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

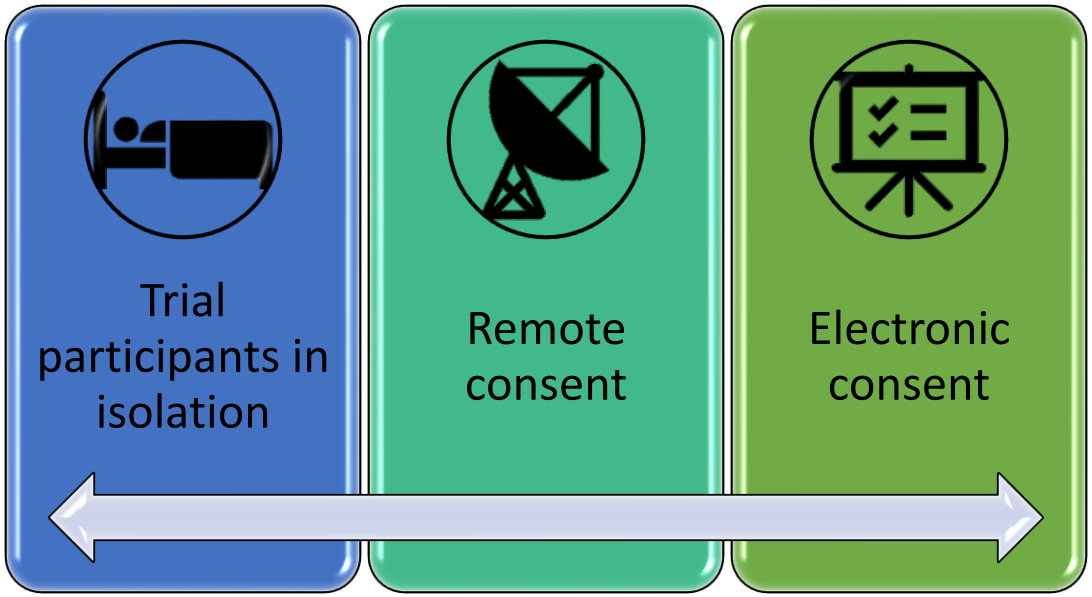
HSA Regulatory Guidance on the Conduct of Clinical Trials During COVID-19

- Important considerations for contingency measures:

Safety of trial participants

Data integrity and quality

Enabling measures for Informed Consent



- **<u>Important considerations:</u>**
  - 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.

Electronic Consent

- **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.

Electronic Consent

- **Guiding principles for secure electronic signatures**

  An electronic signature is considered a secure electronic 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.

Electronic Consent

- **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.

Electronic Consent

- **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:**

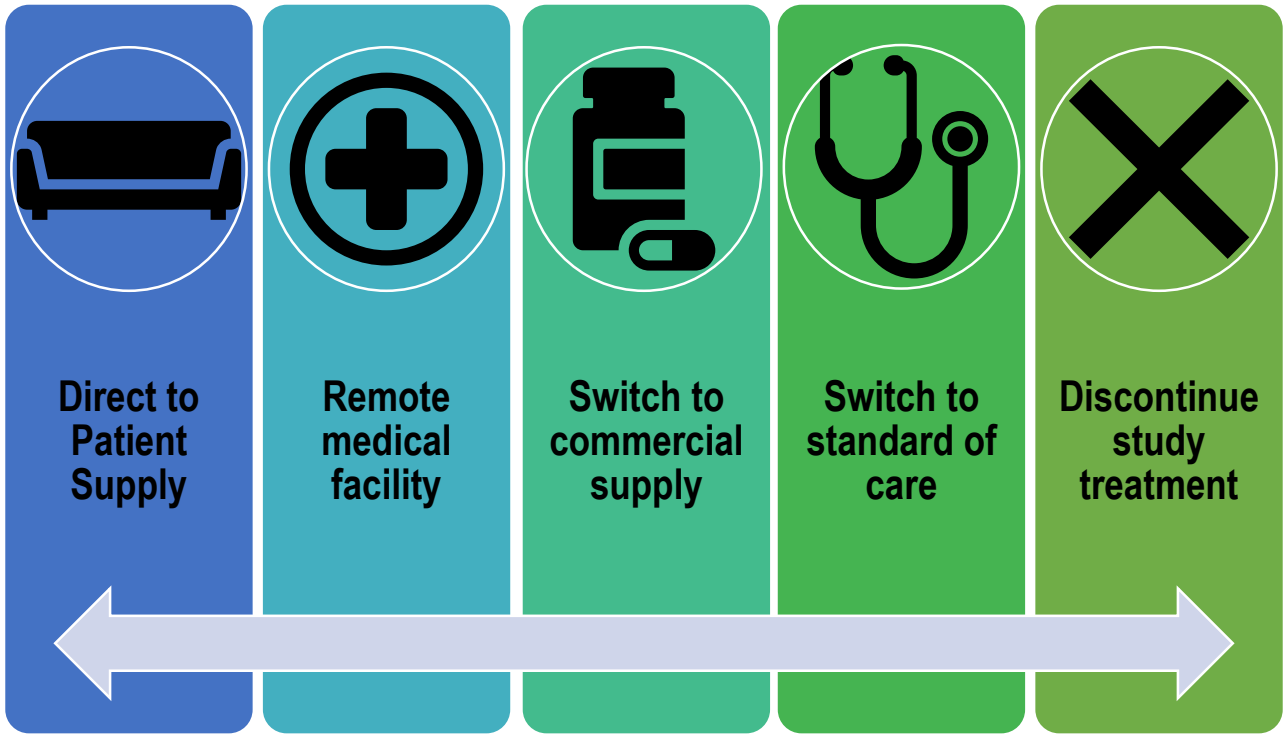
  - Enrollment of new trial participants during a pandemic where it is not possible for trial participants to visit trial sites due to visit restrictions.
    - *Seek IRB and HSA approvals for remote consent.*
    - *Impartial witness required to be present regardless of whether trial participant is unable 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



- **<u>Important considerations:</u>**
  - 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);

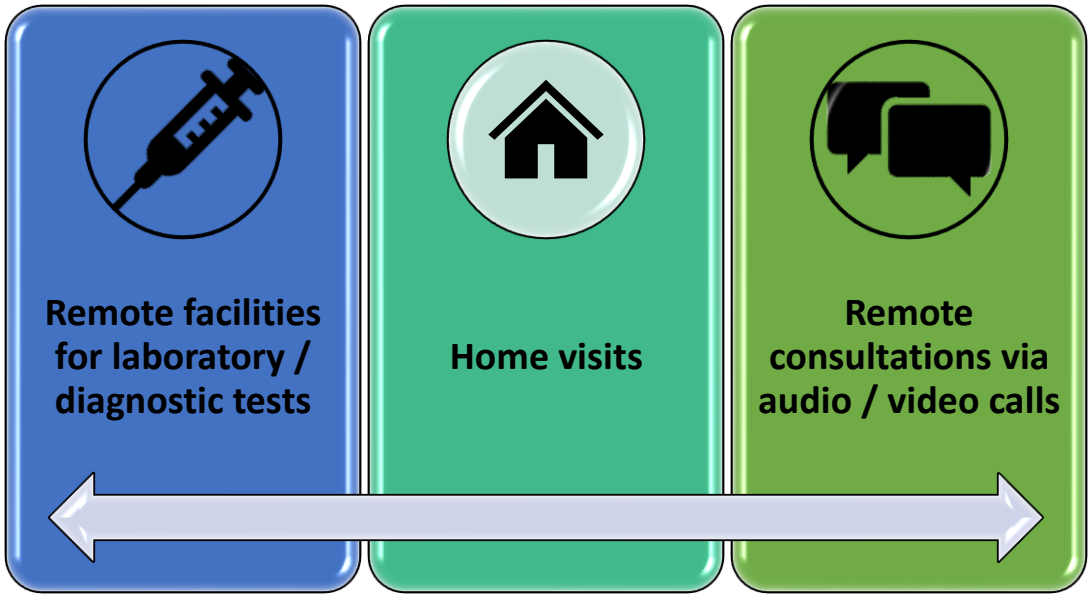
- Request trial participants to acknowledge receipt of IP;

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

- Ensure privacy and confidentiality are safeguarded;

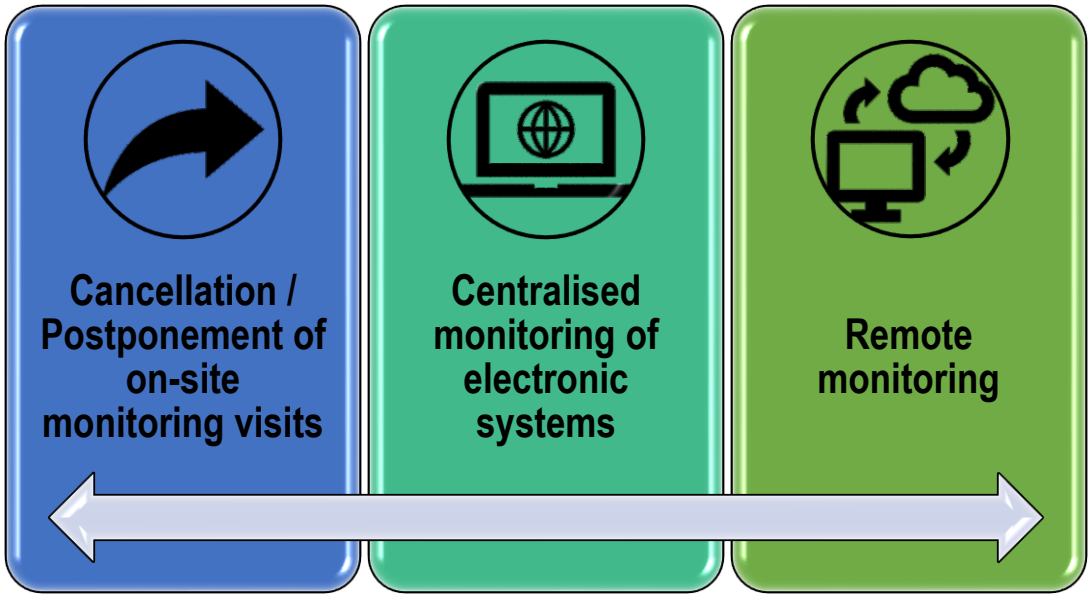
- Maintain IP documentation.

Enabling Measures for Study Visits



- **<u>Important considerations:</u>**
  - 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



- **<u>Important considerations:</u>**
  - 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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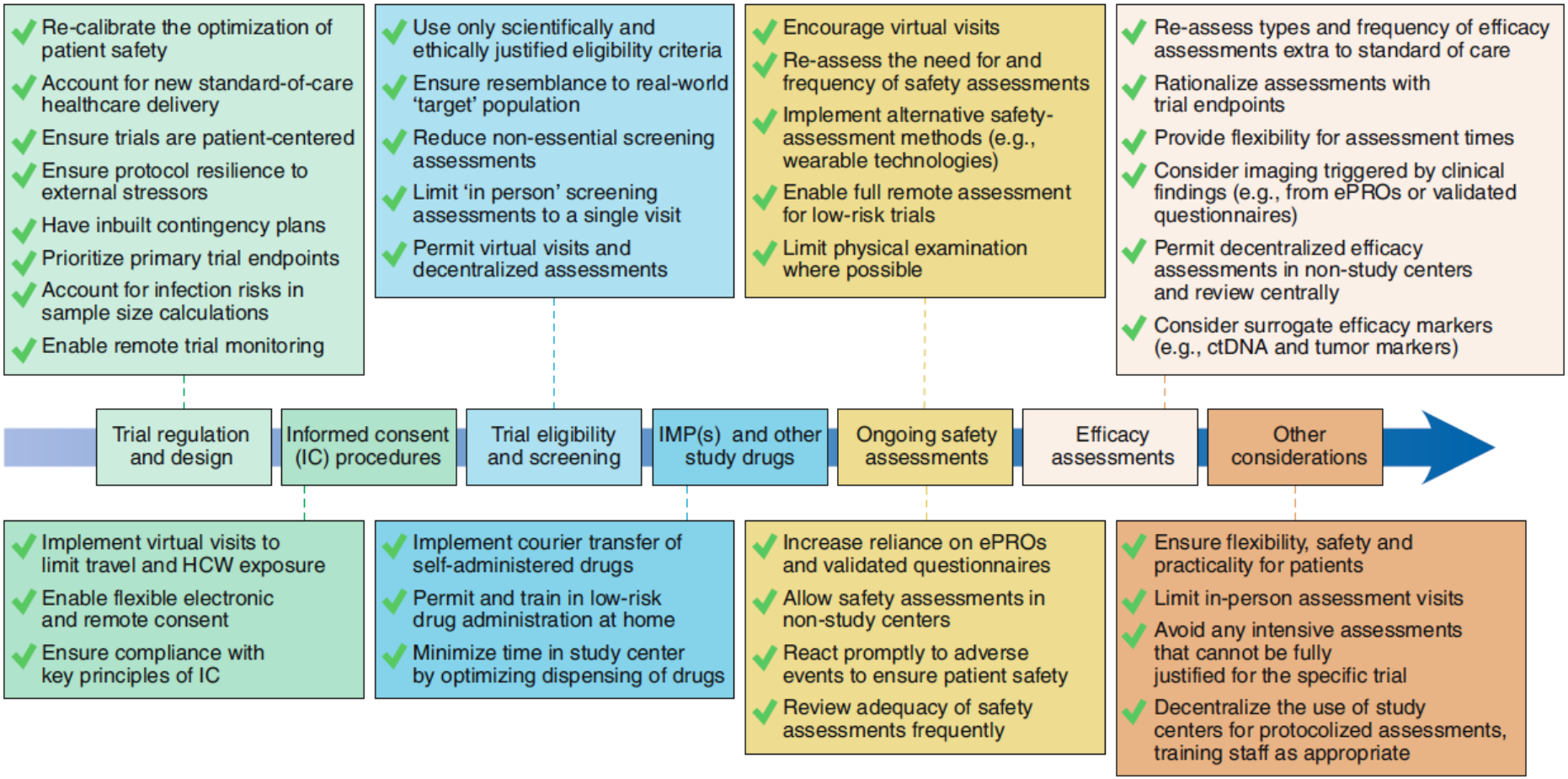
Impact of COVID-19 on the Future of Clinical Trials

Need to future proof and optimise clinical trials



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)

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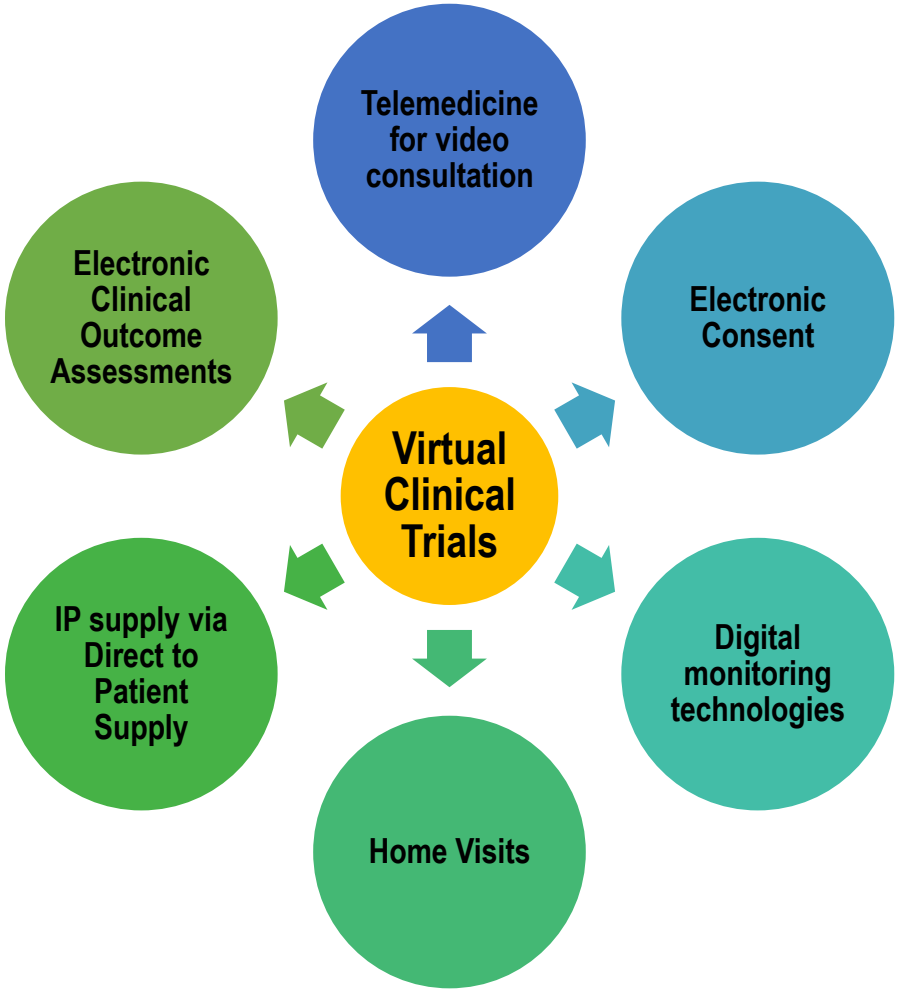

Impact of COVID-19 on the Future of Clinical Trials

- **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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