

Clinical trials during the COVID-19 pandemic: Challenges of putting scientific and ethical principles into practice

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Abstract

Global pandemic of COVID-19 is a serious unmet medical need requiring clinical research into effective therapies. Clinical trials during pandemics of infections face complex challenges of putting scientific and ethical principles into practice. Some of these issues – selection of investigational product and participants, study design, assessment of efficacy and safety, ethics review, informed consent and publication, sample size, and publications – require in-depth consideration in planning and implementation of clinical trials during pandemics.

Keywords: Clinical trial, COVID-19, ethical, pandemic, scientific

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INTRODUCTION

Since December 2019, the world is facing a new humanitarian emergency due to a novel corona virus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus has caused a global outbreak of coronavirus disease COVID-19, which is characterized by severe progressive pneumonia, multi-organ failure, and death.^[1] At present, there is no effective therapy for COVID-19. Diverse therapies that include but not limited to lopinavir–ritonavir, remdesivir, danoprevir, darunavir–cobicistat, ribavirin and interferon beta, chloroquine, hydroxychloroquine, oseltamivir, umifenovir, pifrenidone, bevacizumab, fingolimod, carrimycin, corticosteroids, losartan, tetrandrine, aviptadil, thalidomide, sarilumab, mesenchymal stem cells, and vaccines are undergoing clinical trials (clinicaltrials.gov search March 21, 2020) or have been suggested for use based on limited evidence.

Against this backdrop, researchers conducting clinical trials face huge challenges of generating high-quality data and of putting scientific and ethical principles into practice a few of which are highlighted below.

SELECTION OF INVESTIGATIONAL PRODUCT

In a pandemic setting, investigational products (IPs) to be tried would be approved drugs that are repurposed. The selection of IP could be based on *in vitro* evidence of antiviral activity or plausible disease-modifying mechanisms. However, there would be concerns about the use of IP in the absence of additional preclinical evidence of efficacy and safety.^[2] Selection of investigational interventions for Ebola was based on the World Health Organization's (WHO) ethical framework-Monitored Emergency Use of Unregistered Interventions. This framework recommends that supporting data for the intervention's efficacy and safety should be available, at

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least from laboratory or animal studies.^[3] The recently concluded Lopinavir Trial for Suppression of SARS-Cov-2 in China (LOTUS China) COVID-19 was conducted based on its *in vitro* activity against SARS-Cov. In this trial, lopinavir–ritonavir plus standard care was compared to standard care alone.^[1] Lopinavir–ritonavir group did not show any benefit in primary endpoint – time to improvement – or secondary endpoint – 28-day mortality.

One reason for the lack of efficacy of lopinavir could be high concentration required to inhibit viral replication compared to serum levels found in patients treated with lopinavir.^[1] It would be tempting to conduct a trial with higher doses of lopinavir; the unknown safety profile of higher dose and duration beyond the approved prescribing information in seriously ill patients would be a strong deterrent. However, higher unapproved doses could be used if the rationale for use is justified based on the laboratory and animal studies. In Ebola proof-of-concept trial, the investigators used *in vivo* and *in vitro* data on favipiravir activity against Ebola and pharmacokinetics in uninfected mice and humans to calculate target plasma concentration and to justify the need for higher dose of favipiravir compared to the approved dose for influenza.^[4]

SELECTION OF PARTICIPANTS

In an outbreak setting, clinical trials usually include patients who are most severely affected. LOTUS China trial^[1] included adult patients 18 years of age or older, with confirmed SARS-CoV-2 infection, suffering from pneumonia and SARS.^[1] In contrast, French clinical trial of hydroxychloroquine and azithromycin in COVID-19 included hospitalized patients who were asymptomatic or suffered from upper or lower respiratory infection due to SARS-CoV-2.^[5] The favipavir study included adult patients diagnosed with COVID-19 pneumonia but excluded critical patients whose expected survival time was <48 h.^[6] This study showed a significant clinical recovery in patients who suffered from mild COVID-19 and who were not critically ill.^[6] Late recruitment of patients in infection, who had considerable tissue damage, could be a possible reason for the failure of lopinavir.^[1] *Post hoc* subgroup analysis of patients treated within 12 days after the onset of symptoms showed accelerated clinical recovery and reduced mortality compared to those treated later.^[1] This means that the investigator should make efforts to include COVID-19 patients with a shorter duration of illness. Early recruitment of patients and rapid initiation of treatment would, in turn, require quick turn round of laboratory data and availability of site staff at odd times to complete the clinical study procedures for enrolling patients in the trial.

Exclusion of children could be justified as the incidence of COVID-19 is very low among children. However, in a condition such as Ebola, which has high mortality in children under 5 years, excluding children would compromise trial acceptance.^[4,7] As dose-finding or tolerability data in children were not available for favipiravir, the children were given weight-based doses based on the adult dosage in clinical trial of favipiravir in Ebola, for which safety data were available. Although pregnant women suffering from Ebola had a higher case-fatality rate compared to nonpregnant women, the pregnant women were excluded from this trial due to the potential risk of embryonic teratogenicity and lack of insurance.^[7]

In clinical trials of COVID-19, it would not be ethical to exclude patients with comorbidities, for example, hypertension and diabetes mellitus or restrict concomitant treatment, which could be part of standard care for SARS, for example, oxygen, noninvasive and invasive ventilation, antibiotics, vasopressor support, renal replacement, corticosteroids, and extracorporeal membrane oxygen.^[1]

Selection of participants for clinical trials of COVID-19 requires in-depth attention as it influences the efficacy evaluation of a therapeutic intervention and has impact on wider public use of such intervention.

STUDY DESIGN

It is ethically unacceptable to expose clinical trial participants to risk if the study is not designed to provide valid results.^[3] Hence, methodology – randomization, blinding, and placebo use – for a clinical should be rigorous to enhance the societal value and the scientific validity.^[2,3] However, insisting on randomization in clinical trials of severe epidemics would create a conflict between individual health and societal interests. Randomization would preclude the autonomy of patients in making a choice of therapy.^[2,4,7]

Carazo Perez *et al.* who conducted the clinical Ebola trial recommend that individual patient's interests must prevail over reliability of trial methodology when the patients face a high risk of death.^[7] In a pandemic scenario, high number of serious patients presenting simultaneously and high mortality rate make random allocation of patients from within the same family or location to receive or not receive an experimental drug, ethically unacceptable.^[4] Furthermore, critically ill patients would find randomization procedure difficult to understand. It would be considered unethical and impractical to conduct randomized controlled trial (RCT) asking the patients or family members to consent

to standard care when a potentially beneficial therapy is available. For example, in LOTUS China open-label RCT, families of 31 patients (8.6%) did not give consent.^[1] In the Ebola trial, the investigators decided to conduct single-arm open-label nonrandomized trial, in which all patients received favipiravir along with standardized care.^[4,7] The investigators used historical mortality data to define efficacy endpoints – target mortality threshold – a priori, which was valuable in deciding whether to stop or continue the trial and to guide analysis and interpretation of the data.^[4] Such an approach could improve the utility of efficacy information from nonrandomized trials.

The WHO has planned SOLIDARITY – a large global trial of four drugs – remdesivir, chloroquine and hydroxychloroquine, lopinavir–ritonavir, and lopinavir-ritonavir plus interferon-beta.^[8] Its simple design allows the physician to recruit a confirmed case of COVID-19 after obtaining informed consent and to administer any of the four drugs locally available as per randomization by the WHO. The physicians are required to enter patient's data at randomization and at outcome assessment – recovery or death, the duration of the hospital stay, and requirement of oxygen or ventilation.

Due to the potential for transmission of infection and infection control restrictions in hospitals, paper case records forms cannot leave the clinical trial site. Hence, the use of scanned documents or electronic data capture should be preferred.

EFFICACY ENDPOINTS

COVID-19 trials were not blinded, and investigators were aware of treatment assignment. Hence, there was a potential for information bias in the assessment of clinical endpoints. However, there are also challenges in evaluation of objective endpoint – reduction of viral load. The LOTUS China trial was initiated early in the evolution of COVID-19 when viral testing was probably not fully characterized. Of 199 patients, 69 (35%) who were screened positive for SARS-CoV-2 by respiratory tract sample tested negative at the day 1 visit by the oropharyngeal swab.^[1] In addition, throat-swab specimens have lower viral loads than nasopharyngeal samples.^[1] This variability in viral testing could affect the evaluation of primary efficacy endpoint.

SAFETY ASSESSMENT

The assessment of safety of IP is an important component of any clinical trial. In patients suffering from SARS, severity of disease, use of variety of medical procedures,

underlying comorbidity, and use of concomitant treatments make detection of potential adverse effects of IP complex and difficult. In Ebola studies, the investigators monitored the patients for adverse events (AEs) not corresponding to symptoms of Ebola virus disease and focused on AEs of favipiravir described in the previous trials of influenza infection.^[7] In the LOTUS China study, gastrointestinal AEs were more common in lopinavir–ritonavir group than in the standard-care group.^[1] The incidence of serious AEs was lopinavir–ritonavir group: 20% and standard-care group: 32.3%. There were four gastrointestinal SAEs in the drug group. All deaths were assessed by the researchers to be unrelated to the drugs.

SAMPLE SIZE ESTIMATION

Clinical trials during epidemics are initiated as a rapid response to public health emergency when there is limited information about clinical outcomes making estimation of sample size difficult. In the LOTUS China trial, the initial sample size was 160, assuming that the median time in the standard-care group was 20 days, and difference in median time to clinical improvement would be 8 days, and 75% of the patients would reach a clinical improvement.^[1] When planned enrollment of 160 patients was completed, the investigators realized that the trial was underpowered and decided to continue enrollment.^[1]

ETHICS COMMITTEE APPROVAL

The need for rapid action to conduct clinical trial of an infectious disease outbreak will require expedited review of the study proposal by the ethics committee (EC), which will have limited information to evaluate risk–benefit ratio of IP in participants who are vulnerable. The EC can review clinical research proposal during epidemic outbreaks through an expedited review or unscheduled full committee meetings.^[9] Hydroxychloroquine trial was approved by the French EC within 1 day of submission.^[5]

If face-to-face meetings are not possible, virtual or teleconferences should be attempted. If members of local ECs cannot participate in meeting due to the emergency, the ethics review may be conducted by any other registered Indian EC. The EC should ensure that participant selection is fair and there are no additional burdens imposed on research participants.^[9] The EC should conduct ongoing risk–benefit assessment. Setting up Data Safety Monitoring Board could be considered for frequent review of data for monitoring quantum of risk.

In an Indian situation, there is a big difference between standard care for critical illness available in private and

public hospitals. As trials conducted in severe COVID-19 will require robust intensive care support, they are likely to be conducted in private hospitals. This would deprive socioeconomically disadvantaged who visit public hospitals from getting benefits of participation in trial. It would be desirable to conduct a centrally supervised trial by a government agency to allow all COVID-19 patients to be considered for enrollment in clinical trial irrespective of their socioeconomic status.

The EC is responsible for closely monitoring the conduct of clinical trial. However, this would be difficult as the study conduct processes – consent, recruitment, follow-ups, clinical procedures, and serious AEs – would be managed by the investigator and her team rapidly while attending to the critically ill patient. Furthermore, the EC members cannot physically meet the patient or the site in a potentially infectious environment. A review of scanned documents could be an option. Otherwise, the monitoring should be conducted when the study is completed to ensure that the investigator team complied with the protocol and good clinical practice during the conduct of the trial.

When a study is conducted in community setting, frequent and regular communication with community is vital.

INFORMED CONSENT PROCESS

In a setting of outbreaks, obtaining valid informed consent from vulnerable participants with impaired decision-making capacity would be extremely demanding. As the consent process would be conducted by the investigator team wearing full personal protective equipment, the communication would be problematic.

The EC could assess the study proposal before the emergency has occurred and decide who could be an acceptable Legally Acceptable Representative (LAR) in the absence of authorized LARs.^[9] If it is not possible to obtain consent of the participant or LAR, for example, family members infected and hospitalized, the informed consent could be administered to the participant/LAR at a later stage when the situation improves. However, this must be done only if the EC has given prior approval.^[9]

PUBLICATION OF RESULTS

The investigator has fundamental moral obligation to share available results as soon as these are adequately quality controlled for release.^[3] There is high social, media, and political pressure to disseminate the results

without waiting for publication in scientific journals. The researcher can post preliminary reports of clinical study on electronic platforms such as medRxiv preprint server, without waiting for peer review. MedRxiv cautions that such preprints should not be relied on to guide clinical management and should not be considered by the news media as proven information. However, as soon as the results are available in public domain, medical practitioners, society, and media will put pressure on the government to support the use of any therapeutic intervention reported which appears to benefit the seriously ill patients. The government agencies have a responsibility to ensure that such rapid publications are reviewed judiciously, and the new therapy is used rationally.

CONCLUSIONS

Humanitarian emergencies such as COVID-19 outbreak pose complex scientific and ethical challenges for the clinical researchers, which must be addressed to successfully implement a clinical trial during a pandemic.

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Conflicts of interest

There are no conflicts of interest.

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