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Challenges in operationalising clinical trials in India during the COVID-19 pandemic

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The global outbreak of COVID-19 has had a substantial effect on the conduct of scientific research worldwide. More than 2000 trials registered on ClinicalTrials.gov were terminated because of the challenges of doing clinical research during the pandemic.[1] Our research group from the George Institute for Global Health initiated three trials (NCT04483960),[2,3] including the hydroxychloroquine prophylaxis evaluation (HOPE) trial in India,[2] but encountered several challenges that were unique to India in terms of the operationalisation and execution of these trials. This Comment provides insight into these challenges and presents possible solutions to facilitate the conduct of clinical trials during the current COVID-19 pandemic and during future pandemics.

To facilitate research during the COVID-19 pandemic, the Indian Council of Medical Research approved a joint review of multicentre research by one main designated ethics committee to fast-track decision making.[4] However, in practice, individual hospital ethics committees rarely accepted previous review by the central ethics committee. Among the 42 sites participating in the COVID-19 trials coordinated by the George Institute for Global Health, only three accepted central ethics committee approval. The median (IQR) duration between submitting applications and ethics committee approval was 59·5 (28–73) days, with substantial delays introduced by infrequent meetings, adherence to the traditional format of initial scientific subcommittee review before full ethics committee review, and the mandate for legal approval for clinical trial agreements before considering the ethics application. Individual ethics committees raised

	Recommended strategies
Regulatory and ethics considerations	
Delays in approval from regulatory agencies	Prioritise investigator-initiated trials of public health importance Expedite review of academic trials that address questions of public health importance Streamline regulatory approval processes with prescribed timelines for review of proposals Eliminate redundancy in approval processes
Delays between ethics submission and approval	Trial sites and ethics committees to comply with the Indian Council of Medical Research guidelines to facilitate urgent public health trials, including accepting approvals from a central ethics committee
The unfamiliarity of ethics committee members with the Indian Council of Medical Research guidelines for the conduct of clinical trials during a pandemic	Education of ethics committees and introduction of uniform processes
Infrequently scheduled ethics committee meetings	Schedule ethics committee meetings virtually Ethics committee secretariat to prioritise urgent public health trials for expedited review or emergency meeting of full committee
Site-level considerations	
Issues with site set-ups and delegation of site-level responsibilities	Hospitals to recognise research as a public health need and develop internal capacity
Lack of previous experience with trial conduct and digital platforms	Regular good clinical practice training and simulation activities for the core trial staff Incorporation of research into medical and nursing curricula Training on use of electronic case report forms
Limited scope for site visits by trial management team due to travel restrictions	Trial supervision by the local site-level investigators with remote virtual monitoring
Source data verification and ensuring data integrity	Real-time data entry into electronic case report forms with validation rules Use of virtual tools for source document verification
Lack of participation by remote and smaller health units	Expand the pool of potential research sites with oversight by regional established clinical trial sites
Misinformation	
Premature recommendations for treatments without scientific data	Frame evidence-based recommendations Responsible reporting in the media
The reluctance of clinicians to participate in randomised controlled trials	Prioritise urgent public health research by apex medical bodies, such as the Medical Council of India Advocate for the importance of high-quality trials as the mechanism to establish the safety and efficacy of interventions Information generation and myth-buster programmes

Table: **Challenges and potential supportive strategies for the initiation and conduct of clinical trials in India during the COVID-19 pandemic**

different queries, the responses to which were not considered until the next formal meeting. The need for approval for international collaborative trials from the Health Ministry Screening Committee was not waived, which added further delays to trial commencement. Many ethics committees were unable to differentiate between academic-led and industry-led trials. This lack of differentiation resulted in demands for approval from the Drug Controller General of India, despite the New Drugs and Clinical Trial Rules 2019 granting exemption for non-regulatory academic trials of repurposed drugs.[5] There were also several important site-level challenges. Despite the existence of a common forms template from the Indian Council of Medical Research for submissions for ethical approval,[6] all sites insisted on receiving applications in their respective templates, adding to delays in approval.

The extraordinary caseload in India and the reduced per capita workforce made the organisation of a combined-site start-up meeting for all sites unfeasible. Persistent electricity outages, poor internet connectivity, and the large digital divide were some of the additional obstacles that the trial team had to negotiate at sites. Internet quality was inconsistent, meaning that accessing study websites for randomisation and entering data into electronic case record forms was difficult. Participants were reluctant to comply with the follow-up needed in clinical trials. For instance, electrocardiograms were recommended as a safety procedure in the HOPE trial. About 19% of the participants refused the procedure, because of pandemic-imposed travel barriers or general discomfort with having tests at health-care facilities during the peak pandemic period. The stigma associated with testing positive for or being at risk of acquiring COVID-19,[7] and the reported discrimination of affected individuals, was another barrier to recruitment to trials and to the assessment of primary outcomes.

For more on the **RECOVERY trial** see https://www.recoverytrial.net/

There was mixed messaging from various bodies—including leading research organisations—about the efficacy of COVID-19 treatments, despite an absence, at that stage, of scientific evidence supporting their use. For example, around the commencement of the HOPE trial, the Indian Council of Medical Research issued advisories recommending hydroxychloroquine for health-care workers as prophylaxis against SARS-CoV-2 infection on the basis of in-vitro and observational studies,[8] while simultaneously advocating proof-of-concept studies to guide recommendations. Calls from the medical community—including an approach by the George Institute for Global Health, the sponsoring organisation of the HOPE trial—to the Indian Council of Medical Research for a randomised controlled trial of hydroxychloroquine went unheeded. Direct consequences were uncertainty in the minds of health-care workers, and a loss of clinical equipoise when enrolling participants into the control group of a trial, because clinicians felt legally vulnerable if hydroxychloroquine was not prescribed to health-care workers. Funding was also affected, with one funding agency citing the Indian Council of Medical Research advisory as a reason not to provide funding support for the HOPE trial.

In addition, 8 months into the HOPE trial, the product advisory for Covaxin (Bharat Biotech, Hyderabad, India)—the COVID-19 vaccine developed in India—advised against the concomitant intake of chloroquine analogues, without providing supporting data. Therefore, health-care workers who were enrolled into the intervention group of the trial could not continue taking hydroxychloroquine if they had received Covaxin, which further stalled recruitment and trial conduct.

Recommended strategies to facilitate the conduct of clinical trials in India are provided in the table. As part of future pandemic preparedness, India needs a coordinated strategy to facilitate pragmatic, investigator-led clinical trials—such as the UK RECOVERY trial—to rapidly answer questions of public health importance.

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