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Clinical Trial Compliance Program

Management of clinical trials during the COVID-19 pandemic

Online Presentation
Toronto June 18, 2020

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Overview

- Health Canada roles and responsibilities in clinical trial oversight
- Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors
- Strategy and methodology for the conduct of virtual clinical trial inspections
- Plan and scope of clinical trial inspections for fiscal year 2020/21

Health Canada Roles and Responsibilities in Clinical Trial Oversight

Health Products and Food Branch (HPFB)

Therapeutic Products Directorate (TPD) and Biologic and Radiopharmaceutical Drugs Directorate (BRDD)

- Clinical Trial Application (CTA)
- CTA-Amendment (CTA-A)
- CTA-Notification (CTA-N)
- Adverse Event (AE) Reporting
- No Objection Letter (NOL), Suspension, Cancellation

Collaboration

Regulatory Operations and Enforcement Branch (ROEB)

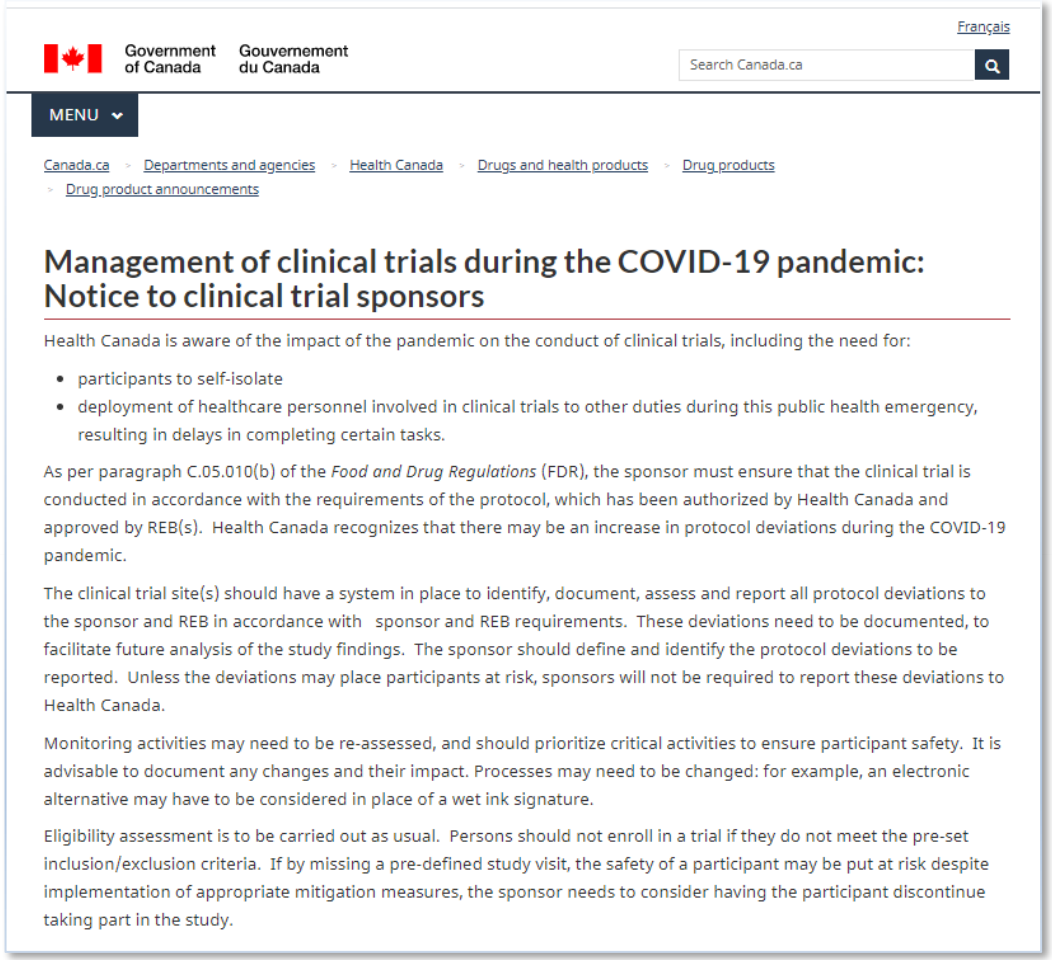
Medical Devices and Clinical Compliance Directorate (MDCCD) – Clinical Trial Compliance Program (CTCP)

- Inspection
- Compliance Verification
- Investigation
- Compliance Promotion

Notice on management of clinical trials during the COVID-19 pandemic

- Published online on March 23, 2020 (updated April 3, 2020) www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/management-clinical-trials-during-covid-19-pandemic.html

- Health Canada is aware of the impact of the pandemic on the conduct of clinical trials, including the need for:
  - participants to self-isolate
  - deployment of healthcare personnel involved in clinical trials to other duties during this public health emergency, resulting in delays in completing certain tasks.



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Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors

Health Canada is aware of the impact of the pandemic on the conduct of clinical trials, including the need for:

- participants to self-isolate
- deployment of healthcare personnel involved in clinical trials to other duties during this public health emergency, resulting in delays in completing certain tasks.

As per paragraph C.05.010(b) of the *Food and Drug Regulations* (FDR), the sponsor must ensure that the clinical trial is conducted in accordance with the requirements of the protocol, which has been authorized by Health Canada and approved by REB(s). Health Canada recognizes that there may be an increase in protocol deviations during the COVID-19 pandemic.

The clinical trial site(s) should have a system in place to identify, document, assess and report all protocol deviations to the sponsor and REB in accordance with sponsor and REB requirements. These deviations need to be documented, to facilitate future analysis of the study findings. The sponsor should define and identify the protocol deviations to be reported. Unless the deviations may place participants at risk, sponsors will not be required to report these deviations to Health Canada.

Monitoring activities may need to be re-assessed, and should prioritize critical activities to ensure participant safety. It is advisable to document any changes and their impact. Processes may need to be changed: for example, an electronic alternative may have to be considered in place of a wet ink signature.

Eligibility assessment is to be carried out as usual. Persons should not enroll in a trial if they do not meet the pre-set inclusion/exclusion criteria. If by missing a pre-defined study visit, the safety of a participant may be put at risk despite implementation of appropriate mitigation measures, the sponsor needs to consider having the participant discontinue taking part in the study.

Clinical Trial Applications (CTA)

- Health Canada will prioritize the review of CTAs designed to investigate the diagnosis, treatment and/or prevention of COVID-19.
- Sponsors may continue to file other CTA and CTA amendments according to Health Canada guidance.
- During the course of a CTA review, if sponsors are unable to respond to an Information Request (IR) within specified time lines, consider withdrawing the submission without prejudice and refiling when the information is available.

Participants Affected with COVID-19

- Sponsors must decide quickly whether:
  - the study is to placed on hold (i.e. not administering the investigational product (IP) until the participant has recovered)
  - the participant's involvement in the study is to be discontinued

- Documentation pertaining to all participants affected by a COVID-19 related study disruption should include:
  - unique participant identifier, site
  - raison for holding the study treatment or discontinuation of the participant in the trial
  - how the individual's participation was altered.

Trial Participants

- **The ongoing safety of trial participants is primary concern and must be maintained.**
- Risks and risk mitigation strategies related to use of any immunosuppressive agents should be discussed with medical professionals with expertise in immunology.
- Study participants need to be informed of any risks/changes to the study and monitoring plan that could impact on their wellbeing.
- Documentation of medical oversight is required to determine participants' eligibility to take part in study.
- Sponsors should discuss with Qualified Investigators (QIs) and Research Ethics Boards (REBs):
  - whether it is in the best interest of the safety, welfare and rights of the participant to continue the participation as per the study protocol or to halt the study
  - alternative methods of informed consent for the study or amendments to the study protocol if in-person visits are not possible (e.g. electronic consent, recorded telephone consent).

Consent Process

- Written consent not always possible at this time
  - Alternative consent method may be used; however, a discussion with the participant (telephone, videoconference, etc.) must take place.
  - That alternative method must be approved by a REB and should be explained to the participant who must be comfortable with this approach.
  - The method follows a standard operating procedure (SOP) and the participant consent process is documented.
- Electronic consent (e.g. via emails, eICF)
  - Remote written informed consent
  - When applicable written re-confirmation of informed consent from participant
- Non-written informed consent (verbal)
  - Receive the individual's informed consent before a witness
  - Written attestation by the witness that the consent was given (as soon as possible)
  - When feasible, written re-confirmation of informed consent from participant

Clinical Trial Visits

- Need to evaluate alternative methods for safety assessment if participants are not able to come to the investigational sites as specified in the study protocol
  - Examples: phone contact, virtual visits via telemedicine or alternative care sites, alternative locations for imaging studies/laboratory tests
- If an alternative method is used, documentation is required for:
  - why it was done
  - the method used to collect the information
  - what data was collected
  - who collected and who provided the information
  - how the source of the information was verified
- **Study protocol amendments are not needed.**

Clinical Trial Visits *(cont'd)*

- The use of alternative sites may create issues of confidentially related to participant's medical records (Electronic Health Record)
- Participants need to consent to any identifiers leaving the original site and be assured that their confidentially will be protected
- Electronic systems used to transfer or store participant information should be secured and access controlled

Getting Investigational Product to Participant

- Sponsors can ship clinical trial investigational products (IP) from Canadian sites directly to participants, but the the following considerations and/or requirements should be kept in mind:
  - Applies to all product formulations (e.g. tablets, injectables)
  - Applies to drugs that a subject could take on their own (e.g. subject already in a trial and on medication, IP doesn't have to be administered in a hospital/clinic setting or have any special conditions for handling)
  - IP must be transported, handled and stored done in a manner that mitigates the risk of exposure to temperatures outside labelled storage conditions
  - Verification that the investigational drug has been received by the participant
  - Accurate documentation of the process in the participant's study record is required (including training for individuals involved in the transport and receipt of the IP)
  - Must comply with the regulatory requirements of sections C.05.010 (Good Clinical Practices), and C.05.012 (Records) of the Food and Drug Regulations

Participant recruitments

- Eligibility assessment is to be carried out as usual.
- Subjects should not enroll in a trial if they do not meet the pre-set inclusion/exclusion criteria.
- The sponsor needs to consider having the participant discontinue taking part in the study:
  - If by missing a pre-defined study visit, the safety of a participant may be put at risk despite implementation of appropriate mitigation measures
- Sponsors should consider suspending additional site activation and recruitment.

If Site Monitoring Not Possible

- Document reasons for delayed site visits
- Sponsor should consider:
  - central monitoring of clinical trials (ICH E6)
  - amending the monitoring plan
- Monitoring activities may need to be re-assessed, and should prioritize critical activities to ensure participant safety
- Electronic system used to share, transfer or store participant information should be secured and access controlled

Validation of Electronic Systems

- Sponsors are referred to ICH E6 Section 5.5.3 for guidance on management of electronic records
- GUI-0100 Section 5.12 (C.05.012) provides additional details
- **Any** electronic system used to capture, process, manage and/or archive clinical trial information should be adequately validated and evidence of validation should be readily available to Health Canada's Inspectors
- The validation plan should include:
  - Objectives and scope
  - Nature of and time at which validation activities should be performed
  - Personnel delegated for the conduct of the validation
  - Security measures
  - Main features of the system, including the mode of interaction with other systems and procedures

Protocol Deviations

- Health Canada recognizes that there may be an increase in protocol deviations during the COVID-19 pandemic
- The clinical trial site(s) should have a system in place to identify, document, assess and report all protocol deviations to the sponsor and REB
- Document deviations to facilitate future analysis of the study findings – Sponsors should:
  - define and identify the protocol deviations to be reported
  - consider alternate methods to prevent protocol deviations and document the reasons
- Unless the deviations place participants at risk, sponsors are not required to report these deviations to Health Canada
- Sponsors may consider submitting at regular intervals a cumulative list of deviations occurring in a particular study, rather than individual notifications

Putting a Study on Hold

- Halting recruitment / temporarily halting the trial may be required in some circumstances
- Sponsor must document reason for halting recruitment / temporarily halting trial in study records
- Notify Health Canada as clinical trial notification (CTA-N)

Strategy for the Conduct of Virtual Clinical Trial Inspections

The Clinical Trial Compliance Program (CTCP) is exploring using virtual inspections to adapt to the current situation and to minimise the impact of COVID-19 pandemic on its every-day activities.

This will:

- ensure that the rights, safety and well-being of the trial participants continue to be protected
- ensure that data used to support marketing authorisation continue to be accurate and reliable
- help CTCP to evaluate the application of virtual inspections in the future in situations where on-site inspections are not feasible.

Methodology for Virtual Clinical Trial Inspections

- The virtual inspection will be similar to the current on-site inspection process; however, documents/records will be reviewed from the inspector's workplace.
- Correspondence with the regulated party, including requests for documentation will be performed electronically or by phone.
- Time spent for documents review could increase to **2 weeks** instead of current 1 week
- **2 inspectors** will conduct each inspection

Plan and Scope of Clinical Trial Inspections for Fiscal Year (FY) 2020/21

- The proposed timelines and approach are based on the current situation of the COVID-19 pandemic and may change as the situation continues to evolve.

  - **Phase 1**: Virtual inspections for sponsors and CROs that were inspected during the 2017 pilot: implementation of CAPA verified, systems that were not inspected may be looked at too
  - **Phase 2**: System inspections of newly selected sponsors and CROs: systems selected in advance, virtual inspections
  - **Phase 3**: Continue with the inspection of sponsors and CROs, introduce qualified investigators (QIs) depending on situation: combination virtual/on-site
  - **Phase 4**: Back to regular process and inspections of QIs on-site in FY 2021/2022

- Approximately 20-30 inspections will be conducted in total (FY 2020/21).

Approach Related to COVID-19 Clinical Trials

- Focus will be more on compliance promotion targeting COVID-19 human drugs trials
- Trials conducted at the hospitals treating COVID-19 patients will not be conducted to avoid:
  - burden to QIs
  - safety issues for inspectors
- If an inspection is necessary, other options will be considered to perform the inspection (i.e. telephone follow-ups or virtual inspections)
- The inspection will focus on clinical trials that support drug submissions once they are completed (data integrity inspections)
- Compliance verifications (CV) and follow-ups on complaints will continue as usual

Useful Health Canada References

- Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/management-clinical-trials-during-covid-19-pandemic.html

- Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19: Notice www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/interim-order-respecting-clinical-trials-medical-devices-drugs/notice-interim-order.html

- For detailed guidance on how to comply with Part C, Division 5 of the Food and Drug Regulations, refer to the **Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects" (GUI-0100)** www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices/guidance-documents/guidance-drugs-clinical-trials-human-subjects-gui-0100.html

Thank you! / Questions?

- For any questions related to clinical trial applications (CTA), please contact:
  - **For pharmaceutical drugs**:

    Therapeutic Products Directorate (TPD) at hc.oct.enquiries-requetes.bec.sc@canada.ca
  - **For biologics and radiopharmaceuticals**:

    Biologic and Radiopharmaceutical Drugs Directorate (BRDD) at hc.brdd.ora.sc@canada.ca
- **For clinical trial compliance** (GCP issues):

  Clinical Trial Compliance Program (CTCP) at GCP_BPC@hc-sc.gc.ca