Societal interest vs individual rights

Post-trial access to COVID-19 vaccines to trial participants is fraught with several ethical dilemmas

Post-trial access (PTA) of an investigational new product is an ethical right of the clinical trial participants. Usually, the option of PTA is available to the participants after the clinical trial is completed. As treatments are available for most therapeutic areas, a delay in PTA is less likely to impact the patient's medical condition. However, given that no vaccines are available for COVID-19, PTA becomes critical for trial participants who received a control vaccine or a placebo. At the same time, this option also poses ethical dilemmas as these vaccines have only received emergency use approval (EUA) based on the interim data of two months' follow-up among participants.

For COVID-19 vaccines, long term, two-year post-vaccination follow-up data are essential to address uncertainties around a) the duration of the protective efficacy of the vaccines; b) the predictive value of neutralising antibody titres vis-à-vis the waning of immunity; c) the relationship between waning immunity and enhanced vulnerability to the disease following vaccination; d) the effectiveness of vaccines in diverse demographic groups; and e) long-term safety. This scientific requirement for long-term data is essential to support the regulatory assessment of risks and benefits for wider usage in the population. When a participant on a placebo or control arm is provided PTA to an approved COVID-19 vaccine, the opportunity to obtain valuable long-term data would be lost. However, giving priority to society over clinical trial subjects' interests violates ethical requirements for ICH Good Clinical Practice, which recommends that the rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over the interests of science and society. If the current phase 3 clinical trials of vaccines are continued as planned, placebo recipients would not get access to vaccines till 2023. Hence, sponsors and investigators have an obligation to explore options to balance the scientific need and ethical imperatives when EUA is given to COVID-19 vaccines.

Potential alternative trial designs could be: 1) Open-label design – placebo participants given approved COVID-19 vaccine and followed up 2) Double-blind crossover design - participants who initially received placebo will be given the approved COVID-19 vaccine and those who received the vaccine will be given the placebo. This design will allow a comparison of the efficacy between participants who received vaccines in the study with those who received the vaccine several months later. However, both the designs would require amendments to the protocol and informed consent documents, regulatory and ethics committee approvals, and re-consent from thousands of clinical trial participants. This would be a time-consuming process. Unless a majority of participants consent to continue in the double-blind crossover trial, the usefulness of data would be uncertain.

Another ethical concern would be equity of vaccine deployment for placebo group participants. Most of these young healthy participants may not be in high-priority vaccination groups e.g., health care workers, people with comorbidities. However, if placebo participants fall into a high-priority population, they should be given the vaccination.

A pragmatic approach is essential for resolving ethical issues related to the PTA of the COVID-19 vaccine!

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