



Guidance for the Management of Clinical Trial Activities in response to COVID-19 **Pandemic**

Recommendations from ISCR

Background and Introduction:

This document provides guidance for those involved in clinical trials on specific issues which may arise as a result of COVID-19 pandemic, and what they are required to do. We understand that a pragmatic solution to deal with the clinical trial activities and meet regulatory requirements could be a challenge due to inadequate resources and several logistics restrictions due to COVID – 19 outbreak.

Irrespective of any disruptions, the priority should be the safety of trial participants and this will remain our focus. The guidance will be updated as the situation evolves.

This guidance covers the following topics:

- ✓ Considerations for Regulatory submissions
- ✓ Considerations for managing conduct of Clinical Trials at Investigational Site for Ongoing Trials for
 - Scheduled F2F visits of Clinical Trial Participants
 - Patient's Safety First
 - Study Visit Scheduling
 - Protocol Deviations/Violation
 - Clinical Trial Supplies & Biological Sample Management
- ✓ Considerations for new clinical trials

✓ **Considerations for Regulatory submissions**

1. Adverse Event (AE) and Serious Adverse Event(SAE) reporting:

Safety Reporting (SAE/ADR/PSUR): In order to enable the companies to comply with the safety reporting timelines in the current COVID-19 pandemic scenario, email submission of soft copies of following reports with electronic signatures will be accepted until the resolution of this crisis.

- SAE “due analysis” report from clinical trials (sae@cdsco.nic.in and dci@nic.in)
- Serious unexpected ADRs from post market surveillance (pharma.covig@cdsco.nic.in)
- PSUR/PBRER submissions (psur.drugs@cdsco.nic.in)

This email submission will allow timely reporting of safety documents without the risk of company representatives to the respective offices. The date of



submission of above listed safety reports via email will be considered as the actual date of submission to the Directorate.

2. Hard copy submission: Hard copies of the documents where there is no provision of digital submission such as compliance submissions include amendments, changes related to Investigator site, IB updates, Quarterly enrollment report, Clinical Trial six monthly status report, etc. will be submitted by email to the respective CDSCO divisions in the wake of the pandemic. The email address of each division will be issued via a notification to enable digital submissions. Till such notice, companies will send soft copies of such submission on GCT email ID.

3. Signature and stamping of documents and forms: Since almost all employees across companies are working from home, printing and signing the forms (Clinical trial forms, NDA forms, RC forms, IL forms) or application cover letter is an issue, thus digitally signed cover letters + forms without stamps may be accepted by CDSCO for at least the next three months instead of wet ink signatures. Signed copies of the legal documents can be submitted at a later date to the Directorate. This will not necessitate employees to go to company offices for printing, signing and stamping.

5. Relaxation of Timelines: Timelines for post approval commitments shall be relaxed for e.g. submission of 6 monthly status report and quarterly enrolment status report and Ethics Committee (EC) approval submissions till the Corona virus impact period. Further guidance and updates shall be provided soon.

6. CDSCO to Send Query by email: CDSCO will send "queries by the CDSCO" to the firm directly via email than by hard copies and receipt of the responses thereof vide emails until the situation is normalized.

7. Share Approval letters by email: A system of receipt of Approval Letters through emails will be set up until the situation is normalized

8. Review of the CT application submitted and coming up for review of SEC meeting: Due to domestic and international travel curbs, participation in the SEC meeting may be difficult for applicants as well as SEC members. The Directorate would consider review & approval outside the SEC meeting or add the provision of discussion via teleconference/video conference.

9. Possibility of helpline for applicants: For situations outside of the above-mentioned points where applicants or investigators may need the guidance from CDSCO for the ongoing clinical trials and patient safety, a helpline/contact no. on which members can reach and seek advice, guidance will be communicated via a notification.



✓ **Considerations for ongoing trials:**

1. **Scheduled face-to-face visits of Clinical trial patients:** Ensuring the safety of trial participants is paramount during this COVID-19 situation. Sponsors should consider evolving circumstances, focusing on the potential impact on the safety of trial participants, and modify study conduct accordingly. Such study decisions may include those regarding continuing trial recruitment, continuing use of the investigational drug/device for patients already participating in the trial, managing collection of biological samples and reporting of Serious Adverse Events (SAEs).

Key points-

✓ **Patient's Safety First:**

- Investigator should do a risk-benefit assessment at a trial level and assess the possibility of postponing site visits or transforming them into telephonic visits wherever possible preserving the integrity of the trial. Any protocol allowed visit window should be explored while performing such assessment.
- The Sponsor can provide a generic notification for the approach(es) that it intends to take for the studies being conducted at a given site. 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 decision is made it can be communicated upon request by CDSCO, EC/ Sponsor. The site assessment with the study list must be recorded appropriately in the source documentation per good documentation practices. A substantial amendment to protocol will not be required in such cases.
- Suspension of ongoing recruitment for trials and temporary halt of the ongoing trials: Investigator/site may decide to discontinue the recruitment and treatment of patients completely in order to avoid unnecessary risks and ensure the best possible health care to all patients for the period of the COVID-19 pandemic. This analysis is particularly relevant for clinical trials which are time-bound & protocol driven and needs to be communicated with rationale to the ethics committee, sponsor and CDSCO and as soon as such a decision is made by the investigator/site.



- Protocol amendments are typically not implemented before review and approval by the IRB/IEC, and in some cases by CDSCO. Sponsors and clinical investigators are encouraged to engage with IRBs/IEC 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 IRB approval but are mandatorily to be reported afterwards once there is further direction from the CDSCO post COVID-19 epidemic. CDSCO encourages sponsors and investigators to work with their IEC/IRBs to prospectively define procedures to prioritize reporting of deviations that may impact the safety of trial participants. The Investigator and IEC/IRB Chairperson/ Member Secretary must make all efforts to communicate with each other via teleconferences/ email etc. for seeking appropriate guidance.

2. **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 case report form (CRF) 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). This information, summarized in the clinical study report, will be helpful to the sponsor and CDSCO.

With respect to efficacy assessments, if there are immediate patient safety hazards then EC should be notified regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible. If there are no safety hazards, then the usual pathway for protocol amendment should be instituted- applying on SUGAM and awaiting CDSCO approval to go forward with the amendment.



For individual instances where efficacy endpoints are not collected, the reasons for failing to obtain the efficacy assessment should be documented in the source documentation. (e.g., identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessment).

All the above points must be considered under the larger purview of the safety precautions already announced by the MOHFW

3. Protocol Deviations:

- a. In the case of rescheduling of visits undertaken as a precautionary measure for COVID-19, these protocol deviations will not be considered as violation unless they put the patient's safety at risk.
- b. The above pointers must be considered while site and study inspections are undertaken in the future.

4. Clinical Trial Supplies & Biological Sample Management:

- a. There may be a need to provide patient with adequate clinical supply for the trial to minimize site visits which do not impact the safety of the patient/study endpoints. If the patient is not able to visit the site, then other appropriate measures to provide uninterrupted supply of the investigational product to the patients, for e.g., distributing the investigational products direct to patient (DTP)

Before initiating the DTP, ensure that you have exhausted all available options to maintain dosing. Below is a list of potential mitigations that can be utilized prior to requesting DTP.

e.g. – utilize the dosing windows to move visits without deviating from the protocol scheduled visits; determine whether a care giver can pick up the IMP/Non-IMP from the site; if the site is willing to allow the hospital's pharmacy to be the place from where the IMP/Non-IMP can be picked up in case the clinical trial site is shut down or patients are not allowed in the hospital.

- b. The Sponsors will need to have adequate safeguards to maintain product safety, security and patient's confidentiality while implementing such



approaches in collaboration with sites. For other investigational products that are normally administered in a health care setting, the study clinician in consultation with the patient can look at provisions to provide alternative administration (e.g. from the patient's local healthcare provider). In all cases, existing regulatory requirements for maintaining investigational product accountability remains and should be addressed and documented.

- i. Participants must consent verbally (and this should be documented in their source notes) to providing contact details for shipping purposes. If the participant does not want to sign for the delivery due to self-isolation, then a follow up phone call could be used to confirm they have received the package.
- ii. Pre-requisites for DTP:
 - The IMP should be an oral-solid dose and non-temperature controlled ambient (-20 to +60 deg C). The sponsor needs to confirm that the product is ambient non-temperature controlled
 - In case the product is temperature controlled ambient or cold (-2 to 8 deg C) then stability requirements need to be further evaluated. DTP should be undertaken only if the stability can be maintained for the estimated transit duration.
 - In the case of self-administered non oral- solid dosage forms can also be considered for DTP and the stability requirements should be assessed for the same from a transport perspective.
- iii. The sponsor should also consider if any training is required for administration and storage of the IMP especially for IMP with a narrow stability range. Adequate provision should be made to assure integrity of the product during transit.
- iv. Sponsor should define the mechanism with the investigator prior to initiating the process of dispatch, for confirming the IMP accountability process and changes thereof.
- v. There might be a need to conduct local lab testing for safety monitoring which has to be decided in consultation and agreement of Sponsor and recorded remotely by the investigator.
- vi. Thus, for purposes of patient safety protection - new processes for COVID-19 situation alone may need to be in place or to modify existing processes which will vary by the protocol and local situation. For example, 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.

✓ **Considerations for new clinical trials:**

▪ **Screening and Recruitment of new clinical trial participants:**

- a. **Hospital Restrictions:** Investigators in hospitals restricting / prohibiting clinical trial participants from visiting the facility (due to COVID-19 risks at their facility) for routine site visits must intimate the temporary closure of site facility to the sponsor, IEC / IRB with immediate effect.
- b. **Routine screening of new clinical trial participants:** Will not be prohibited by CDSCO. This will be decided by the Investigator / the hospital/ ethics committee/ sponsor (under appropriate precautions) keeping in mind risk/benefit assessment done by the investigator for new screenings.

References:

1. **Country Guidances on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic**

Country	Link to Guidance
Austria	https://www.basg.gv.at/en/healthcare-professionals/clinical-trials/klinische-studien-und-covid-19
Belgium	https://www.afmps.be/fr/news/directive_sur_la_delivrance_directe_de_medicaments_aux_patients_dans_le_cadre_dessais_cliniques
Denmark	https://laegemiddelstyrelsen.dk/en/news/2020/extraordinary-measures-for-clinical-trials-due-to-covid-19/
Estonia	https://www.ravimiamet.ee/en/guidance-clinical-trial-management-context-covid-19-pandemic
Hungary	https://ogyei.gov.hu/tajekoztatas_klinikai_vizsgalatok_folytonossagarol



Ireland	Guidance on the Management of Clinical Trials during COVID-19 (Coronavirus) – Ireland HPA - http://www.hpra.ie/homepage/medicines/regulatory-information/clinical-trials/covid-19-(coronavirus)-and-cts
Italy	https://www.aifa.gov.it/documents/20142/871583/Comunicato_gestione_studi_clinici_in_emergenza_COVID-19_EN_12.03.2020.pdf/ee1f33e3-bb3_e-9ce9-2a93-b33e88eea94d
Netherlands	https://english.ccmo.nl/latest/news/2020/03/16/recommendations-for-the-conduct-of-clinical-research-at-the-time-of-restrictive-measures-due-to-the-coronavirus
Peru	https://ensayosclinicos-repec.ins.gob.pe/images/comunicados/Comunicado_2020/COMUNICADO-001-2020-OGITT.pdf
Spain	https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/2020-medicamentosusohumano-3/medidas-excepcionales-aplicables-a-los-ensayos-clinicos-para-gestionar-los-problemas-derivados-de-la-emergencia-por-covid-19/
United Kingdom	https://mhrainspectorate.blog.gov.uk/2020/03/12/advice-for-management-of-clinical-trials-in-relation-to-coronavirus/ (Blog Post) https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19 (Guidance Document)
United States	https://www.fda.gov/media/136238/download
EMA	https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
Korea	As attached