

Challenges and opportunities for sponsors in conducting clinical trials during a pandemic

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Abstract

The COVID-19 pandemic may impact the conduct of clinical trials of medical products. Challenges have arisen, from country/ state lockdowns, site closures due to hospitals being taken over / sites being taken over for COVID-19 related care, travel limitations to sites for patients, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-scheduled visits and laboratory/ diagnostic testing. This position paper from the perspective of Indian Society for Clinical Research (ISCR) aims to provide guidance to both frontline Clinical Research Professionals and sponsors on measures that can be taken while continuing ongoing clinical trial activities at site as well as resuming site level activities in the post COVID setting. Broad guidance is also given to sites and sponsors on use of Direct to Patient drug shipments, supplies and cold chain management and use of technologies to support enhanced remote functioning during and post COVID.

Keywords: Clinical trials, coronavirus 2019, direct to patient, home health care, Indian Society for Clinical Research, patient safety

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INTRODUCTION

The coronavirus 2019 (COVID-19) pandemic has an ongoing impact on the conduct of clinical studies across different geographies including India.^[1-4] The disease has the potential to impact the scientific integrity and patient safety of ongoing trials,^[5] add to the operational burdens on trial programs; and limit access to trials and newer therapies for all patients, especially the most vulnerable populations. Issues related to scientific integrity stem from the need for sponsors and trial programs to maintain compliance with good clinical practice during the pandemic. This is due to

several reasons most notably self-isolation/quarantine by participants and study-site personnel, travel restrictions generally in a region/country, blocked access to clinical trial sites in hospitals which may be converted into COVID treatment center or due to study sites being reassigned to other critical tasks (e.g. administrative center, drug storage site etc.). The limited availability of ancillary services (e.g. radiology and surgery) at sites also led to challenges with sites where some of these departments were not functioning or not catering to noncritical/routine patient needs. The sponsor of the study will have to give careful

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consideration on how these scenarios will impact ongoing studies (e.g., missing data, inability to verify source data for completeness/database lock, and safety monitoring) and the ability to start new studies that are approved at sites. They need to plan for the future “new normal” when new studies are placed in India as part of global development. The Indian Society for Clinical Research (ISCR)^[6] would like to articulate the challenges and also provide broad guidance for sponsors involved in clinical trials on specific issues, which may arise as a result of COVID-19 pandemic and some potential solutions.

MANAGEMENT OF THE CLINICAL STUDY DURING THE IMMEDIATE HEALTH-CARE CRISIS PERIOD

Irrespective of any crisis/disruptions, the priority should be the safety of trial participants and this will remain the focus of all stakeholders: sponsor, investigator, ethics committee (EC), and regulatory agency. Sponsors need to take study decisions which may include those regarding continuing trial recruitment, continuing use of the investigational drug/device for patients already participating in the trial, managing collection and processing of biological samples, and reporting of serious adverse events (SAEs). The study project managers and the clinical research associates (CRAs) need to be engaged in an ongoing discussion with the site at different levels – with investigator, clinical research coordinators (CRCs), and often the EC/institutional review board (IRB) – in case the site is not able to do so due to site staff getting infected or if the site is shut down temporarily. The investigator and EC/IRB chairperson/member secretary must make all efforts to communicate with each other via teleconferences/email, etc., for seeking appropriate guidance.

The sponsor can provide a generic notification to the sites on the approach (es) that it intends to take for the studies being conducted at a given site. This can be either in the form of an organizational guidance for all studies done by that entity across the globe or tailored specifically to India (especially when the sponsor is based in India). The investigator must consider this guidance (if provided) and decide keeping in mind the safety of the patient and the type of study. Once the joint decision is made, it can be communicated upon request to the Central Drugs Standards Control Organization (CDSCO) Directorate and EC/IRB that give oversight for the study at the site.

Considerations for ongoing trials

Patient participation

Investigator should do a risk–benefit assessment at a study

level and assess whether the patient should be continued in the study in case there is a possibility that the patient will not be able to access the site for some time and this can lead to missed visits/dosing. She should also assess the possibility of postponing site visits as per the protocol allowed visit window or transforming them into telephonic visits wherever possible thereby preserving the integrity of the trial. This assessment is particularly relevant for clinical trials which are time bound and protocol driven and needs to be communicated with rationale to the EC, sponsor, and CDSCO and as soon as such a decision is made by the investigator/site.^[1] Participants who are discontinued due to missing doses may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment). The sponsor should send a notification to the CDSCO Directorate and EC/IRB on pausing or stopping of enrollment in a study with reasons for the same.

Protocol amendments

Protocol amendments are typically not implemented before review and approval by the EC/IRB and in some cases by the CDSCO. Sponsors and clinical investigators are encouraged to engage with the EC/IRB as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated as a result of COVID-19 impact. Such changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research patients (e.g., to limit exposure to COVID-19) may be implemented without EC/IRB approval, but are mandatorily to be reported afterward once there is further direction from the CDSCO post-COVID-19 epidemic. It will also be appropriate for sponsors and investigators to work with their EC/IRB to prospectively define procedures to prioritize reporting of deviations that may impact the safety of trial participants.

India does not have regulations with respect to capturing efficacy assessments, such as use of virtual assessments, and hence, sites should not be encouraged to collect efficacy endpoints using virtual technology as of yet until there is maturity in the ecosystem. If there are no safety hazards to the patient, the sponsor should apply on eSUGAM portal and await CDSCO approval to go forward with any amendment to efficacy endpoints. For individual instances where efficacy endpoints are not collected, the reasons for failing to obtain the efficacy assessment should be captured in the source documents (e.g., identifying the specific limitation imposed by COVID-19, leading to the inability to perform the protocol-specified assessment).

Study visit scheduling

Changes in study visit schedules, missed visits, or patient

discontinuations may lead to missing information (e.g., for protocol-specified procedures). It will be important to capture specific information in the source documents as well as in the electronic case record form that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19). The sponsor also needs to think if changes need to be made to the statistical analysis plan (SAP) or data management plan (DMP). If changes are necessary to the DMP and SAP before locking the database, then these should be communicated to the CDSCO with special consideration as to how the SAP will address how protocol deviations (PDs) related to COVID-19 will be handled for the prespecified analyses. This information, summarized in the clinical study report, will be helpful to the sponsor and the CDSCO.

Protocol deviations

In case of rescheduling of visits undertaken as a precautionary measure for COVID-19, these PDs will not be considered as violation unless they put the patient's safety at risk. In case of patients missing study drug/non study drug doses due to either their inability to visit the site or their drug supply getting exhausted, this should be captured by the site as a PD and reported to the EC/IRB as per the standard practice. An assessment should be done by the study physician as to whether a patient missing several study drug doses will benefit from continuing in the study as per the study protocol. This discussion between the investigator and the study physician should be documented in the source notes of the patient and informed to the EC/IRB.

Clinical trial supplies management

There may be a need to provide patient with adequate clinical supply to ensure that there is no absence of medication between scheduled visits and also to minimize site visits, thereby ensuring the safety of the patient/protecting the study endpoints. The CRA should work closely with the site to check on the status of the investigational/noninvestigational drug supply at site to ensure no stock outs when patients come to the site. In India, many sites have experience with appropriate measures to provide uninterrupted supply of the investigational product to the patients, e.g., distributing the investigational products direct to patient (DTP) through courier service. Before initiating the DTP in the study, ensure that the site has exhausted all available options to maintain study drug dosing, e.g., utilizing the dosing windows to move the visits without deviating from the protocol-scheduled visits, facilitating patient assistance vehicles (ambulances) to ferry the patient

to the site so as to ensure doses are not missed (especially in case of injections), whether a caregiver can pick up the investigational drug/noninvestigational drug from the site etc.

Sponsor should define the mechanism with the investigator before initiating the process of dispatch, for confirming the IMP accountability process, temperature control management, and changes thereof. The sponsor will need to have adequate safeguards to maintain product safety, security, and patient's confidentiality when implementing such approaches in collaboration with sites. In all situations as detailed *vide supra*, existing regulatory requirements for maintaining investigational product accountability remains and should be addressed and documented. To initiate DTP, participants must consent verbally (and this should be documented in their source notes) to provide contact details for shipping purposes. If the participant does not want to sign for the delivery of the drug due to self-isolation, a follow-up phone call could be used to confirm they have received the DTP package delivered by the designated agency.

Prerequisites for initiating DTP for a study by the sponsor include ensuring that the IMP is an oral-solid formulation and is non-temperature controlled ambient shipment (-20°C to $+60^{\circ}\text{C}$). In case the product is temperature-controlled ambient or cold (-2°C – 8°C), stability requirements need to be further evaluated. DTP should be undertaken only if the stability can be maintained for the estimated transit duration from the site to the patient's residence. In case of self-administered non oral-solid dosage forms, DTP can still be considered and the stability requirements should be assessed from a transportation perspective. The sponsor should also consider if any training is required for the administration and storage of the IMP, especially for IMP with a narrow stability range.

Biological sample management

There may be a need to conduct local laboratory testing for safety monitoring, which has to be decided in consultation with of the sponsor and recorded remotely in the source documents by the investigator. Thus, for the purpose of patient safety, new processes for COVID-19 situation alone may need to be in place or existing processes may need to be modified, which will vary by the protocol and local situation. This assessment could include consideration of whether it is appropriate to delay some assessments for ongoing trials or, if the study cannot be properly conducted under the existing protocol, whether to stop ongoing recruitment, or even withdraw trial participants. The site staff needs to "time" the sample pick up working closely

with the CRA and the courier agency keeping in mind the stability of the samples which will need to be exported to the central laboratories.

Adverse event and serious adverse event reporting

Sponsor must report to the CDSCO any SAE that is both unexpected and for which there is a reasonable possibility that the drug caused the SAE, i.e., there is evidence to suggest a causal relationship between the drug and the adverse event (relatedness). Participants in a clinical trial may be diagnosed with COVID-19 and experience SAEs associated with the disease that are not causally related to the investigational drug. It is also possible that an investigational drug might be causally related to a SAE associated with COVID-19 by making subjects in the trial more susceptible to complications from COVID-19. Establishing this potential causal relationship (related or notrelated) likely requires analysis of the unblinded data and will be the role of the data monitoring committee rather than the investigator or sponsor. To enable sponsors to comply with the safety reporting timeline in the current pandemic scenario, e-mail submission of reports with electronic signatures will be accepted until the resolution of this crisis as per the CDSCO.^[1] SAE “due analysis” report from clinical trials needs to be submitted to sae@cdsco.nic.in and dci@nic.in, and the sponsor should track these submissions from the site. This e-mail submission will allow timely reporting of safety documents without the risk of company representatives having to visit their respective offices. The date of submission of above-listed safety reports via e-mail will be considered as the actual date of submission to the Directorate. Digital submissions, such as amendments, changes related to investigator site, IB updates, quarterly enrollment report, and clinical trial six monthly status report, should be submitted by e-mail to the respective CDSCO divisions in the wake of the pandemic. Digitally signed cover letters and forms without stamps may be accepted by the CDSCO instead of wet ink signatures. Signed copies of the legal documents can be submitted at a later date to the directorate.

Data entry in electronic case record form/electronic data capture software

It is possible that the CRC at the site is not able to come to the site or access the electronic data capture (EDC) remotely due to lack of access. In such a situation if the investigator is seeing study patients at the sites as per the protocol-scheduled visits, the investigator needs to capture the details of the review visit in the source notes of the patient without fail. The CRC should then complete the EDC data entry as soon as he/she gets access to the site.

Monitoring visits

If planned on-site monitoring visits are no longer possible, sponsor should consider optimizing use of central and remote monitoring to maintain oversight of ongoing clinical sites during the COVID-19 pandemic.^[2] Sponsors should work to find alternative approaches to maintain trial participant safety and trial data quality and integrity. These include activities such as enhanced central monitoring/risk based monitoring, telephonic contact with the sites to review study procedures, trial participant status or remote monitoring of enrolled trial participants, where appropriate and feasible. It is possible that delays in on-site monitoring (source data verification) may result in delayed identification of major PDs, nonreporting of SAEs, etc., at the clinical trial site (including PDs not due to the impact of COVID-19). Sponsors should document situations where clinical research associates/monitors were unable to access Electronic Data Capture (EDC), or had to delay monitoring of, a clinical site. CRAs should include in their documentation of PDs or other GCP issues identified at clinical sites whether delayed identification was due to delayed monitoring due to COVID-19 pandemic. Sponsor should consider using a risk-based approach to prioritize sites for remote monitoring, including as many study sites as feasible (and with a frequency as close to that described in the site monitoring plan). The decision regarding which sites to prioritize for remote monitoring should be guided by centralized monitoring (risk-based monitoring) or other information available about site performance (e.g., frequency and severity of PDs previously identified during routine monitoring visits or currently identified by centralized monitoring, number of randomized active trial participants, level of experience of site staff, known site history of prior major audit, or inspection findings). During remote monitoring, the CRA should focus more on trial activities that are essential to the safety of trial participants and/or data reliability/integrity.

AS THE HEALTH-CARE SYSTEM SHIFTS TO RECOVERY AND SETTling INTO A NEW “NORMAL”

Considerations for new clinical trials

If you are the sponsor designing the study protocol, it will be good to learn from the disruption that has been caused by the pandemic in implementing the protocol. Many trials currently include tests, procedures, and strict data collection requirements and windows for assessment that are intended to maximize knowledge gained, but may prove burdensome for both patients and trial programs. During the pandemic, some of these common requirements have not been able to be met, leading to protocol modifications and/or

PDs (intentional or unintentional). As a local sponsor, you should evaluate the impact of these protocol modifications or PDs on the scientific integrity, interpretation, and conclusions of trials. It is likely that many trials moving forward could be designed with expanded and/or flexible timelines and reduced data collection requirements without negative consequences. This would also be beneficial to patients and research programs.^[7]

Screening and recruitment of new clinical trial participants

Investigator who has been conducting patient visits during the COVID-19 period would be comfortable with screening and enrolling new patients in the study. All precautions as per the Ministry of Health and Family Welfare/Home Affairs/Indian Council of Medical Research need to be followed to ensure that patients being evaluated for studies are not unduly exposed to the COVID-19 infection at the hospital site. The investigator would need to strategize the enrolment of new patients at the hospital site, keeping in mind the location of the hospital, time taken by the patient to travel to the site, social distancing between patients if they come into the clinic at the same time, the mental status and vulnerability of the patient due to the COVID-19 situation, inclination to adherence of subject's responsibility in the clinical trial, and their ability to consent for the trial. Patient safety, comfort, and protection need to be kept by the investigator as the main pivot. In addition, the investigator would need to think about the space to be provided for monitoring post-COVID-19 as there might be missed monitoring visits in the lockdown period, and due to the monitoring backlog, there might be a rush by the sponsors to increase the number of visits at site. Furthermore, the investigator would need to adapt to the immediate call to action to facilitate the monitoring via remote means, i.e., become more digitally savvy and allocate CRC's, who can support the monitoring remotely ("upskilling of the CRC").

Study visit scheduling

If there are no safety hazards anticipated to the patient, the investigator should be able to allow for protocol-scheduled visits to occur at the site. All precautions to minimize infection to the patient should be taken as per local guidelines. There is great potential for telehealth visits and remote patient review of symptoms as a potential improvement to clinical trial conduct for the future.^[7]

Protocol deviations

In case of patients missing doses due to either inability to visit the site due to the hospital being a COVID treatment center or because the site has been taken over by the hospital for COVID-19-related management or their site

staff is infected, this should be captured by the site as a PD and reported to the EC/IRB as per the standard site procedures. Many sponsors have guidance to highlight these PDs as "COVID-19 PDs" such that these can be differentiated from the other PDs which can occur during this time.

Clinical trial supplies management

In case there is a continuing requirement to provide with DTP services to the patient, this has to be discussed between the investigator and the sponsor and the reasons documented. The sponsor will need to have adequate safeguards to maintain product safety, security, and patient's confidentiality when implementing continued DTP to the patients. It will also be important to assess whether, within a study, some of the protocol-scheduled patient visits can be carried out by home health care/nursing specialist or trained professional. Since there are no regulations around the same, it will be appropriate to keep both the EC/IRB/CDSO before this is implemented. If the scheduled protocol visit does not have any assessments (other than biological sampling/diagnostics) that have an impact on the study endpoints, this could be an option to evaluate. If the study has injections/infusions being administered as part of the protocol, the patient can be administered the same at home (if this is allowed by the study and the complexity of the medication administration).

Monitoring visits

Sponsor should consider optimizing use of technologies such as central/risk-based monitoring and remote monitoring to maintain oversight of clinical sites. These technologies can ensure that the trial participant's safety and trial data quality and integrity are being closely monitored. Given the uncertainty around the pandemic and whether this will have further waves into the near-term future, monitoring will be a balance between onsite/remote monitoring to ensure that CRAs are not exposed/infected.

In summary, ISCR recommends that sponsors should work in collaboration with the sites to design effective strategies to manage both ongoing and new studies from the perspective of patient safety, ensuring data integrity and improving ease of participation in research. The changes to the ways of operating at the sponsor and site level have the advantage that they will make clinical trials more patient-friendly and reduce the time and expense of participating in clinical trials. It will be immensely helpful to sponsors, sites, and EC/IRBs to develop formal COVID-19 standard operating procedures for clinical trials that could be repurposed with other disease outbreaks.

This is an opportunity and also a wakeup call for all the stakeholders to think about the need for initiating/refining their respective business continuity plans in the light of the turmoil of the COVID-19 pandemic. As both sponsors and sites gain better understanding of how to manage ongoing studies, many of these efficiencies gained during the pandemic scenario will lead to lessons learned, imbibed, and incorporated into operating in the “New Normal.”

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Nil.

Conflicts of interest

There are no conflicts of interest.

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