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

Version Date: 26 Aug 2022

Key Changes from previous version dated 29 Jul 2020, relating to:

(i) New clinical trials conducted to address the needs of a public health emergency [Section 2];

(ii) Documentation of contingency measures [Section 3.5];

(iii) Considerations for home visits [Section 3.7.8];

(iv) Removal of the need for sponsors to notify HSA of the following contingency measures prior to implementation [Section 4]:

a) Direct to Patient (DTP) services for Investigational Product (IP) supply;

b) Remote Source Document Verification (remote SDV) plans.

NOTE: The guiding principles outlined in this guidance may also be applied to other emerging public health emergencies, as defined by the Ministry of Health.

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, 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 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 and other emerging public health emergencies, as defined by the Ministry of Health, 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 NEW CLINICAL TRIALS CONDUCTED TO ADDRESS THE NEEDS OF A PUBLIC HEALTH EMERGENCY

2.1. If a clinical trial is to be conducted locally in the context of a public health emergency like the COVID-19 pandemic, the clinical trial application should still be submitted to HSA for review and approval in accordance with the applicable clinical trials regulations.

2.2. HSA exercises the necessary regulatory agility in such a situation in enabling rolling submissions and expedited approvals, as appropriate, to address the specific needs of the public health emergency. Clinical trial applications that are submitted to address the needs of the public health emergency will be prioritized and the review of such trials expedited. HSA will be flexible and accommodate sponsor's requests for a shortened review time (e.g., less than 15 working days, excluding stop-clock time), where appropriate.

2.3. HSA will also prioritize requests made by sponsors and investigators to the Innovation Office for rapid scientific and regulatory advice on the regulatory requirements for the development of novel vaccines and therapeutics to address the public health emergency. The matters for which advice may be sought include the adequacy of the non-clinical, clinical and/or CMC/manufacturing supporting documentation to support the relevant stage of the development of the product. Please email HSA_InnovationOffice@hsa.gov.sg with a list of questions and outline of the proposal.

3. CONSIDERATIONS FOR ONGOING CLINICAL TRIALS

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

3.2. 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.

3.3. 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.

3.4. 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.

3.5. Sponsors and investigators should ensure that the contingency measures are described in the study protocol or alternative documentation, including where applicable:

a) Rationale for implementing the contingency measures;
b) Whether the contingency measures will be implemented for local trial sites;
c) Procedures for informing trial participants about the contingency measures;
d) Study visits and study procedures that will be performed remotely;
e) Plans for Direct to Patient (DTP) services for Investigational Product (IP) supply;
f) Measures in place to safeguard trial participant privacy and data confidentiality;
g) Maintenance of oversight by the Principal Investigator; and
h) Whether the sponsor will cover the costs incurred.

3.6. 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.

3.7. **Remote study visits**

3.7.1. 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.

3.7.2. If trial participants are unable to visit the trial sites for study assessments and procedures in relation to the COVID-19 situation, sponsors may consider implementing remote study visits as alternative methods for efficacy and safety monitoring.

3.7.3. Examples of remote study visits may include the following:

a) Conducting laboratory tests or diagnostic tests (e.g. X-ray, CT scan, MRI scan etc.) at remote facilities;
b) Conducting remote consultations with trial participants via audio / video calls; or
c) Home visits by qualified healthcare professionals or study staff.

3.7.4. Sponsors should consider whether the safety of trial participants can be reasonably assured with the implementation of the alternative efficacy and safety monitoring approach.

3.7.5. 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.

3.7.6. Investigators may want to consider the following when conducting laboratory tests or diagnostic tests at remote facilities 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.

3.7.7. Investigators may want to consider the following when conducting remote consultations with trial participants via audio / video calls:

a) Consult the institution (e.g. IT department) on the acceptable telemedicine software to be used for remote consultation;
b) Ensure that the remote consultation is conducted in a secure manner, and adequate measures are in place to safeguard trial participant privacy and data confidentiality;
c) Verify the identity of the trial participant during the remote discussion; and
d) Document details of the remote consultation in the trial participant's source documents.

3.7.8. Investigators may want to consider the following when implementing home visits by healthcare professionals or study staff:

a) Ensure that the healthcare professionals or study staff involved in conducting home visits are adequately qualified by education, training and experience to conduct the study assessments and procedures;
b) Ensure that adequate measures are in place to safeguard trial participant privacy and data confidentiality; and
c) Maintain adequate oversight of the trial participants.

3.7.9. 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 and list of normal reference ranges 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 4 of this guidance for further details.

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

3.8.1. 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.

3.8.2. 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.

3.8.3. 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 the supplier (e.g. manufacturer, sponsor, central depot or distributor etc.) to trial participants' homes, the sponsor should ensure that there are additional measures to safeguard trial participant privacy and data confidentiality.

3.8.4. 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

3.8.5. 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 and seek their consent to provide their contact details to the vendor. Consent may be obtained verbally and documented in the trial participants' medical records.
c) Ensure that the trial participants' contact details are not divulged to the sponsor;
d) Ensure the IP is delivered to trial participants' homes within the recommended storage temperature for the IP and in a secured manner;
e) Consider viable alternatives in the event the trial participant / trial participant's legal representative is unable to receive the IP personally at home;
f) Provide written instructions to trial participants on using the IP, returning the used 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;
g) Ensure traceability throughout the IP supply chain;
h) Maintain documentation relating to shipment, receipt, storage, dispensing and accountability, return and destruction;
i) Ensure that trial participant privacy and data confidentiality are safeguarded; and
j) Ensure that treatment blinding is not compromised by the DTP approach.

3.8.6. **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.

3.9. **Informed consent**

3.9.1. Informed consent is a fundamental ethical and legal requirement in clinical trials. Freely given informed consent should be obtained from every trial participant or his/her legal representative (where applicable) prior to clinical trial participation. Informed consent from the trial participant or his/her legal representative is generally required to be obtained in writing, and personally signed and dated by the person giving consent at the time of consent.

3.9.2. There may be situations where alternative ways of obtaining and documenting informed consent may need to be considered if the trial participant (or his/her legal representative, where applicable) is in isolation or subject to a quarantine, stay home notice, or visit / travel restrictions, due to the COVID-19 situation.

3.9.3. Regardless of the informed consent process implemented, sponsors and investigators should ensure the following for informed consent:

(i) Rights, safety, well-being and privacy of trial participants are safeguarded;
(ii) Data security, confidentiality, reliability, integrity and quality are assured;
(iii) Basic principles of informed consent (i.e. information, comprehension and voluntariness) are assured;
(iv) Regulatory provisions for informed consent as specified in the clinical trials regulations and ICH E6 GCP guidelines are complied with.

3.9.4. Please note that references to trial participants in this guidance also apply to legal representatives of trial participants who are minors or adults lacking capacity.

3.9.5. **Trial participants in isolation and subject to infection control measures due to COVID-19**

3.9.5.1. If the trial participant is in isolation and subject to the healthcare institution's infection control policies, the investigator may consider conducting the informed consent discussion with the trial participant via any of the following methods:

a) Face to face discussion;

b) Remote consent via audio / video calls (see Section 3.8.6 below);

NB: Electronic consent may be used for either options, if technology is available (see Section 3.9.7 below).

3.9.5.2. In situations where the informed consent discussion is conducted face to face and it is not possible to remove the hard copy of the signed ICF from the isolation ward due to the healthcare institution's infection control policies, sponsors and investigators may consider the following approach to retain a signed copy of the ICF on site and provide a signed copy of the ICF to the trial participant.

a) The investigator, who participated in the face to face informed consent discussion, may take a photograph of the signature page of the signed ICF, print a copy of the photograph and certify it as a true copy. The photograph of the signature page should capture the version of the ICF used. The study staff involved in the face to face informed consent discussion may assist with taking, printing and certifying a copy of the photograph;

b) The study staff should then combine the certified true copy of the signature page with an uncontaminated copy of the corresponding Patient Information Sheet for retention on site and provision to the trial participant for safe keeping. The original photograph of the signature page should be deleted to protect the privacy of the trial participant and confidentiality of the data. Alternatively, the signed

ICF may be saved electronically in a manner that has secure and limited access and prevents unauthorised editing;

c) A copy of the signed ICF should be provided to the trial participant;

d) The documentation of the informed consent process should include details of how the copy of the signed ICF had been retained on site and provided to the trial participant.

3.9.6. **Remote consent**

3.9.6.1. In situations where trial participants are in isolation or unable to visit trial sites due to quarantine / stay home notice / visit or travel restrictions, investigators may consider conducting the informed consent discussion with the trial participants remotely.

3.9.6.2. Remote consent may be implemented in the following scenarios during the COVID-19 situation:

a) Enrollment of potential trial participants into COVID-19 clinical trials;

b) Re-consent of trial participants when new information (e.g. remote study visits, IP supply via DTP, updated safety information etc.) becomes available during the clinical trial that may affect the trial participants' willingness to continue trial participation.

3.9.6.3. For clinical trials where remote consent is being considered for the enrollment of potential trial participants, sponsors and investigators should submit a detailed plan of the remote consent process as part of the clinical trial application to HSA for review. Furthermore, an impartial witness should be present during the remote consent process as an additional safeguard, regardless of whether the trial participant is able to read or sign/date the ICF. The role of the impartial witness in this case would be to ensure that the identity of the potential trial participant had been verified and consent had been freely given.

3.9.6.4. Investigators may want to consider the following for remote consent:

a) Electronic consent may be considered, if the technology is available (see Section 3.9.7 below);
b) Consult the institution (e.g. IT department) on the acceptable telemedicine software to be used for remote consent;
c) Ensure that the informed consent discussion is conducted in a secure manner, and adequate measures are in place to safeguard trial participant privacy and data confidentiality;
d) Provide a copy of the ICF to the trial participant via snail mail / courier / email / messaging to read before the informed consent discussion;
e) Verify the identity of the trial participant during the remote consent discussion;
f) Request the trial participant to sign and date on the ICF and return a signed copy of the ICF to the trial site via snail mail / courier / email / messaging;
g) Sign and date the ICF with the current date upon receipt. It is important to note that the ICF should not be back dated;
h) Document details of the remote consent process in the trial participant's source documents. The discrepancy in the consent dates should be explained if all parties had signed and dated the ICF on different dates; and

i) Retain the signed copy of the ICF (signed by all parties) on site in a manner that has secure and limited access and prevents unauthorised editing. The trial participant should also be provided with a signed copy of the ICF in a similar manner.

3.9.6.5. For clinical trials where new information is available which may affect the trial participants' willingness to continue trial participation, it would not be required to notify HSA about the remote consent process for re-consent. Furthermore, an impartial witness would be required to participate in the informed consent discussion only if the trial participant is unable to read or sign/date the ICF.

3.9.7. **Electronic Consent (e-consent)**

3.9.7.1. E-consent refers to the use of electronic systems to:

(i) convey information related to the clinical trial to obtain informed consent; and/or

(ii) document informed consent, via electronic signature / digital signature, using an electronic device such as a smartphone, tablet or computer.

3.9.7.2. E-consent may either be used at the trial site or remotely to obtain informed consent from the trial participant.

3.9.7.3. Sponsors and investigators must comply with the regulatory requirements for informed consent as specified in the applicable clinical trials regulations and ICH E6 GCP guidelines. Additionally, they must comply with the Personal Data Protection Act (PDPA) for regulatory requirements on the collection, use and disclosure of personal data, and the Electronic Transactions Act (ETA) for regulatory requirements on the use of electronic signatures, digital signatures and electronic records.

3.9.7.4. Sponsors and investigators should submit a detailed plan of the e-consent system to HSA for review prior to implementation. It would be recommended to submit the following to HSA along with the clinical trial application:

(i) Screen shots and/or demonstration video of the e-consent system;

(ii) Measures in place to safeguard trial participant privacy and data security, confidentiality, reliability, integrity and quality;

(iii) Proposed e-consent process; and

(iv) Measures in place to safeguard trial participant privacy and data confidentiality during centralised monitoring / remote monitoring (if applicable).

3.9.7.5. Please refer to our Regulatory Guidance on Electronic Consent for further details.

3.10. Sponsor Site Monitoring Visits

3.10.1. There may be situations where the sponsor may be unable to conduct on-site monitoring visits as the trial sites may be unable to accommodate the monitors or the monitors may be unable to travel to the trial sites.

3.10.2. Sponsors should consider adopting a risk-based approach to monitoring, focusing on data and processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity and quality of the trial data.

3.10.3. The sponsor should consider the extent and nature of monitoring that would be required in each specific trial under this exceptional situation, and weigh this against the extra burden that introduction of any alternative measures would put on site staff and facilities. The monitoring plan should then be revised in accordance with these considerations, in order to strike an acceptable balance between appropriate oversight and the capacity of the trial site.

3.10.4. Sponsors may consider adjusting the monitoring plan by either:

a) Cancelling or postponing on-site monitoring visits;

b) Conducting centralised monitoring of electronic systems like electronic Case Report Forms (eCRFs), central laboratory / ECG / imaging data, electronic Patient Reported Outcomes (ePROs) etc.; or

c) Conducting remote monitoring via audio / video calls or electronic systems.

3.10.5. If remote monitoring involves remote Source Document Verification (i.e. remote SDV),

3.10.5.1. Sponsors should obtain a written agreement from the trial sites for remote SDV prior to implementation. The written agreement may be documented as addendum to the clinical trial agreement or via email.

3.10.5.2. Sponsors and investigators should consider the following to safeguard trial participant privacy and data confidentiality during remote SDV:

a) All trial participant identifiers should be removed from the source documents prior to transmission or screen-sharing, 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 or screen-shared;

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, unless otherwise justified by the sponsor; and

g) The monitor should destroy the redacted source documents and document the destruction.

4. REGULATORY NOTIFICATIONS

Sponsors and investigators should take note of the following regulatory notifications:

Note: *It is not required to submit plans for Direct to Patient (DTP) service for IP supply and remote Source Document Verification (remote SDV) plans to HSA prior to implementation, as long as the guiding principles outlined in this guidance are adhered to.*

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

4.1.1. 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.

4.1.2. The sponsor should submit a Trial Status Report to HSA once recruitment suspension has been lifted.

4.2. **Non-compliances**

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

4.2.2. Sponsors should assess the impact of the non-compliances to determine if they 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.

4.3. **Urgent Safety Measures**

4.3.1. 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. Information on the affected trial participants, study visits, study procedures that will be / will not be performed, and investigator oversight should be provided.

4.3.2. Subsequent updates to the Urgent Safety Measures may be notified to HSA via email.

4.4. **Substantial Amendments**

4.4.1. 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.

4.5. **Informed Consent**

4.5.1. Sponsors should submit detailed plans of the informed consent process for the following scenarios to HSA for review prior to implementation:

a) Alternative approaches to retain and provide the signed ICF for trial participants who are hospitalised and in isolation due to COVID-19;

b) Remote consent for enrollment of potential trial participants; or

c) Electronic consent (e-consent).

5. CLINICAL STUDY REPORT

5.1. Sponsors should ensure the following are included in the Clinical Study Report:

a) All contingency measures implemented in relation to COVID-19 situation.

b) Trial Participant 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.

6. REFERENCES

6.1. FDA Guidance on Conduct of Clinical Trials of Medicinal Products during COVID-19 Situation

6.2. EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) situation

6.3. HSA Regulatory Guidance on Electronic Consent