New Investigator Collaborations and Interactions: Regulatory

NCIC Clinical Trials Group
New Investigator Clinical Trials Course

Queen's University, Kingston, Ontario
August 23, 2013

Canada

Disclaimer

This document does not constitute part of the Food and Drugs Act (Act) or its associated Regulations and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

Overview

- Organizational overview, roles and responsibilities
- Regulatory Framework
- GCP Inspections
- Compliance Considerations for Investigators
- Program Updates

Health Canada's Clinical Trial Oversight

Health Products and Food Branch Inspectorate

L'Inspectorat de la Direction générale des produits de santé et des aliments

Roles and Responsibilities

Health Canada

Therapeutic Products Directorate (TPD) and Biologics and Genetic Therapies Directorate (BGTD)

- CTA
- CTA-A, CTA-N
- AE Reporting

Communication

Inspectorate

- Coordination

Communication

Regions

- Inspections
- Compliance verifications and investigations

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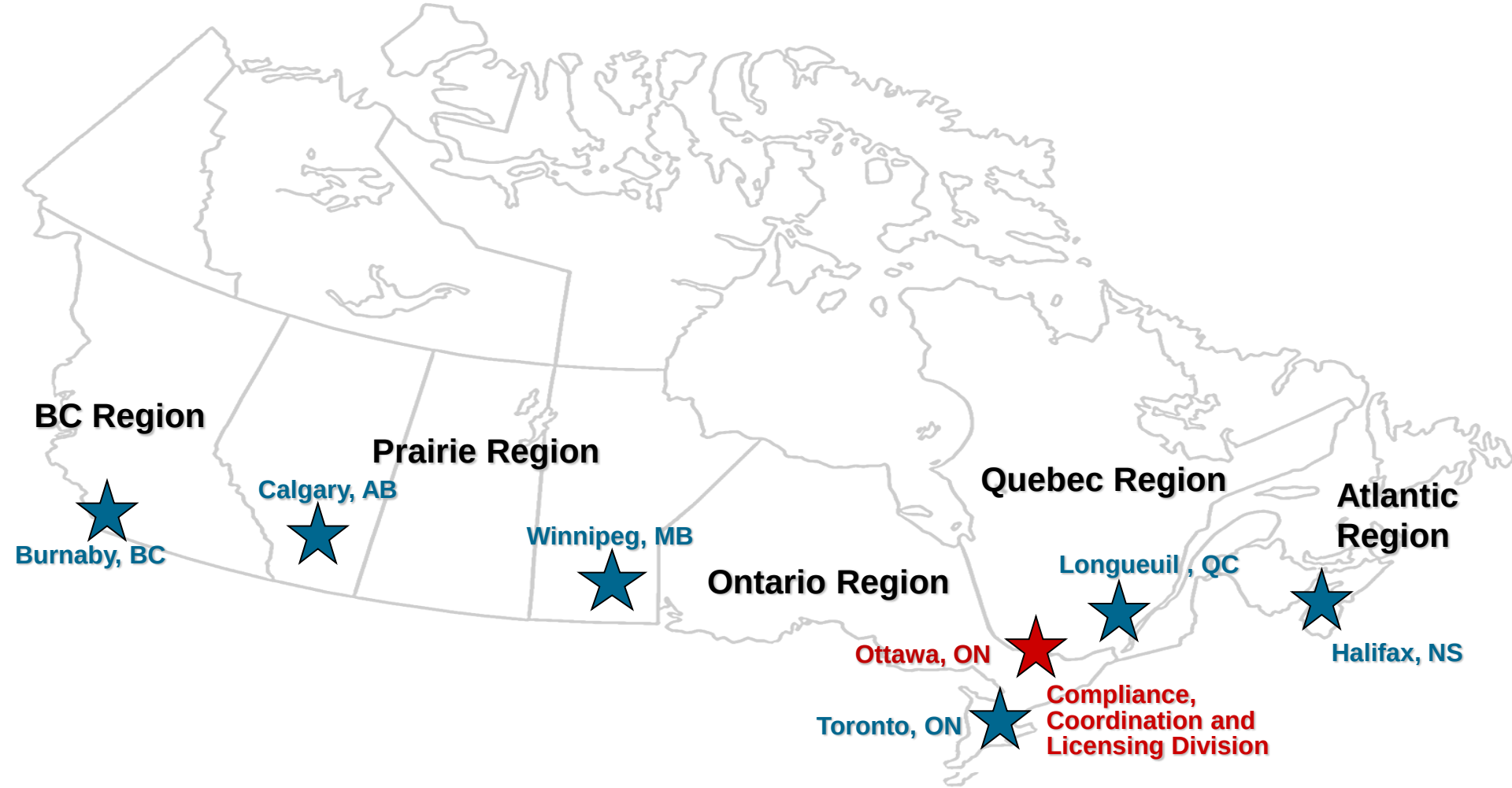
Clinical Trial Oversight



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Regulatory Framework

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Clinical Trials Regulatory Framework

Food and Drugs Act

- Authority to inspect under Section 23 of the *Food and Drugs Act*
- POL-0001 *Compliance and Enforcement Policy*

Food and Drug Regulations, Division 5
"Drugs for Clinical Trials Involving Human Subjects"

- Came into force on September 1, 2001
- Includes the requirements for good clinical practices
- Does not apply to Natural Health Products or Medical Devices (other regulations apply)

Clinical Trials Regulatory Framework

Food and Drug Regulations (FDR)

- Requirements apply to marketed drugs used in the study (but not included under the NOL)

Natural Health Product Regulations (NHPR)

- Requirements apply to natural health products used in the study (which are not the investigational product)

Medical Devices Regulations (MDR)

- Requirements apply to medical devices imported/sold as part of a drug clinical trial
- Medical devices used in drug clinical trials must be licensed
- Devices under study are subject to the submission of an Investigational Testing Application

International Conference on Harmonisation (ICH) E6

- ICH Topic E6, “Good Clinical Practice: Consolidated Guidance” was adopted by Health Canada in 1997
- Supports and further describes the good clinical practices required by the Food and Drug Regulations
- An international, ethical, and scientific standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials
- Consistent with the Declaration of Helsinki
- Internationally adopted in order to increase confidence that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

Clinical Trial Inspections

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Clinical Trial Inspections

- Average time of 5 days per inspection
- 1 or 2 inspectors per inspection
- Inspections are scheduled and announced
- The notification occurs a minimum of 5 days before the inspection is conducted
- The notification is sent to the Sponsor and the site
- Unannounced inspections may be conducted when deemed necessary

Inspection Overview

- Inspections follow a general format which may vary in duration or order, according to the site, study, or other logistics, and usually include the following:
    - Notification and preparation
    - Opening meeting
    - Site tour
    - Document review
    - Staff interviews
    - Closing meeting
    - Exit meeting and draft exit notice issuance
    - Final Exit notice issuance
    - Corrective actions and follow up (as required)

Inspection Process

During an inspection, inspectors will review and seek documentation or other demonstration of the following:

- Required REB and regulatory authorizations, approvals, and correspondence
- Informed consent
- Adherence to protocol
- Adherence to other sponsor or site procedures
- Training, licensing (as applicable) and qualification of staff
- Drug quality, handling, accountability and disposition
- Adverse event reporting
- Verification of source data reported on Case Report Forms (CRFs)

Inspection Report

- Deviations from regulatory requirements are noted in an Inspection Exit Notice as observations.
- Each observation is given a risk rating – Risk 1(critical), Risk 2 (Major), or Risk 3 (Minor).
- Based on these observations, including their risk ratings and number, an overall rating of the inspection is given – “C” compliant or “NC” non-compliant.
- Most inspections will result in several major and minor observations which are expected to be corrected and receive a “C” rating.
- Inspections of studies which receive an “NC” rating are given consideration for suspension of the trial.

Compliance Considerations for Investigators

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Institutional Studies

- Recognized that resources may be an issue
- Challenges inherent in working within a large, multi-unit organization, aspects over which the sponsor-investigator may not always have direct control
- Division 5 does not distinguish between industry and academic/institutionally sponsored studies.
- The underlying principle in systems implemented should always be reduction of risk and assurance of quality.

Investigator Responsibilities

From Division 5…

- “Qualified investigator” means the person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located.
- At each clinical trial site, there must be no more than one qualified investigator.
- At each clinical trial site, medical care and medical decisions, in respect of the clinical trial, must be under the supervision of the qualified investigator.

Investigator Responsibilities

In practice…

- During and following (as applicable) a subject's participation in a trial, the qualified investigator must ensure that
  - Patient medical care, including medical assessments, review of laboratory results, dosing decisions, and assessment of eligibility for participating/continuing in, the study is provided by the QI or appropriately qualified and delegated medical practitioners within the scope of their practice.
  - Adverse events must be assessed for severity and causality by a QI (or physician delegate) and adequate medical care must be provided to a subject for any AEs, including clinically significant laboratory values, related to the trial.
  - Staff under the QI's supervision are appropriately trained, qualified, and delegated to perform their study-related duties.

Monitoring

- Adequate monitoring of a trial is essential.
- Section 5.18 of ICH E6: GCP provides detailed guidance with respect to monitoring.
- Frequency and scope of monitoring should be risk-based, taking into consideration:
    - objective
    - design
    - complexity
    - blinding
    - size, and
    - endpoints of the trial

Monitoring

- For on-site or off-site monitoring, monitors and QIs should follow a sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.
- For qualified investigator sponsored studies conducted by a group of physicians at different sites, it is the physician identified as the sponsor on the CTA who is required to monitor the trial at all investigative sites and verify that:
  - The requirements of Division 5 of the *Food and Drug Regulations* are met at each site and,
  - The trial is conducted according to the principles good clinical practices of ICH E6: GCP.

Maintenance/Calibration of Equipment

- Regular and proper maintenance of equipment used in a study is critical to patient safety and the integrity of data collected in a clinical trial.
- Maintenance and calibration of equipment is considered to be a requirement under Division 5 and documentation of this must be available upon inspection.
- Documentation may include (but not limited to):
  - Routine calibration records and procedures
  - Maintenance and repair records
  - Equipment manuals

Labelling

- Labels are required to include the required information in both English and French.
- The definition of a label permits that some information may accompany the drug as a package insert, or affixed to the secondary container.
- Identification/traceability must be maintained via a lot number, barcode, or other identifier, and this must be affixed to the primary container.
- Blinding must be protected whichever system is used.

Labelling

- Drugs being used in a study within their labelled indication may be labelled with their market authorized labels (provided this does not compromise any blinding required by the protocol).
- Market authorized drugs used outside of the approved indication must be labelled in accordance with C.05.011.
- Lot numbers are still expected to be documented in accordance with Division 5 requirements for records, which include records respecting the shipment, receipt, disposition, return and destruction of the drug.

Training

- Regulations require that each individual involved in the conduct of the clinical trial is qualified by education, training and experience to perform his or her respective tasks.
- Delivery, content, manner of documentation, and frequency of training not specified in *Regulations*
- Acceptable documentation of training may include:
  - Meeting minutes (including attendees)
  - Slide decks to reflect content
  - Sign off sheets for protocols/IB/work instructions/SOPs

Training

- In general, staff involved in the study are expected to have documented training on those aspects of the study for which they have been delegated responsibilities
- Study staff, commensurate with their involvement in clinical research, should be knowledgeable of good clinical practices and Canadian regulatory requirements
- Frequency of “refresher” training should be in accordance with an individual’s involvement in clinical research and ongoing familiarity with the requirements.

Records

- Retention of study records for 25 years is required for all studies which have been issued an NOL, or for which a CTA-A has been filed since September 1, 2001.
- Sponsors are required to record, handle, maintain and store all information that pertains to their activities in a way that allows complete and accurate reporting as well as its interpretation and verification.
- Information should be recorded in a way that allows to establish that the clinical trial is conducted in accordance with GCP and the *Regulations.*
- All records (including electronic records) should be readily available and located in Canada (refer to section 8 of ICH E6: GCP for guidance on maintenance by sponsor/site).

Records

- Sponsors are referred to ICH E6 Section 5.5.3 for guidance on management of electronic records.
- Study records may be transferred to electronic media storage, preferably at the completion of a trial, and only if:
  - Corrections to the original data clearly captured in the secondary medium
  - Person performing the transfer attests (signs and dates an attestation) that the secondary documents are true copies of their respective primary documents
  - Transfer process fully validated (evidence of validation should be available for inspection)
- When transferring to a secondary medium, a standard, such as those developed by the Canadian General Standard Board, or equivalent, should be utilized.

Shipping and Transportation

- The sponsor is responsible for ensuring that the clinical trial is conducted in accordance with GCP; this includes controlling the factors which affect the quality of an investigational product (IP) during its storage and transportation.

- Systems must be in place for the monitoring, storage conditions, transportation and disposition of investigational products.

Shipping and Transportation

- The sponsor must ensure that investigational product is transported in a manner that ensures the products will be maintained within an acceptable temperature range as defined in the approved labeling and supported by stability data.

- This may include shipment temperature monitoring, route mapping studies, and/or other additional transport studies to demonstrate adherence to labeled storage conditions.

Program Updates

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Guidance for CT Sponsors

- New *Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications* was published in May 2013
  - revised based on stakeholder consultation processes
  - consistent with the new Common Technical Document (CTD) format
  - includes application requirements for comparative bioavailability trials and filing requirements for the importation of clinical trial supplies
  - clarifications to amendment and notification requirements, study termination and closure criteria, application and review processes, and adverse drug reaction reporting criteria as well as format requirements
- Guide is available on Health Canada's website at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php

Clinical Trials Database

- Health Canada's Clinical Trials Database was launched in May 2013.
- Provides a public listing of specific information relating to phase I, II and III clinical trials in patients.
- The database is not a registry, but is managed by Health Canada and provides a source of information about authorized Canadian clinical trials involving human pharmaceutical and biological drugs.
- The database lists trials that were authorized by Health Canada starting April 1, 2013. The database will be populated with information about each clinical trial after Health Canada issues its No Objection Letter (NOL).

Canada Vigilance E-reporting

- New electronic adverse drug reactions (ADR) reporting is currently in pilot with some sponsors.
- For the sponsors who have not yet established this connection, they should continue submitting their reports by fax or by courier.
- For more information on E-reporting, contact:

  CanadaVigilance@hc-sc.gc.ca

- Additional guidance on adverse event reporting can be found on Health Canada's website at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e2a_pre_notice_avis-eng.php

Questions?

E-mail: GCP_BPC@hc-sc.gc.ca

Further information available online at:

Health Canada → Drugs and Health Products → Compliance and Enforcement → Good Clinical Practices

www.healthcanada.gc.ca/gcp

www.santecanada.gc.ca/bpc

Thank you!

Candice Hilder

Manager, Good Clinical Practices Compliance Unit

Compliance and Enforcement Coordination Division

Health Products and Food Branch Inspectorate

Health Canada