

GUIDANCE ON THE CONDUCT OF CLINICAL TRIALS IN RELATION TO THE COVID-19 SITUATION

1. INTRODUCTION

- 1.1. The Health Sciences Authority (HSA) recognises that the COVID-19 (Coronavirus Disease 2019) situation may impact the conduct of clinical trials of therapeutic products and medicinal products in Singapore. This may be a result of trial participants being unable to visit trial sites due to quarantines / stay home notices / visit restrictions at trial sites / travel restrictions, study staff redeployment, interruption of Investigational Product (IP) supply chain or challenges in conducting on-site monitoring visits by sponsors.
- 1.2. Sponsors and investigators may be required to implement contingency measures to mitigate these challenges during the COVID-19 situation.
- 1.3. HSA recognises the difficulties faced by sponsors and investigators in managing clinical trials during the COVID-19 situation. This guidance is to provide general considerations to sponsors and investigators to ensure the safety of trial participants, compliance with the clinical trials regulations and ICH GCP (R2) Guidelines, and minimise risks to trial integrity.
- 1.4. **Sponsors and investigators should note that the advice in this guidance applies only for the COVID-19 situation, unless otherwise agreed by HSA in writing.**
- 1.5. **Please email us at HSA_CT@hsa.gov.sg if you require any clarifications on this guidance.**

2. CONSIDERATIONS FOR ONGOING CLINICAL TRIALS

2.1. Ensuring the safety and well-being of trial participants is paramount.

2.2. Sponsors and investigators should consider the specific context and circumstance of each clinical trial, and focus on the potential impact on the safety and well-being of trial participants, when considering potential modifications to trial conduct in relation to the COVID-19 situation.

2.3. Sponsors may want to consider the following prior to implementing contingency measures for their clinical trials in relation to the COVID-19 situation:

- a) The nature of, and extent of clinical experience with, the investigational product;
- b) The nature of the disease under study in the clinical trial;
- c) The availability and feasibility of alternative methods for appropriate efficacy and safety monitoring of trial participants;
- d) Whether the alternative methods for safety monitoring and assessment would be sufficient to assure the safety of trial participants;
- e) The ability to appropriately manage adverse events / toxicity and/or to implement dose modifications or discontinuations in accordance with the protocol, in a timely manner with the proposed contingency measures;
- f) Where there are compelling reasons for certain efficacy and safety assessments not to be completed, to use best medical judgment in weighing the benefits and risks of continuing treatment in the absence of such study assessments;
- g) The potential impact on the IP supply chain and accountability; and
- h) The potential impact on data credibility and trial integrity.

2.4. Sponsors and investigators should document the reasons for any contingency measures implemented and perform an impact assessment of the implemented measures on trial participant safety and on data credibility and trial integrity. Any missing trial data in the case report forms due to these measures should be explained and documented.

2.5. The implementation of any contingency measures should be done in early consultation with the sponsor, the local investigators/trial sites, Institutional Review Boards (IRBs) and HSA. It is important that trial participants are kept informed of changes to the clinical trial that could impact them.

2.6. **Remote study visits**

2.6.1. If trial participants are unable to return to the trial sites for study assessments and procedures in relation to the COVID-19 situation, sponsors may consider alternative methods for efficacy and safety monitoring, for example, alternative locations for laboratory tests and CT/MRI scans, remote follow-up with trial participants via telephone / video calls. Sponsors should consider whether the safety of trial participants can be reasonably assured with the implementation of the alternative efficacy and safety monitoring approach.

2.6.2. If remote study visits are to be implemented urgently for the safety of trial participants, these may be considered as Urgent Safety Measures. Sponsors should notify HSA of these Urgent Safety Measures. Please refer to Section 3 of this guidance for further details.

2.6.3. Investigators may want to consider the following for remote study visits for trial participants:

- a) Obtain sponsor approval for use of the remote facility;
- b) Provide trial participants with written information on the type and frequency of study procedures and protocol-specific parameters (where required) to be performed remotely;
- c) Collect information on the name and contact details of the remote facility;
- d) Establish timelines for transfer of source documents (e.g. laboratory test results, CT/MRI scan results etc.) from the remote facility / trial participant to the trial site;
- e) Review the results of all study procedures performed promptly and contact trial participants to follow up on laboratory results, adverse events, and concomitant medications in order to assess trial participant safety; and

- f) Document all contacts between trial sites and trial participants / remote facilities / sponsors and maintain them on file.

2.6.4. Sponsors may want to consider the following for remote study visits for trial participants:

- a) Determine if remote facilities are able to perform the study procedures in accordance with the protocol. Accreditation certificates, list of normal reference ranges and laboratory director's curriculum vitae may be collected from the remote facilities, where possible;
- b) Reimburse trial participants for additional costs incurred from remote study visits; and
- c) Assess if the protocol and/or informed consent form should be amended. Refer to Section 3 of this guidance for further details.

2.7. Direct to Patient (DTP) services for Investigational Product (IP) supply

2.7.1. If trial participants are unable to return to trial sites in relation to the COVID-19 situation, sponsors and investigators may consider delivering the IP to the trial participants' homes via Direct to Patient (DTP) service, after the sponsor and investigator(s) have determined that the investigational product can be safely and properly self-administered by trial participants remotely without the supervision of the investigator and/or the study team. Ensuring IP security, accountability, traceability and compliance to IP storage requirements will be pertinent.

2.7.2. Sponsors and investigators should notify HSA about the DTP service via email for their protocols prior to implementation. The implementation of DTP service need not be submitted to HSA as a substantial amendment or Urgent Safety Measure.

2.7.3. The investigator should maintain oversight of the IP delivery to trial participants since the investigator is ultimately responsible for the medical treatment and care of the trial participant.

2.7.4. The DTP service should only involve supplying the IP from the trial site directly to the trial participants' homes. In the event the sponsor is planning to supply the IP from alternative locations (e.g. manufacturer, sponsor, central depot or distributor etc.) to trial participants' homes, the sponsor should provide details on additional measures to safeguard trial participant privacy and data confidentiality to HSA before implementing this plan.

2.7.5. The sponsor may wish to refer to the Singapore Standards for Guidelines for the Supply and Delivery of Medication (SS 644:2019) from Enterprise Singapore for further guidance on DTP services.

<https://www.singaporestandardseshop.sg/Product/SSPdtDetail/f886eaf3-b1e1-4d8a-82c5-c83179bb87bd>

2.7.6. Sponsors and investigators should take into consideration the following for DTP services for trial participants:

- a) Provide written instructions to trial sites on handling and storage of the IP when using DTP services;
- b) Inform trial participants about the DTP service. The information may be conveyed to trial participants verbally and documented in the trial participants' medical records;
- c) Ensure the IP is delivered to trial participants' homes within the recommended storage temperature for the IP and in a secured manner;
- d) Consider viable alternatives in the event the trial participant / trial participant's legal representative is unable to receive the IP personally at home;
- e) Provide written instructions to trial participants on using the IP and contact details of the study staff for any enquiries. The investigators should ensure that trial participants use the delivered IP correctly in accordance with the protocol;
- f) Ensure traceability throughout the IP supply chain;
- g) Maintain documentation relating to shipment, receipt, storage, dispensing and accountability, return and destruction;

- h) Ensure that trial participant privacy and data confidentiality are safeguarded; and
- i) Ensure that treatment blinding is not compromised by the DTP approach.

2.7.7. DTP service for early phase clinical trials

In early phase clinical trials where there is limited experience with the dose level being tested and safety of the dose level is still being assessed, it is generally not recommended to send more than 1 cycle/visit of IP to trial participants. In the event the investigator is planning to send more than 1 cycle/visit of IP to trial participants beyond what is planned in the protocol, please consult the sponsor and HSA.

2.8. Site Monitoring Visits

- 2.8.1. Sponsors should assess whether the monitoring plan requires adjustment in relation to the COVID-19 situation if monitors are unable to conduct on-site monitoring visits. Sponsors may consider implementing centralised monitoring or remote monitoring (i.e. remote Source Document Verification) as alternative options for site monitoring visits.
- 2.8.2. Sponsors and investigators should notify HSA about the remote monitoring for their protocols prior to implementation. The implementation of remote monitoring need not be submitted to HSA as a substantial amendment or Urgent Safety Measure.
- 2.8.3. Sponsors should obtain a written agreement from the trial sites for remote monitoring prior to implementation.
- 2.8.4. Sponsors and investigators should consider the following to safeguard trial participant privacy and data confidentiality during remote monitoring.
 - a) All trial participant identifiers should be removed from the source documents prior to transmission, and replaced with trial participant ID;

- b) The site staff should implement a quality control process to verify that trial participant identifiers have been removed for every redacted source document being transmitted;
- c) The redacted source documents should be transmitted in a secure manner to the monitor;
- d) The transmission and receipt of the redacted source documents should be documented;
- e) The sponsor should implement a quality control process to verify that trial participant privacy and data confidentiality have been safeguarded in the redacted source document;
- f) The monitor should re-verify the data from the corresponding source documents during the subsequent on-site monitoring visits; and
- g) The monitor should destroy the redacted source documents and document the destruction.

3. NOTIFICATIONS

Sponsors and investigators should note the following:

3.1. **Temporary suspension of screening and recruitment**

3.1.1. If the sponsor decides to temporarily suspend / halt screening and recruitment of trial participants in relation to COVID-19 situation, the sponsor should notify HSA of the temporary suspension of screening and recruitment by submitting a Trial Status Report to HSA within 15 calendar days of the temporary suspension.

3.2. **Non-compliances**

3.2.1. There may be an increased incidence of non-compliances reported in relation to the COVID-19 situation.

3.2.2. Sponsors should assess if the non-compliances fulfil the definition of Serious Breach. If the non-compliance is deemed to be a serious breach, the sponsor should notify HSA as soon as possible and no later than 7 calendar days from the sponsor's awareness of the Serious Breach. Please refer to the regulatory guidance on Serious Breach Notifications for further information.

3.3. **Urgent Safety Measures**

3.3.1. In the event that contingency measures (e.g. remote study visits) need to be implemented urgently for the safety of trial participants in relation to the COVID-19 situation, sponsors may consider implementing these contingency measures as Urgent Safety Measures. Sponsors should notify HSA of the Urgent Safety Measure as soon as possible and no later than 7 calendar days from the implementation of the Urgent Safety Measure.

3.4. **Substantial Amendments**

3.4.1. If contingency measures in relation to the COVID-19 situation fulfil the definition of substantial amendments, sponsors should submit the substantial amendments to HSA for review and approval. Please refer to the regulatory guidance on Determining Whether an Amendment to a Clinical Trial is a Substantial Amendment for further information.

4. **CLINICAL STUDY REPORT**

- 4.1. Sponsors should ensure the following are included in the Clinical Study Report:
- a) All contingency measures implemented in relation to COVID-19 situation.
 - b) Subject IDs of all trial participants affected by the COVID-19 situation and how their participation had been altered.
 - c) Impact of the contingency measures on safety and efficacy data for the clinical trial.



5. REFERENCES

- 5.1. FDA Guidance on Conduct of Clinical Trials of Medicinal Products during COVID-19 Situation – March 2020
- 5.2. MHRA Advice for Management of Clinical Trials in relation to Coronavirus – 12 March 2020
- 5.3. EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) situation – 20 March 2020