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## Clinical Trial Conduct During COVID-19 times

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# Addressing challenges due to the COVID-19 pandemic – A site and investigator perspective

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**Abstract**

The coronavirus disease-19 pandemic has affected all aspects of health care including clinical research, as the focus of health-care systems has shifted to maintaining essential care. The impact on clinical research has been profound. In this article, we have enlisted the multiple challenges faced by investigators and sites in carrying out clinical research activities during this crisis and the steps which can be taken by them to reduce the impact of this evolving pandemic on clinical research.

**Keywords:** Challenges, clinical research, pandemic

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## INTRODUCTION

The current coronavirus disease (COVID-19) pandemic has affected 215 countries across the world, infecting nearly 5.5 million people and causing over 3 lakh deaths.[1] The impact of the pandemic has been catastrophic, affecting individuals, populations, and systems at multiple levels. The focus of health care has shifted to provision of patient care while fields like education and research have taken a back seat. In this article, we examine the impact of the pandemic on clinical research activities at institutes and identify measures that can be taken to address research activities within the existing constraints, even as the pandemic continues to evolve.

## MEASURES TAKEN TO MITIGATE THE IMPACT OF THE PANDEMIC

### Country-level measures

Most countries have imposed various degrees of lockdown, leading to restrictions on the movement of individuals. This has been in an attempt to flatten the curve so as to get the health system in readiness for patient care.

### Hospital-level measures

Considering that hospitals are likely to be hotspots of infection and to decrease crowds, patients have been asked to avoid all nonessential hospital visits. Most hospitals have curtailed outpatient appointments and have replaced them with telephonic or videoconferencing alternatives. In addition, the working patterns of hospital staff have changed dramatically. First, the workforce has been decreased – partly as a deliberate measure – to allow social distancing, to minimize the number of health-care workers getting exposed at any point, and to allow periods of rest to prevent fatigue and burnout in a stressful situation, but also in part unplanned – due to logistics of travel and inability to reach the workplace or due to staff being unwell or quarantined. Second, there has been restructuring of staff within hospitals so that research and other support staff

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can help with the maintenance of essential clinical services. Third, diagnostic facilities such as imaging and laboratory services have minimized nonurgent testing.[2]

## IMPACT ON PATIENTS AND PARTICIPANTS

The overall impact of these measures on clinical research is that patients are unwilling and/or unable to visit hospitals, and even if they do, the available infrastructure is not able to support research activities. The limitations on movement and transport have also affected other aspects of research – for example, investigational products (IPs) cannot be delivered to research sites and sponsor or contract research organization (CRO) teams cannot conduct monitoring or other site visits.

## GUIDELINES TO ADDRESS CONDUCT OF CLINICAL RESEARCH DURING AN OUTBREAK

Several organizations such as the United States Food and Drug Administration, the European Medicines Agency, and, closer home, the Indian Council of Medical Research have issued guidelines to deal with deviations and modifications to research activities.[3-5] The key message from these guidelines is that for any ongoing or new research during the pandemic, participant safety is paramount, adherence to good clinical practice is essential, and that integrity of study data must be protected.[6]

Table 1 enumerates the challenges faced by different stakeholders in the clinical research process during this pandemic. In this article, we specifically focus on how investigators and clinical research sites can address research activities in this situation.

## SITE AND INVESTIGATOR RESPONSES DURING THE COVID PANDEMIC

These are some of the measures which can be instituted during the pandemic to facilitate research activities.

### Postponement of new studies and changes in ongoing studies

Sites must consider postponing the initiation of new trials and withholding recruitment on ongoing trials to the extent possible. For participants in ongoing studies, investigators must make a benefit–risk assessment for the individual patient and see if the trial medication can be delivered to the patient, a family physician locally available can give the medication, or if a local nursing home may be willing to treat the patient. For life-threatening conditions or when the trial is the only way the patient can access the medicine, every attempt must be made to help the patient. For example, one of the authors (NG) has an ongoing trial in animal bites where completing all doses of the vaccination is crucial as rabies is a disease that is 100% fatal. On the other hand, in oncology, because the outcomes of COVID may be worse in immune-suppressed individuals, the investigator can take a call on either going ahead with the study treatment or deferring it, particularly when the treatment can lead to an immunosuppressed state (trials involving high-dose steroids or immune checkpoint inhibitors) and therefore expose the patient to greater risk.[3] After discussion with the sponsor, less essential blood draws and nonessential visits can be done away altogether to ease the burden on both the investigator and patient.

### Ongoing studies

For each ongoing trial, the investigator must identify essential and nonessential aspects. Of these, the nonessential aspects (e.g., routine site visits or monitoring) can be delayed. For essential aspects, such as response assessments or laboratory tests, alternate methods need to be established. For example, one could adopt virtual or telephonic assessments or authorize laboratories and centers close to the participants' residence to facilitate testing and response evaluation. If an in-person visit to the site is deemed mandatory, precautions should be taken to minimize the risks to participants. Participants who are considered high risk for COVID complications (elderly and those with comorbidities) should be excluded. The timing of the study visit can be modified to coincide with a visit for routine clinical care. There should be a separate waiting room for research patients. Hospital entrances, waiting rooms, and pathways should be clearly demarcated so that research subjects do not interact with potentially infected patients.

### Challenges with investigational products

There may be issues with access to IPs. Sponsors can use emergency courier services to arrange delivery of high-priority research medications to sites. Direct shipping to participants can be considered to circumvent the need for site visits. To decrease the frequency of visits, larger quantities of IP can be issued at each visit.

### Addressing protocol deviations and violations and serious adverse events

Because participants are likely to have delayed or missed visits and assessments, protocol violations will increase. These need to be informed to the institutional review board (IRB). Investigators should have a dialog with the IRBs to address these and follow revised IRB standard operating procedures on protocol deviations and violations. Various changes in the protocol and the possibility of infection with COVID may alter the risk–benefit to

**Table 1: Challenges faced by clinical research stakeholders during the coronavirus disease-19 pandemic**

| Stakeholder | Challenges |
|---|---|
| Investigator | Shifting focus to patient care rather than research |
| | Giving up research to a greater or lesser extent to focus on patient care |
| | Difficulty in investing time and energy in ongoing studies |
| | Unwillingness to take up new studies - COVID or non-COVID |
| | Fear and anxiety of themselves contracting the disease while treating patients |
| | Constant protocol deviations/violations and repeated communications with IEC |
| | Skeletal staff to handle studies due to lockdown |
| | Sicker patients due to lockdowns and inability of the patient to meet the investigator to seek medical attention |
| | Colleagues or dedicated research staff testing positive for the disease |
| Institution/ research center | Shifting the focus to COVID-19/pandemic care rather than research |
| | Need to do COVID-19-specific research in the face of mounting pressure for patient care |
| | Allocation/re-allocation of the already-scarce resources to research particularly in low- and middle-income countries |
| | Taking decisions on stopping research altogether |
| | Payment of research staff |
| | Laying off dedicated research staff |
| | Employees testing positive |
| Patient/ participant | Difficulty in traveling to the site due to the lockdown |
| | Risk of contracting COVID-19 during the travel or while at the hospital if able to travel |
| | Need to travel as the study may be the only source of access to medication for that disease condition |
| | If the study entails hospitalization, additional testing for COVID-19 prior to IP administration |
| | Occurrence of COVID-19 while on a research study and additional burden of disease including quarantine, hospitalization, and isolation for even mortality |
| | Caregiver burden due to the pandemic |
| | Anxiety, mental distress in the face of the pandemic, and difficulty in accessing the investigator |
| Ethics committees | Limited or no support staff due to the lockdown |
| | Need for modifications in SOPs due to the pandemic to conduct virtual meetings |
| | Inherent challenges of virtual meetings |
| | Need to stay updated with changes in IEC and regulatory guidance released by diverse agencies |
| | Decision-making to prioritize COVID studies over non-COVID studies |
| | Pressure from investigators and administrators for rapid turnaround time for COVID projects |
| | Difficulty in decision-making due to uncertain risk-benefit assessment of experimental medications |
| | Difficulty in causality assessment of SAEs if the hospitalization (SAE) is due to COVID-19 in an ongoing study |
| | Need for more frequent meetings |
| | Expedited reviews of COVID-19 studies |
| | Greater difficulty for IECs that still work with paper-based systems |
| | Employees testing positive |
| Regulator | Bringing out guidance documents in time that are relevant to the country and its context |
| | Pressure to approve experimental medication on a fast track basis |
| | Pressure to waiver clinical trials in favor of compassionate or emergency use |
| Sponsor/ pharmaceutical industry | Rapid development of protocols of drugs involving uncertain risk-benefit assessment of experimental drugs or repurposed drugs |
| | Keeping track of evolving guidance |
| | Sudden investment of finances or shifting finances to drugs that may be effective for SARS-COV-2 |
| | Protocol deviations and violations at study sites |
| | Resistance from investigators and institutions to new studies including non-COVID studies |
| | Difficulty in IP shipment and expired IPs at sites |
| | Frequent reporting of SAEs |
| | Layoffs |
| | Employees testing positive |
| | Rapid assessment of uncertain and evolving risk-benefit assessment of experimental drugs or repurposed drugs |
| | Setting up of taskforces to monitor experimental drugs |
| | Increased SAEs in the face of the pandemic |
| | Political pressure for drug approvals |
| | Public anger/mistrust due to lack of drugs that work and lack of a vaccine candidate and changing risks and benefits |
| | Employees testing positive |
| | Delay in drug development processes |
| Contract research organizations | Investigators unwilling to invest time and energy in new studies |
| | Difficulty in investing time and energy in ongoing studies |
| | Protocol deviations and/or violations in ongoing studies |
| | Need to keep pace with the evolving guidance |
| | Remote monitoring rather than onsite monitoring |
| | Resistance from investigators to devote monitoring time |
| | Layoffs due to the economic downturn |
| | Difficulty in couriers and IP shipment and other trial logistics |

IP=Investigational products, COVID=Coronavirus disease, IECs=Independent Ethics Committees, SOP=Standard operating procedure, SAE=Serious adverse event

participants, which necessitates changes in the informed consent. This new information needs to be shared with participants telephonically and documented in the source files. For regulatory studies, investigators and sponsors can discuss with regulatory authorities for flexibility in conducting/completing the study. Site personnel can be given remote access to electronic medical records to enable them to complete study-related documentation. Reporting of serious adverse events should continue as per standard requirements. In addition, if the study participants develop COVID, this should be reported to the sponsor and the ethics committee, and causality (relatedness to study intervention) should be determined. This is essential as some interventions may increase the susceptibility of the participant to COVID.

### Study timelines

The changes listed above may necessitate additional research funding. In addition, slow accrual will result in prolongation of study duration. This needs to be intimated to and approved by the IRB. Similarly, reimbursement for study-related expenses may be delayed – investigators should prioritize this to avoid inconveniencing participants. They should also establish communication with sponsors for funded studies to find pragmatic solutions to accrual and funding. For multicentric studies, sponsors can come up with a central plan of modifications to the trial so as to keep all centers on the same page.

### Addressing psychological impact

Investigators need to consider the psychological impact of the pandemic on research participants. While they may be anxious about COVID and its consequences, there may also be concerns about interruptions in study treatments or assessments. Investigators should be available to allay these fears and to provide risk-stratified options to individual research subjects for continuing research participation during this period. Finally, as the pandemic recedes, there should be caution in re-starting studies as a second wave of infection is very likely.

In summary, the COVID pandemic has created an unprecedented situation, which is likely to negatively impact the conduct of clinical research. The various stakeholders in the clinical research process need to work out strategies to ensure that research activities are maintained as much as possible, and that the safety of participants and integrity of research data is not compromised.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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