

Review Article

Clinical research during coronavirus disease pandemic: Challenges and way forward

Pankaj Kumar Panda¹, Martin R Stockler², Ashish Gulia³

¹Department of Clinical Research, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, ²Department of Oncology, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia, ³Department of Bone and Soft Tissue, Tata Memorial Hospital, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India.



***Corresponding author:**

Ashish Gulia,
Department of Bone and Soft
Tissue, Tata Memorial Hospital,
Homi Bhabha National Institute
(HBNI), Mumbai, Maharashtra,
India.

aashishgulia@gmail.com

Received : 06 June 2020

Accepted : 25 June 2020

Published : 21 August 2020

DOI

10.25259/IJMS_125_2020

Quick Response Code:



ABSTRACT

With the novel coronavirus disease (COVID-19) being declared a global pandemic by the World Health Organization, the Indian health-care sector is at the forefront to deliver optimal care but with constrained resources and several challenges. The pandemic has also brought about a state of urgency to develop suitable management principles for COVID-19 with the help of suitably designed clinical trials. However, the pandemic along with the lockdown and other restrictions has affected the conduct of clinical trials in terms of restrictions on travelling, trial site staff availability, investigational product availability, and medical oversight among others. This article provides structured recommendations for sponsors, investigators, clinical trial personnel to adapt to the situation by identifying potential risks and challenges and mitigating them to conduct clinical trials well within the ambit of local regulatory guidelines and requirements during the COVID-19 pandemic.

Keywords: Clinical trials, Research, Coronavirus disease, Severe acute respiratory syndrome coronavirus 2, Regulatory

INTRODUCTION

The World Health Organization declared a global pandemic of the novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on March 11, 2020.^[1] With millions infected worldwide, and resources diverted to managing COVID-19, the pandemic has strained health-care systems around the world. In the absence of any proven, specific therapies for COVID-19, management has been restricted to supportive care. This has created a state of urgency to develop effective interventions for the detection and management of COVID-19, requiring the conduct of suitably-designed and powered clinical trials that protect the rights, safety, and well-being of participants.^[2]

The pandemic has also affected the conduct of clinical trials unrelated to COVID-19, due to lockdowns, quarantining, and travel restrictions; limitations on the production, distribution, and dispensing of investigational product (IP); and, constraints on other critical resources, particularly health-care professionals and other trial staff. These limitations have had major effects on trial activities, including medical assessment and oversight of trial participants that may constitute unavoidable deviations from trial protocols. These circumstances necessitate a concerted effort by sponsors, investigators, and staff to identify potential risks and challenges, and formulate appropriate solutions that satisfy the relevant regulatory frameworks for conducting clinical trials.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

©2020 Published by Scientific Scholar on behalf of Indian Journal of Medical Sciences

In this paper, we list and organize these risks and challenges, along with possible remedial actions that meet local guideline and regulatory requirements.

INITIATING NEW TRIALS, SITES, AND RECRUITING NEW TRIAL PARTICIPANTS^[3]

During the COVID-19 pandemic, limited access to health-care facilities, resources, and manpower constraints - including availability of trial site staff, diagnostic, and other medical facilities - are likely to impact the initiation and conduct of clinical trials. Opening a new trial site in an ongoing clinical trial, continuing accrual of new trial participants, or starting a whole new trial, all require careful consideration during a pandemic emergency, with reference to all the national and state restrictions enacted during an enforced lockdown. Strict adherence to the study protocol, the dictum for any clinical trial, may be compromised by delay or missed conducting and documenting study procedures, reporting of adverse events, and performing assessments for safety or efficacy. Inability of trial participants to visit health-care facilities may put severe strains on medical management and oversight.

RISK ASSESSMENT FOR CONDUCTING CLINICAL TRIALS

The decisions to activate a new trial, open a new site, or recruit trial participants should all be critically evaluated by sponsors and investigators. The safety of trial participants is paramount, and an explicit assessment of the potential harms versus benefits must be done to weigh the risks to participants and staff due to the added challenges of the COVID-19 pandemic, versus the potential benefits for specific participants, and for the broader community in general (ref: principle 2.2 of ICH GCP).^[4] Risk assessments should be conducted by all involved parties and documented carefully. The reassessments of risk should be repeated as the pandemic, or other extenuating situations, evolve, and circumstances change.^[5]

CONSIDERATIONS FOR ONGOING TRIALS

Ensuring the safety of trial participants is critical. Decisions regarding recruitment of new participants, use of IP in existing participants, and modifications to scheduled assessments must be documented and communicated appropriately to trial participants, sponsors, ethics committee (EC), and regulatory authorities. All relevant stakeholders, including the sponsor, investigators, Institutional Review Boards (IRB), and/or ECs must determine the feasibility of continuing trial activities including considerations of safety, the nature of the IP, availability of the IP, and the nature of the medical condition being studied. Participants who no longer have access to IP

and/or direct access to the trial site (health-care facility) may need additional safety assessments.

Testing and/or screening procedures for COVID-19 mandated by health-care facilities or other jurisdictions where a trial is being conducted must be documented and/or reported according to the prevailing regulatory guidelines, and as protocol amendments if the sponsor wishes to include the data collected as part of a new research objective.^[6]

Varying local conditions and the consequences of the COVID-19 pandemic may lead to different risk-mitigation strategies for different sites participating in the same multi-center trial. Therefore, any additional measures need to be considered, documented, and communicated to sponsors and regulatory authorities. The potential impact of COVID-19 on trial participants at increased risk of infection should be carefully considered before deciding whether to continue their participation in a trial, or withdraw them from it.

Due to physical and social restrictions during the COVID-19 lockdown, study participants may not be able to attend trial sites for required study assessments. Sponsors and investigators should consider provisions for contact that meet local regulatory requirements, for example, by telephone, videoconference, or at alternative assessment centers. In deciding whether to continue with the investigational therapy, the investigators must ensure the safety of trial participants regardless of changes in medical oversight.

Amendments to the protocol, informed consent documents (ICDs), and other study documents are usually not implementable before IEC/IRB review and approval; and in some cases require approvals by regulatory agencies. However, urgent amendments to minimize or eliminate immediate risks due to the COVID-19 pandemic can be implemented by sponsors and investigators before these approvals have been granted, post-submission.^[3]

The implementation of changes to trial procedures during the COVID-19 pandemic needs to be as consistent as possible with the study protocol. Proper documentation must be maintained regarding any changes in study conduct, which trial participants were affected, and how they were affected. The anticipated duration of any changes should also be documented.^[7]

Missed study assessments and investigations may affect the scientific integrity of a study by hampering the analysis and reporting of major endpoints. The nature and reasons for any such protocol deviations should be documented, including any relationship with the COVID-19 pandemic.

The assessments for the efficacy of study treatment should be carefully monitored and any necessary protocol amendments should ensure their accuracy and timelines, even if done remotely by telephone or other means. Delayed assessments,

and changes to schedules for follow-up or sample collection, should also be documented.

If changes to the study protocol could affect the statistical analysis plan, then sponsors and investigators should consider and specify how any such changes and protocol deviations will be considered and managed in the statistical analysis, before locking the study database.^[7]

COMMUNICATION WITH REGULATORY AUTHORITIES AND SAFETY REPORTING

Regulatory authorities and ECs must consider the COVID-19 pandemic and adjust their processes to cope with the unprecedented conditions.^[8,9]

- New clinical trial applications related to the management of COVID-19 infection should be prioritized and receive expedited evaluation and approval, if appropriate.
- Priority should also be given to applications for crucial amendments to protocols for ongoing studies required as a result of COVID-19.
- In cases, where events due to the COVID-19 pandemic may pose risks to the safety of trial participants and unfavorably alter the balance of risks versus benefits for the trial, sponsors and investigators may implement immediate actions without prior approval to the regulatory authorities. However, the sponsor and investigators must inform regulatory authorities of these changes providing relevant details and justifications.
- Sponsors, investigators, and other study staff must continue their required regular reporting of adverse events to EC and regulatory authorities (as required), and to continue appraising them of any relevant safety issues and remedial measures to maximize the safety of trial participants.

Informed consent

Amendments to the patient information and ICDs necessitated by the COVID-19 pandemic must comply with applicable regulatory requirements. Amendments and approvals for trials investigating the management of COVID-19 and related conditions should be prioritized. Obtaining physical informed consent from participants in such trials may be particularly challenging because of isolation measures required for COVID-19 patients.^[7]

- Participants with COVID-19 who are in isolation may not be able to provide written consent. Oral consent observed by an impartial witness may be obtained according to the applicable regulations. The impartial witness must sign and date the consent document.
- In situations where vulnerable participants are unable to give consent, for example, minors, those with severe debilitating conditions, or severe COVID-19, a legally

acceptable representative must be present during the consent process (ref: ICH GCP E6 4.8.9).^[4]

- Patients can be recruited without prior consent if it is not possible to obtain prior informed consent from the patient or her/his legal representatives(s), and the protocol specifies the required provisions for recruitment of such patients, and there is documented prior approval from the responsible IRB/EC and regulatory authorities to allow recruitment of such patients. All of these requirements must be met before recruiting a patient without prior consent. The patients or their legal representative must be informed about the trial as soon as possible and their consent requested and documented in accordance with applicable guidelines (ref: ICH GCP E6 4.8.15).^[4]
- Modifications of the patient information and ICD may require re-consenting of patients in ongoing trials. Patients should be provided with the updated information before re-consenting. Alternative methods of re-consenting after due approval from the EC through telephone or videoconferencing must be recorded and documented in the patient's medical record (source files). Once the lockdown and/or other restrictions are relaxed allowing participants to visit the study site, consent obtained virtually, or orally should be confirmed and suitably documented in the source files.^[10]
- Validated and secure electronic systems already approved for obtaining consent in a trial can be used according to the standard practice in compliance with national legislation.

MONITORING AND AUDITING OF CLINICAL TRIALS

Monitoring and quality assurance activities should take into account the national and state restrictions, the necessity and availability of trial staff, and other limitations of resources during the COVID-19 pandemic. Changed monitoring plans should aim for an optimal balance between adequate oversight, practicalities at sites, and compliance with the relevant regulations. Modifications to monitoring can include:

- Increased use of central and remote monitoring.^[11]
- Virtual on-site monitoring plans using telephone or video calls.
- Adaptive monitoring plans with increased use of remote or central monitoring.
- Postponing or cancelling on-site monitoring visits.

Clinical trial audits should be delayed and only conducted during the COVID-19 pandemic if they are essential, or required to investigate serious deviations or non-compliance.^[11]

ROLES OF SPONSORS, CONTRACT RESEARCH ORGANIZATIONS, AND ACADEMIC RESEARCH ORGANIZATIONS

IP management

- Sponsors must ensure adequate stocks of IP at study sites to allow ongoing conduct of the trial and to reduce avoidable visits of participants to study sites.
- For externally-sponsored trials, study sites are responsible for dispensing IP to trial participants (ref: ICH GCP E6 4.6). If restrictions due to the COVID-19 pandemic hamper the participants' ability to visit study sites, then sponsors may decide to allow supply of IP from study sites to participants' homes using secure, authorized delivery services.
- IP requiring administration by health-care professionals at study sites set-up may require alternative arrangements for administration by suitably trained staff who are not

on the study-delegation log and should be notified to EC.

- IP accountability must be maintained strictly in accordance with applicable guidelines.

There may be circumstances in which a trial participant may be benefitting from the IP. During the challenging conditions of the COVID-19 pandemic, distribution of IP from the sponsors to the trial sites may be difficult or impossible. In such cases, the sponsor needs to work with investigators to solve distribution problems.

The risks of continuing study treatment versus switching to an alternative, or stopping treatment, need to be considered carefully on a case-by-case basis. In study, participants for whom discontinuing the IP might present substantial risk, protocol amendments can be made to specify criteria to redistribute the limited stocks of IP to trial participants most in need, and discontinuing it in other participants. In

Table 1: Frequently encountered scenarios and relevant suggestions	
New trials Should new trials be initiated during this time?	After due risk assessment by the sponsor or investigator in case of investigator initiated trials (ICH GCP section 5.0)
Ongoing trials Documentation How to overcome shortage of trial staff to document deviations, violations, SAE? How to address the issue of missing information due to missed visits due to COVID-19 pandemic? How to manage increased number of protocol deviations and violations during the COVID-19 pandemic	Consider alternative means such as phone calls, emails, and other online tools to maintain medical oversight of patients. Record all deviations and reporting of SAE. Specific information needs to be recorded in the source documents (participant's medical records) and trial CRF that explain the basis of any missing information Should be managed as per SOP. Periodic assessments should be done regarding the nature and frequency of deviations to assess whether protocol amendments are needed.
Communication Can urgent amendments to study protocol or documents be made without informing regulatory authorities when it concerns patient safety?	If the amendment or changes concern potential threats to participants' safety and are intended to protect the trial participants' safety, then the sponsors/ investigators can proceed. However, the ethics committee and regulatory bodies should be informed in due to course of time
IP management Decision to continue administration of study treatment that appears to be benefitting a trial participant	Sponsor should consider amending the protocol, for example, to limit investigational product use to those patients with apparent benefit and discontinue investigational product use to other participants.
Informed consent Recruiting or re-consenting trial subjects who are being isolated according to the COVID-19 infection control policies	Oral consent observed by an impartial witness In case of vulnerable population, in the presence of a LAR All of this should be followed by regular consent process once situation normalizes
Monitoring and auditing Regular onsite monitoring may not be feasible due to the COVID-19 pandemic restrictions	Consider risk-based monitoring, centralized monitoring using telephone, videoconferencing, email, or other online tools with robust follow-up when circumstances allow
Trial participants' site visit Trial subjects are not able to reach trial sites during scheduled visits	Virtual medical oversight through telephone, video calls can be arranged
CRF: Case report form, SAE: Serious adverse event, SOP: Standard operating procedure, LAR: Legally acceptable representative	

participants who stop or change study treatment, additional visits, or tests may be required for safety assessments.

Trial-monitoring and quality assurance activities need to be reassessed and temporary, alternative mechanisms for oversight may need to be implemented to assess the impact of changing conditions due to the COVID-19 pandemic.

SUSAR reporting must be done as diligently as possible, and any delays in reporting must be reported as deviations with appropriate corrective actions documented and implemented.

Inadvertent expenses for study participants due to conduct of a trial during the COVID-19 pandemic must be reimbursed by the sponsor according to applicable local policies.^[12]

CONSIDERATIONS FOR INVESTIGATORS AND TRIAL SITE STAFF

Challenges such as difficulty in visiting health-care facilities for the trial participants and trial staff will impact medical oversight and could adversely impact activities required for trial conduct such as completion of study assessments, study visits, and the availability of investigational drugs and therapies.^[13]

- Appropriate risk-benefit assessments should be done to confirm that the required study assessments for eligibility, safety, and efficacy can be completed safely. Consideration should be given to suspending trial recruitment, at least temporarily. Investigators and sponsors should consider whether it is safe for participants to continue study treatment.^[5]
- If study participants are unable to attend their site for clinical assessments of follow-up or adverse events, then contact by telephone, video, or home nursing might be suitable to maintain medical oversight.
- Participants at increased risk, for example, the immunocompromised, elderly, or debilitated - should be assessed carefully to decide whether they should continue trial participation.
- Protocol deviations are likely to occur more frequently during the COVID-19 pandemic. These should be appropriately documented and reported to ECs and regulatory authorities according to the applicable timelines and guidelines.
- If increased risks due to COVID-19 are anticipated for trial participants, and the decision is to proceed with recruitment and/or study treatment, then suitable amendments to the study protocol, participant information, and ICDs must be made and must be approved by the EC and regulatory agencies before any further study related procedures are conducted.

COVID-19 RESEARCH

In the absence of proven, specific treatments for COVID-19, clinical trials of diagnostics, treatments, and management

strategies for COVID-19 are of high priority. There have been many reports of *in vitro* studies suggesting anti-coronaviral activity of drugs including hydroxychloroquine, lopinavir-ritonavir, remdesivir, and IL-6 inhibitors. However, there is limited clinical evidence about the safety or efficacy of drugs directed against SARS-CoV-2.^[2] Off-label “compassionate” use of these drugs has not resulted in reliable observations or actionable conclusions. Serious concerns have also been raised about the risk of adverse drug reactions associated with these agents. Suitably-designed, randomized clinical trials of the most promising candidates for treatments are desperately needed to provide reliable evidence to guide research and practice.^[14] We cannot afford to cut corners in the design and conduct of trials testing new treatments for COVID-19. Adaptive and platform designs that test the most promising candidates with a background of optimal supportive care are sorely needed.

Declaration of patient consent

Patient’s consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors Pankaj Kumar Panda and Ashish Gulia are the editors of this journal. They do not have any competing interests.

REFERENCES

1. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. [Last accessed on 2020 Apr 12].
2. Kalil AC. Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA*. 2020;323(19):1897-8. Doi:10.1001/jama.2020.4742
3. Available from: <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/clinical-trial-conduct-during-covid-19-pandemic>. [Last accessed on 2020 Apr 12].
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. [Last accessed on 2020 Feb 25].
5. Lantos JD, Wendler D, Septimus E, Wahba S, Madigan R, Bliss G. Considerations in the evaluation and determination of minimal risk in pragmatic clinical trials. *Clin Trials* 2015;12:485-93.
6. Implications of Coronavirus Disease (COVID-19) on Methodological Aspects of Ongoing Clinical Trials. Available from: <https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19methodological-aspects-ongoing>

- clinicaltrials. [Last accessed on 2020 Apr 12].
7. Available from: https://www.ec.europa.eu/health/sites/health/files/files/eudralex/vol10/guidanceclinicaltrials_covid19_en.pdf. [Last accessed on 2020 Apr 12].
 8. Code of Federal Regulations. Protection of Human Subjects. Expedited Review Procedures for Certain Kinds of Research Involving no More Than Minimal Risk, and for Minor Changes in Approved Research. Available from: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.110>. [Last accessed on 2015 May 18].
 9. U.S. Food and Drug Administration Website. FDA Policy for the Protection of Human Subjects. Available from: <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm118893.htm>. [Last accessed on 2015 Jan 16].
 10. Dal-Ré R, Avendaño C, Gil-Aguado A, Gracia D, Caplan A. When should re-consent of subjects participating in a clinical trial be requested? A case-oriented algorithm to assist in the decision-making process. *Clin Pharmacol Ther* 2008;83:788-93.
 11. Hamrell MR, Mostek K, Goldsmith L. Monitoring of clinical trials-are remote activities helpful in controlling quality? *Clin Res Oct* 2016;2016:18-21.
 12. Perez C, Olivier P, Lortal B, Duranton S, Montastruc JL, Colin AL, *et al.* Detection of drug safety signals from clinical trials data: Role of SUSARs. *Pharmacol Res* 2018;131:218-23.
 13. Available from: [http://www.hpra.ie/homepage/medicines/regulatory-information/clinical-trials/covid-19-\(coronavirus\)-and-cts](http://www.hpra.ie/homepage/medicines/regulatory-information/clinical-trials/covid-19-(coronavirus)-and-cts). [Last accessed on 2020 Apr 12].
 14. Bhatt DL, Mehta C. Adaptive designs for clinical trials. *N Engl J Med* 2016;375:65-74.

How to cite this article: Panda PK, Stockler MR, Gulia A. Clinical research during coronavirus disease pandemic: Challenges and way forward. *Indian J Med Sci* 2020;72(2):101-6.