**Continuing use of placebo in covid-19 vaccine trials: should data quality be prioritised over participants’ rights?**

The race for covid-19 vaccines has been crowded and chaotic. There are 80 candidate vaccines in 212 human clinical trials as of February 2021. Eleven vaccines have received emergency use authorisation from one or more regulatory authority on the basis of interim data of varying quality. The safety and efficacy of all vaccines must be established through ethically and scientifically conducted research. The guidance of scientists and ethicists is needed in this.

However, the recommendations of the WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation (1) unequivocally prioritise data quality over participants’ rights and safety. Participants in trials of vaccines which have received emergency use listing or authorisation would be denied availabletreatment. Placebo-controlled trials would be permitted in poor countries that would be impossible to conduct in rich countries. If implemented, these suggestions would legitimise unethical research. A major beneficiary of such recommendations would be the vaccine industry.

The expert group – which includes the director general of the Indian Council of Medical Research and the chief scientist of the World Health Organisation -- makes three main suggestions to be implemented “while vaccine supplies are limited, available vaccines are still investigational or public health recommendations to use those vaccines have not been made”, in order to get the best quality of data in ongoing placebo-controlled trials of covid-19 vaccines, as well as in future covid-19 vaccine trials. No ethics-based argument is given in support of these suggestions. Nor is there any reference to the factors determining access to covid-19 vaccines across the world, which have a bearing on the ethics of this research.

The first recommendation of the expert group is in line with existing recommendations on emergency use authorisation (EUA). Since EUA is based on interim data with limited follow-up, ongoing placebo-controlled trials of vaccines that have received such authorisation should go on as planned. Long-term follow-up maintaining the placebo control arm is necessary to collect information such as how long immunity lasts, and whether waning protection could lead to vaccine-enhanced immunity. The group does not state how long this follow-up could be, but emergency use listing by the WHO in the context of a public health emergency is 12 months (2).

However, the authors go beyond asking for such trials to continue, to suggest that it is “ethically appropriate” for trial sponsors to *not* offer their vaccine under EUA to those in the placebo group of their trial. They also consider it appropriate to *refuse* to tell participants if they have taken the placebo, which would have allowed those on placebo to go elsewhere to take another vaccine.

Second, the expert groups proposes that even after some vaccines get full approval, new vaccines should be tested in in placebo-controlled trials. The expert group gives no ethical justification for this suggestion that would violate international research ethics guidelines requiring new interventions to be tested against the “best proven intervention” (3) or an “established efficacious intervention” (4). The group suggests that such trials could be conducted in countries with “limited or no access to a known effective vaccine”, following the “standard of care of the locality”. Such trials would be ethical if the vaccines tested are relevant to the country where they are tested and if once approved, the “community shares in the benefit”.

Third, since even large phase 3 trials of 40,000 participants will not pick up rare side effects, which emerge only after the vaccines are rolled out to millions of people, the expert group proposes placebo-controlled, cross-over trials of hundreds of thousands of people in order to monitor for rare side effects. Presumably such trials are advocated for all 11 vaccines currently being used and all future vaccines.

The expert group does not mention a WHO policy brief published in December 2020 on ethical considerations for placebo controlled trials for covid19 vaccines, though the one of the co-authors is common to both publications. This policy brief (2) holds that continuance of placebo-controlled trials of vaccines under emergency use authorisation is scientifically necessary and does not violate current ethical guidance documents. However, it recommends that as EUA vaccines become available to priority groups, participants from priority groups in trials should be given the option of being unblinded and taking the EUA vaccine. The policy brief also recognises that “The rights and interests of trial participants are also relevant to judgments about the ethics of continuing with these trials.”

**Emergency use designation and the use of placebo**

Standards for the use of placebo in clinical trials are given in the ethical guidelines of World Medical Association’s Declaration of Helsinki (3) and the Council for International Organisations of Medical Sciences (4). The use of placebo is by and large restricted to conditions for which there is no proven/efficacious intervention. Withholding an effective intervention is acceptable only if it is methodologically necessary *and* doing so will not cause severe or irreversible harm (3: para 33). By this standard, the use of a placebo when an effective vaccine against covid-19 exists would be unethical.

The question is whether emergency use authorisation or listing constitutes a proven or efficacious intervention. The policy brief holds that interventions under emergency use may not necessarily be “an established effective intervention” as understood in the DoH or CIOMS guidelines. Approval based on interim analysis of data may not necessarily meet trial stopping rules which would require unblinding and offering the proven effective intervention to the control group.

However, at least one vaccine manufacturer has done a complete analysis of the data, and reported an efficacy of more than 90%. And at least two manufacturers are now offering the vaccine to those in the placebo control, possibly because participants protested and even started dropping out of trials and getting lost to follow-up (5). Vaccines with EUA have been approved with two months of follow-up after the second dose with the understanding that all but the rare side effects should have been identified. Follow-up for long-term safety and efficacy could arguably be conducted by other methods including a crossover of placebo and intervention groups, and surveillance in the community for adverse events following immunisation, which is in any case critical for new vaccines.

In any case, the vaccines with EUA have been distributed to more than 180 million people as of February 2021. In such a situation, the distinction between EUA and full approval may not be significant to the hundreds of thousands of people worldwide who are participating in clinical trials of vaccines against covid-19. Those who gave their informed consent would have joined these trials out of a sense of altruism. The informed consent forms they signed are unlikely to have stated that any request for unblinding would be refused. If they are prevented from taking a vaccine that is being given to millions of people, and that *they would be entitled to outside the trial*, only because it is under EUA, their own wellbeing is clearly secondary to the needs of the trial, contrary to international guidelines stating that the goal of generating new knowledge “can never take precedence over the rights and interests of individual research subjects.” (3: para 8).

Equally important, the recommendation that researchers may refuse to inform a participant whether s/he received the placebo or investigational vaccine in order to take the vaccine elsewhere could be viewed as recommending a violation of participant’s right to withdraw from the study at any time, without fear of reprisal (3: para 26).

**Ethics dumping**

The expert group’s recommendation on the use of placebo in new trials after the approval of effective vaccines would lower standards for all future research in covid-19. It would actually open a door that was shut decades ago, at least officially, on the differential use of placebos in rich and poor countries.

The recommendation that new vaccines must be tested in placebo controlled trials in countries where vaccines are not available advises exploiting poor countries – and exposing poor people to harm -- in order to obtain data that the vaccine industry cannot obtain in rich countries, and towards approval in those rich countries. Inequities in vaccine access across countries are co-creations of the vaccine industry and rich countries. Availability of covid-19 vaccines has been restricted by the vaccine industry that prevents free use of technologies even for a public good, in a pandemic, and by rich countries which can make advance purchase agreements for more vaccines than they need (6). The expert group’s suggestion is vague as to what may or may not be tested in such placebo controlled trials – as long as they are of “potential relevance” to the country where the trial will be done, and vague about how the country should benefit, as long as it would “share in the benefit”.

The argument that placebo controlled trials once an effective vaccine is approved are preferable to other trial designs such as randomized, noninferiority trials is essentially one of convenience and cost. Placebo controlled trials need fewer participants, give clear results faster, and are therefore cheaper to conduct. With a number of vaccines coming close to full approval, there is no urgency, from the public health point of view, to speed up trials of new vaccines. However, this will be useful for industry.

There is a rich history of placebo-controlled trials that would be viewed as unethical in rich countries being conducted in poor countries, on the argument that the poor countries would also benefit, or simply because it is easier, cheaper and faster for industry (7). Criticism of such practices led to amendments in international as well as national guidelines restricting the use of placebo.

Finally, the expert group’s proposal to conduct large placebo controlled trials of approved vaccines to detect rare adverse events has no imaginable justification. The expert group does not explain why such trials are necessary preferable to upgrading existing monitoring mechanisms for recording and investigating adverse events following immunisation. One explanation might be that the data collected in these large placebo-controlled trials could be owned by the vaccine company conducting the trial.

**Research in the vaccine race**

Ethics of research in Covid19 vaccines cannot be separated from the manner in which the vaccines are being tested and rolled out in a pandemic. Vaccines have been tested without collaboration and coordination. The trial designs make it difficult to compare the vaccines.

It has also become clear over the last year that the course of the pandemic across the world is unpredictable. Populations that expected to be decimated by the virus have been the least affected – so far. The virus is constantly mutating, and some of the mutations have emerged that are much more infectious, rendering ineffective at least one vaccine that has already been administered widely. It is possible that minor modifications to these vaccines will become routine, as is done with the influenza vaccine (8).

While ethics demands that research in a pandemic should strive to obtain the best quality of data, randomised placebo controlled trials may not always be the ethical choice, and other methods of collecting data, such as equivalence trials, noninferiority trials, crossover trials, observational studies, and long-term follow-up of vaccinees for immunogenicity and safety contribute to the body of evidence.

Long-term follow-up of trial participants, and information from vaccine adverse events surveillance of the immunisation programme should be part of all vaccine studies. These need sponsors willing to conduct long-term studies and governments strengthening adverse event surveillance, and coordination between governments and between industries. This lack of coordination cannot be solved by placebo controls.

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