' is irrelevant when assessing the design of placebo trials in this context. Fulfilment of the clinical equipoise principle is at the core of justifying the use of placebos in research. To be regarded as ethical RCTs, among other requirements, must fulfil this principle.

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Table 1
Main features and current situation of Sanofi large efficacy randomized controlled trial (NCT04904549)

Feature/Situation	Comment
A. Vaccine type	Adjuvanted recombinant protein vaccines. Monovalent: against Wuhan strain (D614); Bivalent: against Wuhan and Beta (B.1.351) strains [1]
B. Trial design	Phase 3, (observer) double-blind, placebo-controlled randomized controlled trial (1:1 ratio). Data aimed to support licensure of each vaccine candidate. Two-stage design (the trial started in the USA is assessing the monovalent vaccine). Event-driven. $n = 37\,430$ SARS-CoV-2 naïve and non-naïve adult and elderly participants. Two doses, given 21 days apart. One-year post second dose follow-up [1]
C. Trial inclusion criteria	One of the inclusion criteria that participants must comply with is that he/she "Does not intend to receive an authorized/approved COVID-19 vaccine despite encouragement by the investigator to receive the authorized vaccine available to them at the time of enrollment". None of the other inclusion criteria refers to individuals who have a medical contraindication to being vaccinated by available authorized COVID-19 vaccines [1]
D. Unblinding/Blinded cross-over design	"Participants will also have an opportunity to request unblinding to the study intervention at any time during the study if they decide to receive the approved/authorized vaccine. In addition, to minimize the risk of COVID-19, particularly severe COVID-19, to placebo participants in the study, a blinded crossover design is proposed wherein all participants will receive an active vaccine in an expedient manner in the event that one of the vaccine formulations evaluated in this study is deemed safe and effective" [1]
E. Geographical location of sites	Africa, Asia, Latin America and the USA [2]
F. Recruitment initiation	As of 11 June 2021, 21 sites in 14 USA states have started recruitment [3] 49–73% of all adults and 78–92% of the elderly in these 14 states have already received at least one COVID-19 vaccine dose[a] [4]

[a] Recruitment of participants will be increasingly difficult in the USA. It is reasonable to expect that most participants will be recruited in non-USA sites.

Clinical equipoise refers to a state of uncertainty within the scientific community about the merits of the interventions to be assessed in a trial. When an RCT fulfils this principle, participants will be allocated to an intervention that is not inferior to any available alternative [12]. If there is a well-established standard of prevention, as is true for temporarily authorized COVID-19 vaccines in many countries like the USA and Europe, this intervention must be used for the control group. The inclusion of a placebo group in testing novel COVID-19 vaccines is not ethically acceptable, since many participants will receive an inferior intervention to the available standard. This is also applicable to drug placebo-controlled RCTs: once one has proven to be effective in a given patient population, placebos are not ethically acceptable any longer, unless they are used when assessing add-on therapy. Thus, for example, as early as September 2020 data showed that systemic corticosteroids probably reduce 28-day mortality in severe and critical hospitalized COVID-19 patients, and thus they became the standard of treatment in these patients [13]. As a result, assessment of a new medication in these patient populations should require the conduct of RCTs of the experimental drug versus placebo (or usual care) in patients receiving corticosteroids. With this approach, a significant mortality benefit of IL-6 receptor antagonists has been shown in patients receiving systemic corticosteroids [14].

There are two other considerations in the Sanofi trial, which would also be present in other similar trials that could be started in high-income countries. Firstly, as the sponsor aims to have the vaccine candidates licensed, it has designed the trial to include elderly participants (Table 1: B). Close to 15 000 $\geq$ 60-year-olds are to be recruited [1], although it is reasonable to expect that only very few could be recruited in the USA (Table 1: E and F), this age group is at high risk of severe COVID-19, raising additional ethical concerns. Secondly, one might believe, as the trial protocol does (Table 1: C), that there can be some Americans that are not willing to be vaccinated with an available COVID-19 vaccine, but that would be interested in being involved in this placebo-controlled RCT. However, given the safety and effectiveness status of EUA vaccines and calls to use them from government and professional societies this is unlikely. Now that the trial is running in the USA, IRBs should consider its urgent cancelation in all USA sites.

Sponsors of prior trials have recognized the immorality of continuing a placebo-arm when efficacy is established. Thus, Pfizer/BioNTech, Moderna, Janssen and AstraZeneca have unblinded trial participants so placebo recipients could choose to be vaccinated with an available vaccine or on a blinded or unblinded fashion be vaccinated with the one that was being tested once it was shown to be safe and efficacious [8].

The only placebo-controlled RCTs with COVID-19 vaccine candidates that could be ethically acceptable in the USA and Europe, are those conducted in populations that are not included in the already temporarily authorized vaccines. This is the case for children, adolescents and pregnant women. Some of these placebo-controlled RCTs have, however, special design features that differentiate them from the Sanofi trial discussed here, and the other efficacy phase 3 RCTs conducted by other companies. So, in a few placebo-controlled RCTs conducted in adolescents, children (<12 year olds) and pregnant women, vaccine efficacy is a secondary endpoint, whereas immunogenicity and safety are the principal endpoints (NCT04649151, NCT04796896, NCT04816643, NCT04754594). All these 4 trials are conducted in the USA, and two of them in a few European countries.

In the large pivotal phase 3 efficacy placebo-controlled RCT sponsored by Pfizer/BioNTech in adults and elderly (NCT04368728), there was a subset of 12–15-year-olds. The good results obtained [15] permitted its temporarily authorization in both the USA and the EU in this age population. Since this vaccine could be authorized when other COVID-19 vaccines could be running their placebo-controlled RCTs in adolescents, sponsors of these latter trials bear this in mind and the possibility of choosing to be unblinded was included as an inclusion criterion: this happened with the trial run with the Moderna vaccine in 12–17 year olds (NCT04649151). This situation was not replicated when referring to placebo-controlled RCTs for 0.5–11-year-olds. Both Pfizer/BioNTech (NCT04816643) and Moderna (NCT04796896) started their trials in March 2021, and none of the protocols included any inclusion criterion referring to unblinding participants once a vaccine is authorized under an EUA. However, it should be expected that once the first authorized vaccine is available for this 0.5–11-year-old age group, participants will be unblinded so placebo recipients will have a chance to be vaccinated with the authorized vaccine.

In February 2021 Pfizer/BioNTech started a phase 2/3 placebo-controlled RCT in pregnant women enrolled at 24-34 weeks' gestation (NCT04754594). After delivery, all participants will be unblinded and those who were given placebo will receive the vaccine [16].

Finally, efficacy, placebo-controlled RCTs in $\geq$18-year-olds will be ethically acceptable in countries with unlimited access to authorized COVID-19 vaccines when assessing a new indication,

such as a booster dose to previously fully vaccinated individuals (NCT04955626, just started in the USA).

Sanofi's CEO and those of other eight pharmaceutical companies pledged that the safety and well-being of vaccinated individuals is top priority in the development of their COVID-19 vaccine candidates [17]. From the information included in the Sanofi trial protocol [1], this could be the case in settings with limited access to COVID-19 vaccines (Table 1: D), as can be currently found in many low- and middle-income countries [8], but not in the USA. This issue will be replicated if other placebo-controlled RCTs with other COVID-19 vaccine candidates could be started in high-income countries.

It would be important for the clinical trials community to know the reasons why several IRBs have approved the conduct of this placebo-controlled RCT in the USA, in the current situation of no restrictions on access for American adults and elderly to EUA COVID-19 vaccines.

Transparency declaration

Conflict of interest: the authors declare that they have no conflicts of interest. No external funding was received.

Author contributions

R.D.R., conceptualization, investigation, and writing – original draft. Both authors, writing – review and editing.

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