Some reflections on vaccine research ethics during COVID-19 pandemic

As of 15 December 2020, 52 candidate vaccines are under clinical evaluation for novel COVID-19 and one vaccine has received emergency use authorisation. However, vaccine research ethics is evolving and finding urgent solutions becomes paramount. In this article, we highlight such ethical issues in the vaccine trials especially those being faced by low-middle-income countries (LMIC).

1. Review by institutional ethics committees (IECs)

Even after months of pandemic, IECs in LMIC are finding it difficult to balance increasing number of clinical trials with timely review. Political pressure and unusual circumstances are compelling expedited reviews and approvals of seamless phase 1/2 and 2/3 trials. Although these processes provide early access to market, cutting short on vaccine development from 10 to 15 years to 10 to 18 months might compromise safety. Besides, assessment of ethical standards of new trial designs and ways adopted for data capture, recruitment and follow-up during pandemic requires time and vigilance and should not be hurried through.

For instance, some sponsors are omitting the clause, ‘the participant should not have participated in any clinical trials within the last 3 or 6 months’, from the exclusion criteria, that is leading to co-enrolment of participants in multiple trials and acceptance of multiple payments for participation, which violate ethics in research.

2. Research conduct

Smart devices are increasingly being used to address subject recruitment and follow-up during lockdowns. However, such devices are unaffordable for a significant number of people in LMIC. Even when they are provided by trial sponsors, some participants, such as sanitation workers, are not familiar with the language or interface. This prevents them from enrolment leading to increased inequalities and violation of distributive justice.

Second, virtual informed consent (IC) process is compromising of the participant-investigator relationship in LMIC where concepts of clinical research are poorly understood by vast majority. Ethical and unbiased involvement of participants in a clinical research requires face-to-face interaction and physical consent. Gaps in comprehension created by digitisation and the COVID-19 extraordinary state are rendering participants vulnerable because they may ‘unduly be influenced by expectation of benefit from vaccine’.

3. Trial monitoring

Periodic and for-cause on-site monitoring is a challenge during the pandemic. Off-site monitoring misses out discrepancies in study coordination, adverse event reporting and reimbursement. Further, assessment of adequate IC process and protocol deviations gets compromised.

4. Reporting

Use of electronic devices in LMIC with electronic case record forms and participant-reported outcomes might compromise quality of the data. Incomplete information affects the trial outcome and any third person involvement in reporting leads to breach in confidentiality.

Further, participation in multiple prophylactic trials also clouds the findings of the trials, increases error rates and has the potential of altering risk–benefit equation.

5. End of study

a. Disclosure of allocation arms

In a sponsor initiated study, the investigators do not have the information about treatment allocation. In a vaccine trial, it is important that this information reaches the participants. For instance, the trial participants of an approved vaccine candidate now would want to know their treatment arm as it affects their vaccination in future.

Likewise, it is important for investigators, IECs and regulators to address the anxiety of placebo recipients when sponsors submit the efficacy report. Undue delay in market authorisation defers placebo group from accessing a successful vaccine, for which they played a significant role.

b. Vaccine accessibility

Marketed vaccines further introduce issues of affordability and accessibility. Inadequate logistics like cold chain system and sceptical thoughts on vaccines add to political conundrums.

Use of systems for non-smart phone devices such as voice capture systems and use of symbols, mobile applications in local language for smart devices, acceptance of physical consent when electronic consenting is not feasible and consideration of audio or audio-visual recording of consent are some solutions to address issues concerning distributive justice, confidentiality and vulnerability.

To address ethical issues related to multiple enrolments, we suggest a common portal for registration of trial participants such that any multifold participation is identified. There should be also a limit for expedited reviews and approval of seamless trials. Time-tested ethical judgement should outweigh the necessity in order to prevent any future thalidomide-like tragedies. Second, a centralised scientific review committees that assess portfolios of proposed studies, logistical challenges and scientific priority, and provide inputs on key elements so that the trials target different disease pathways and that the population in each such study is diverse, are recommended.

Reduced but mandatory on-site monitoring by IECs may redeem concerns with off-site monitoring. IECs should see to it that data are not generated in undue haste. Further, at the end of the study, investigators and IECs should consider disclosure of allocation arms and post-trial access to placebo group if vaccine shows superiority. For repurposed vaccine trials such as BCG, sponsors should look for additional outcomes that target original indication under the same protocol from eligible participants. Although this is a scientific issue, ‘re-finement’ in the study design may ultimately ‘reduce’ the number of participants required.

For a global equitable access, it is necessary for LMIC to collaborate with international health organisations such as access to COVID-19 tools, led by WHO, and have an ‘international policy’ that addresses and balances the need with an external help from developed countries. Alternatively, licensing agreements between local manufacturers and innovator companies such as that between Serum Institute of India and AstraZeneca help in mass vaccine production and distribution at subsidised rates. Many countries are planning to roll out vaccines in a phased manner by prioritising population groups, which is a welcome development.

The COVID-19 pandemic and efforts to mitigate the impact have shown that simple steps when taken judiciously can take care of many ethical issues in research. Through this article, we have attempted to bring some novel ethical issues concerning vaccine trials to the attention of scientific community and proposed some solutions. A larger discussion on these issues is urgently needed.

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**REFERENCES**