Ethical considerations and clinical trials during a pandemic: A blessing with a burden

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Abstract

Any healthcare systems during a pandemic undergo tremendous pressure in pursuit of effective treatment to treat and limit the spread of the disease and its implications. Conducting clinical trials to find the potential therapy is the only way to battle the current coronavirus disease-2019 pandemic. The majority of the countries have joined the cause and are carrying out clinical studies in various capacities. As a result, the ethical committees have encountered a sudden inflow of a large number of trial proposals that have placed them under pressure. Although ethical committees play a vital role in protecting patient safety and preserving research integrity, they need to make sure the efficiency and integrity of review are preserved and the standards of review are not relaxed. Thus, the participants’ dignity is well guarded while keeping a close check on their safety.

Keywords

Clinical ethics, Legal aspects, Bioethics and medical ethics, Ethics committees and policy guidelines, Human experimentation

The novel coronavirus disease-2019 (COVID-19) pandemic has brought the world to a standstill and caused the panic of uncertainty. Life is oscillating between normalcy and unrest with the risk not completely averted. The healthcare systems, to surmount the public panic and unfortunate deaths are hurled into tremendous pressure in pursuit of effective treatment to treat and limit the spread of the disease and its implications.

Conducting clinical trials to find a potential therapy with the shortest turnaround time is the only way to battle any pandemic. As a response, immediate clinical trials in various capacities have been initiated globally and, needless to say, have imposed immense pressure on all stakeholders of the clinical trials, especially the ethics committees, as they are entrusted to uphold the participant safety and ensure the conduct of clinical trial with the highest integrity.

An ethically sound healthcare framework during these emergencies must balance patient care and intricacies of ethical issues to foster the equality of participants and equity in the distribution of risks and benefits. Although there are many challenges during the crisis, the moral pursuit of research remains the same: to reduce uncertainty and enable caregivers, healthcare systems and regulatory authorities to efficiently tackle individual and public health.1,2

Given the urgency of the pandemic, limitations such as fewer sample sizes, use of unvalidated surrogate end-points and lack of randomisation or blinding may be acceptable. These limitations may be the scenario due to the short learning window during the pandemic and the necessity to balance scientific rigour against speed seems inevitable. On the contrary, a smaller sample size and open-labelled, non-randomised trials may generate false indications that threaten to divert the scarce resources towards futile practices.3

For example, the results of the study entitled – ‘Ethics committee reviews of applications for research studies at one hospital in China during the 2019 novel coronavirus epidemic’, highlighted that the most frequent issues with the study proposals were lack of statistical basis for the sample size calculation, and unclear inclusion and exclusion criteria. The issues associated with informed consent forms, wherein the patients were not informed of the risks and that compensation was unreasonable. Out of 41

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applications, 31 of them needed modifications, which were identified. However, the review standards of the ethics committee were not lowered during the outbreak, ensuring quality results and patient safety.4

According to the World Health Organization (WHO), 2016 – Guidance for Managing Ethical Issues in Infectious Disease Outbreaks, all the clinical trials conducted during the pandemic must be registered in the clinical trial registry, and the pandemic does not serve as a reason to neglect such good clinical practices. Studies should be scientifically valid and add value to society and its health. Anticipated benefits should be reasonable with the acceptable risks, and most importantly the participant’s consent, rights, and overall well-being should be protected irrespective of the magnitude of the study.5 Also, the recruitment of pregnant women, elderly, minorities, children and other groups, who are considered to be vulnerable should not be excluded from the pandemic-related study unless there is robust scientific evidence to do so.6

**Research and social responsibilities:**

Five aspects of research that are necessary to enable the stakeholders to fulfil their research and social responsibilities: the importance of identifying key evidence gaps, rigorous design, analytical integrity, complete reporting and quality control and feasibility.7

**Importance of key evidence gap identification:** The most promising therapeutic and prophylactic alternatives from evidence-based medicine and trials should be given the highest priority, which has clinically significant outcomes. **Rigorous design:** Studies during emergencies often disdain randomisation or use surrogate end-points, and carry a high risk of producing inconclusive findings, which may lead to confusion and necessitate further evaluation. The clinical studies should be designed to detect clinically meaningful outcomes including both positive and negative results. **Analytical integrity:** Study designs should be specified in the protocol and the analysis should be carried out as per the prespecified descriptions. **Complete reporting and quality control:** Primitive publishing of positive findings in preprints before completing the studies, representing negligible non-positive results, and coupled with scarce-quality peer reviews, may lead to dissemination of low-quality evidence and thus complicate decision-making. **Feasibility:** Studies must be designed with the credible prospect of reaching their recruitment target and should be possible to be completed within the time frame where the evidence is still actionable.

Ethicist A. J. London at the National Academy of Medicine Committee reviewed the clinical trials of Ebola (2014–2015) in West Africa. He emphasised the need to initiate clinical trials early on in an emergency or outbreak to reduce preventable deaths. However, studies of poor quality should be condemned as their results are often misleading and may harm than do any good. He also mentioned, despite the lessons from the past, echoes of similar shortcomings are being repeated in the COVID-19 response; for example, the use of hydroxychloroquine in COVID-19, based on small studies, some with methodological shortcomings.8

Further, London emphasised the difference between the clinical outcomes from a drug and a vaccine and stated, ‘There can be a high tolerance for the side-effects in drug treatments because the drug is given to the relatively low number of people, and only to those who are sick unlike, vaccines, which are different, to be given hundreds of millions of healthy individuals. Any side-effect that could impact a minuscule percentage still might be affecting a hundred of thousands of healthy people. Therefore, the bar for tolerability and safety is higher in vaccines’.9

The research needed in low- or middle-income countries is often plagued with a scarcity of resources and poses a challenge in limiting the impact of the pandemic in terms of morbidity and mortality. The ethics committees and review boards of these countries are unprepared for such rapid and extensive review of proposals and trial progression. Added to these issues the research challenges such as expediting ethical and regulatory review, manufacturing, clinical trial support, that is, logistics, data sharing and affordable access. It is worthwhile to remember the lessons learned from the Ebola virus disease outbreak in the West African countries highlighting the ethical challenges faced such as shortcomings in terms of community engagement, access to basic health care and front-line worker’s welfare, which are also applicable to the COVID-19 pandemic.10

The global COVID-19 emergency has caused an increase in the clinical trials assessing the efficacy and safety of repurposed drug candidates to treat or prevent COVID-19 spread at an unprecedented rate. This resulted in excessive trial information flow and too many findings, which would throw healthcare professionals into a quandry. Thus, a model to unify and evaluate the clinical trials is necessary to avoid unnecessary duplication of efforts and preserve valuable resources.10

One such example is the initiative by WHO and its partners, ‘The Solidarity Trial’, which is an international clinical trial to aid in finding an effective treatment for COVID-19, enrolling almost 12,000 patients, as of October 2020 across 500 hospital sites worldwide spanning over 30 countries. This trial permits parallel studies to be conducted, which allows better data flow, sharing, preventing duplication of similar studies, efficient use of limited resources and improved accountability.11

However, the Solidarity Trial is not a double-blinded trial, but an adaptive one, in which unpromising drugs will be dropped and new treatment options will be explored as needed. Currently, hydroxychloroquine and
Lopinavir/Ritonavir arms of the trial have been discontinued on 20 June and 4 July 2020, respectively, as the interim results showed little or no reduction in mortality compared to the standard of care.11

During a pandemic as the panic is too high to immediately bring the situation under control, any slight oversight may compromise overall patient safety. The ethics committee needs to be more cautious and vigilant, as there may be an overwhelming inflow of research proposals, and that may lead to an unnecessary risk of exposing the study participants to futile interventions resulting in waste of resources. Therefore, the ethics committee’s role is very crucial especially during a pandemic to protect the study subject’s overall well-being and preserving the research integrity while the review process is expedited along with efficiency, and the standards of the review are never compromised.

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