Ethical considerations for protecting the options of subjects in primary epidemic vaccine trials

Arthur L Caplan,[1] Jerrold L Abraham[2]

The recent review by Monrad[1] presents several issues about secondary vaccine trials. It lays out the case in which a vaccine has been tested through phases I–III and is being deployed. *Subsequently* (emphasis added), consideration is being given to conducting 'trials for another vaccine for the pathogen'.

Monrad states: 'In summary, we may say that researchers have strong prima facie reasons not to conduct a secondary vaccine trial.'

Monrad discusses several factors meriting careful consideration about the need for developing and testing more than one vaccine: relative efficacy, length of immunity, adverse reactions (reactogenicity), ease of storage and administration, economic and logistical factors.

What is not addressed are the ethical duties that exist when there are competing phase III vaccine candidates for COVID-19. We have serious concerns about potential ethical inadequacies about these ongoing trials and those soon to begin.

Imagine an ongoing double-blind study has randomised volunteers, half will get placebo and half test vaccine. The volunteers get paid (US$100 per visit), and the participating institution gets paid (an undisclosed amount), per visit, dose, and so on by the Pharma company. Say a study is set to last 26 months to be able to study the antibody response intensity and duration, reactogenicity, the frequency of contracting COVID-19, severity, and so on. The informed consent says results will only be released at the end of the study. We are concerned about a scenario in which a volunteer starts a trial but then, before that 26-week study is completed, the Food and Drug Administration (FDA) approves another effective vaccine from another company.

Ethically, a subject is allowed to quit a trial at any time. But how might this work in a vaccine trial with multiple candidates?

If someone has received an experimental vaccine, they need to be informed of what to do should they wish to subsequently try an approved vaccine. But will companies and researchers with financial stakes in one vaccine readily disclose other options either initially or mid-trial?

If a subject got experimental vaccine, there may be more of a chance of having an adverse immune reaction to an additional vaccine that is approved. So they may not wish to do anything.

But if the subject received a placebo, they need to know that. So studies need to both notify recruits of this option and be able to rapidly unblind at subject request.

Thus, as part of all informed consents for phase three trials, participants need to be told that at the time some vaccine is approved, they will be told whether or not they received the test vaccine or the placebo so as to help participants make their decision as to whether to get another approved vaccine or not. This may well occur, since many subjects might feel it is in their personal safety interest to get a tested, approved vaccine more so than to continue as a subject in a double-blind test of an as yet unproven vaccine.

Following these duties may cause financial loss to the institutions getting paid and to the Pharma company that would have invested in the trial. This relates back to the huge general problem in what Monrad discussed with 'secondary' vaccine trials once a first one is approved by the FDA or WHO. But the ethical rights and duties to subjects override all other considerations. So, consent must fully address options and choices in recruiting and monitoring subjects in phase III vaccine trials.

[1]Division of Medical Ethics, NYU Langone Medical Center, New York, New York, USA
[2]Department of Pathology, SUNY Upstate Medical University, Syracuse, New York, USA

Correspondence to Dr Jerrold L Abraham, Pathology, SUNY Upstate Medical University, Syracuse, NY 13210, USA; abrahamj@upstate.edu

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