

MANAGING THE IMPACT OF CLINICAL TRIALS DURING THE COVID-19 PANDEMIC

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Overview

- Challenges encountered during COVID-19 pandemic
- Regulatory facilitation
- Regulatory oversight
- Impact of COVID-19 on the future of clinical trials



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Challenges encountered during COVID-19 pandemic

- Urgent need to develop effective therapeutics and vaccines that are needed to combat the COVID-19 pandemic.
- Conduct of ongoing clinical trials impacted due to:
 - Visit restrictions;
 - Study staff redeployment;
 - Interruption of Investigational Product (IP) supply chain; or
 - Challenges in conducting on-site monitoring visits by sponsors.



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Regulatory Facilitation

- Alternative ways of obtaining informed consent
 - Trial participants in isolation
 - Remote consent
 - Electronic consent
- Investigational Product (IP) supply
 - Direct to Patient (DTP) service to trial participants' homes
- Remote study visits
- Alternative methods for monitoring of clinical trials



HSA Regulatory Guidance on the Conduct of Clinical Trials During COVID-19

 Important considerations for contingency measures:



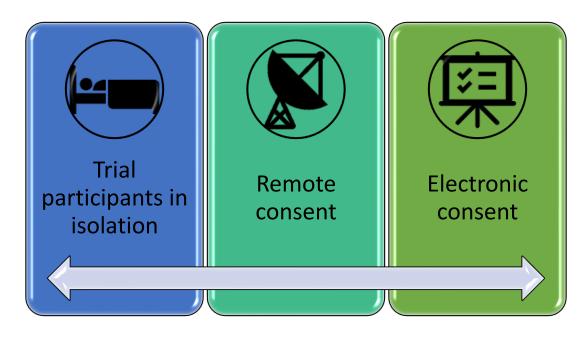
Safety of trial participants



Data integrity and quality



Enabling measures for Informed Consent



Important considerations:

- Rights, safety and well-being of trial participants must be safeguarded;
- Data security, confidentiality, reliability, integrity and quality are assured;
- Basic principles of informed consent (information, comprehension, voluntariness) are assured; and
- Regulatory provisions for informed consent are complied with.



Trial participants in isolation

 It may not be possible to retain and provide a signed copy of the informed consent form (ICF) due to the institution's infection control measures.



Notify HSA about informed consent process.



 Take a photograph of the signed signature page of the ICF (NB: ICF version reference should be included in photograph)



Print the photograph and certify it as a true copy.



Combine the printout with an uncontaminated copy of the ICF.



 Delete the original photograph to safeguard privacy and confidentiality.



 Retain a copy of the signed ICF and provide a copy of the signed ICF to the trial participant.



Document the ICF process in the source documents.



Use of electronic systems and processes to:



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



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



Guiding principles for secure electronic signatures

An electronic signature is considered a <u>secure electronic</u> signature if you can verify:

- (i) that the persons who signed are who they say they are;
- (ii) that the consent form they signed has not been altered; and
- (iii) when the signatures were applied.

Examples of secure e-signatures:

- (i) Signing using a finger / stylus on a touch screen if consent is conducted via face-to-face or video call where the identity of the trial participant can be verified;
- (ii) Ticking a checkbox or clicking 'I accept' button via an electronic system or process that can uniquely identify the trial participant;
- (iii) Digital signature.

NB: It is not recommended to paste a digital image of a manuscript signature.



Additional regulatory requirements:

- Personal Data Protection Act (PDPA); and
- Electronic Transactions Act (ETA) for secure electronic signatures

Sponsors should:



 Notify HSA about the e-consent system prior to implementation.



Consider back-up options (e.g. paper ICF); and



 Notify HSA of subsequent changes to the e-consent system that may significantly impact trial participant privacy and data security, confidentiality, reliability, integrity and quality.



Investigators should:



 Consult their institutions to ensure that the e-consent system is compatible with institutional policies for data protection and electronic / digital signatures;



 Ensure that study staff trial participants are familiar with navigating the e-consent system;



Ensure that correct version of ICF has been uploaded;



Conduct the ICF discussion in person or remotely; and



- Ensure that ICFs are personally signed and dated:
 - Manually or
 - Secure electronic signatures



Remote Consent

- Face to face consent should always be considered the default mode of consent for clinical trials as:
 - Investigator may not be familiar with the trial participant;
 - Investigator should meet the trial participant in person to conduct screening procedures (including physical examination, obtaining medical history, collecting biological samples etc.) to determine eligibility.
- Remote consent may be adopted in certain situations if face to face consent is not possible:
 - Enrollment of new trial participants during a pandemic where it is not possible for trial participants to visit trial sites due to visit restrictions.
 - Seek IRB and HSA approvals for remote consent.
 - Impartial witness required to be present regardless of whether trial participant is unable 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 has been verified and consent has been freely given.
 - Re-consent of ongoing trial participants.
 - Notify IRB about proposed re-consent process.



Remote Consent

Investigators should:



Consult institution on acceptable telemedicine software;



 Ensure that the discussion is conducted in a secure manner, respecting the privacy and confidentiality;



Send ICF to trial participant via registered mail / email / fax / courier;



Verify the identity of the trial participant;



Ensure that all parties personally sign and date the ICF;



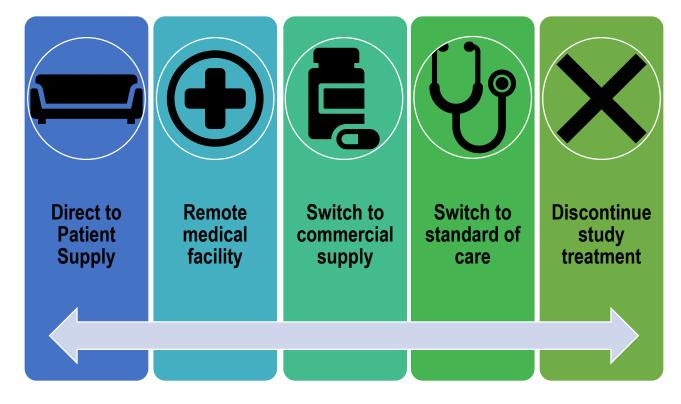
 Document the informed consent process in the trial participant's source documents;



 Retain a copy of the signed ICF and provide a copy of the signed ICF to the trial participant.



Enabling Measures for Investigational Product (IP) supply



Important considerations:

- Safety of trial participants;
- IP security, accountability, traceability and compliance to IP storage requirements; and
- PI oversight.



IP supply via Direct to Patient (DTP) Service



Notify HSA about DTP plans;



Provide written instructions for handling and storage of IP;



Seek consent from trial participants (written or verbal);



Request trial participants to acknowledge receipt of IP;



 Provide written instructions to trial participant on using and returning the IP;



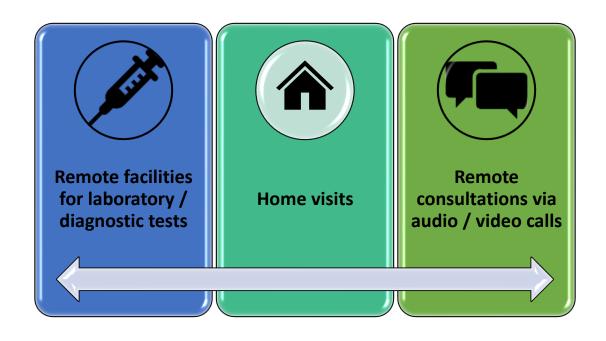
• Ensure privacy and confidentiality are safeguarded;



• Maintain IP documentation.



Enabling Measures for Study Visits

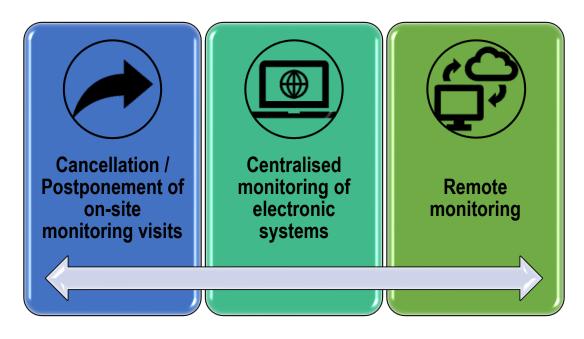


Important considerations:

- Safety of trial participants can be reasonably assured through alternative efficacy and safety monitoring approach;
- Data security, confidentiality, reliability, integrity and quality are assured; and
- PI oversight.



Enabling Measures for Site Monitoring Visits



Important considerations:

- Adopt a risk-based approach to monitoring;
- Focus on data and processes that are critical to protecting the rights, safety and well-being of trial participants, and data integrity and quality;
- Data security, confidentiality, reliability, integrity and quality are assured; and
- Burden that may be imposed on site staff and facilities.



Remote Source Document Verification (remote SDV)



Notify HSA about remote SDV plans;



Obtain written agreement from the trial sites prior to implementation;



 Ensure that source documents are redacted and quality control measures are implemented to verify this;



Transmit redacted source documents in a secure manner;



Document transmission and receipt of redacted source documents;



 Re-verify the corresponding source documents at a subsequent on-site monitoring visit; and



Destroy redacted source documents and document destruction.

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Notifications to HSA

- Temporary suspension of screening and recruitment
- Serious Breach Notifications
- Urgent Safety Measures
- Substantial amendments
- IP supply via DTP service
- Alternative ways to informed consent:
 - 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 into COVID-19 clinical trials; or
 - c) Electronic consent (e-consent).
- Remote SDV



Remote GCP Inspections



- GCP Inspections may be conducted remotely in view of visit restrictions during a pandemic.
 - Remote vs hybrid inspections



- Interviews conducted remotely
 - Enables interviewees from different time zones to be interviewed



- Involves review of electronic systems:
 - electronic Case Report Forms, electronic Trial Master File, electronic Patient Reported Outcomes etc.



- Requires extended timelines for inspection preparation
 - Video Conferencing Apps
 - Remote access to sponsor/site SOPs and electronic systems
 - Training on electronic systems



Remote GCP Inspections

- Challenges:
 - Records access



- Sponsor/site SOPs
- electronic Trial Master Files (e.g. study level documents, unblinded documents)
- Trial participant medical records not reviewed for remote inspections



Access to file sharing portals



Use of acceptable Video Conferencing Apps



Differing time zones of interviewees



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Impact of COVID-19 on the Future of Clinical Trials

Need to future proof and optimise clinical trials

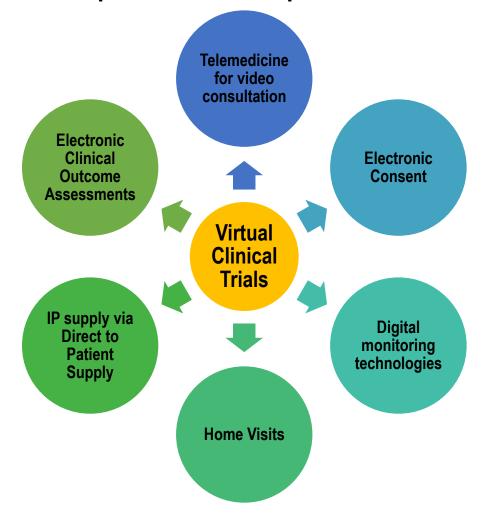
Re-calibrate the optimization of Use only scientifically and Encourage virtual visits Re-assess types and frequency of efficacy ethically justified eligibility criteria patient safety assessments extra to standard of care Re-assess the need for and frequency of safety assessments Account for new standard-of-care Ensure resemblance to real-world Rationalize assessments with healthcare delivery 'target' population trial endpoints Implement alternative safetyassessment methods (e.g., Provide flexibility for assessment times Reduce non-essential screening Ensure trials are patient-centered assessments wearable technologies) Ensure protocol resilience to Consider imaging triggered by clinical findings (e.g., from ePROs or validated external stressors Enable full remote assessment Limit 'in person' screening assessments to a single visit for low-risk trials questionnaires) Have inbuilt contingency plans Permit virtual visits and Limit physical examination Permit decentralized efficacy Prioritize primary trial endpoints decentralized assessments where possible assessments in non-study centers Account for infection risks in and review centrally sample size calculations Consider surrogate efficacy markers Enable remote trial monitoring (e.g., ctDNA and tumor markers) Trial regulation Informed consent Trial eligibility IMP(s) and other Ongoing safety Other Efficacy and design (IC) procedures and screening study drugs considerations assessments assessments Implement courier transfer of Increase reliance on ePROs Ensure flexibility, safety and Implement virtual visits to limit travel and HCW exposure self-administered drugs and validated questionnaires practicality for patients Enable flexible electronic Permit and train in low-risk Allow safety assessments in Limit in-person assessment visits and remote consent drug administration at home non-study centers Avoid any intensive assessments Ensure compliance with React promptly to adverse Minimize time in study center that cannot be fully key principles of IC by optimizing dispensing of drugs events to ensure patient safety justified for the specific trial Review adequacy of safety Decentralize the use of study assessments frequently centers for protocolized assessments. training staff as appropriate

Source: Doherty, G.J., Goksu, M. & de Paula, B.H.R. Rethinking Cancer Clinical Trials for COVID-19 and Beyond. Nat Cancer 1, 568-572 (2020)



Impact of COVID-19 on the Future of Clinical Trials

Need to future proof and optimise clinical trials





Impact of COVID-19 on the Future of Clinical Trials

Virtual clinical trials

 Can complement traditional clinical trials but not completely replace it.

Benefits

- Reduces need for face to face study visits;
- More efficient and less burdensome to trial participants;
- Allows meaningful and complete understanding of trial participants' conditions and responses.

Challenges

- Privacy of trial participants;
- Data security, confidentiality, reliability, quality and integrity;
- Cost;
- Unreliability with trial participant use.
- Sponsors should consult HSA on their plans prior to implementation.



References

- ICMRA Statement on Clinical Trials 24 Jun 2020
- HSA Guidance on the Conduct of Clinical Trials During the COVID-19 Situation – 29 Jul 2020
- HSA Guidance on Electronic Consent 1 Mar 2021
- Doherty, G.J., Goksu, M. & de Paula, B.H.R. Rethinking Cancer Clinical Trials for COVID-19 and Beyond. Nat Cancer 1, 568-572 (2020)
- Goldsack, J.C. et al, Remote digital monitoring in clinical trials in the time of COVID-19. Nature Reviews Drug Discovery 19





Thank You!

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