Regulatory Inspections

An Overview of Process, Observations, and Guidance for Investigators

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NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

Outline

- Regulatory History
- Health Canada Overview
- Inspection Planning
- Inspection Process
- Data and Common Findings
- Resources

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REGULATORY HISTORY

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Regulations

ICH-E6: GCP

- 1996 Good Clinical Practice (GCP)
- International ethical and scientific quality standard for the design and conduct of clinical trials in human subjects as well as for the recording and reporting of clinical trial data
- Describes the responsibilities of those conducting clinical trials

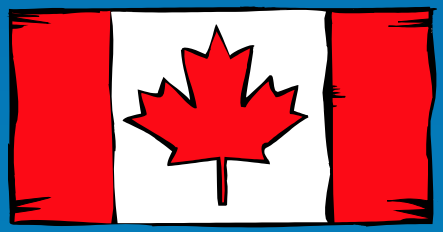
Regulations

Health Canada – FDA/FDR

- Health Canada Food and Drug Act (FDA)
- Food and Drug Regulations (FDR), Division 5 “Drugs for Clinical Trials Involving Human Subjects”
  - Came into force on September 1, 2001
  - Include GCP (C.05.010)
  - Apply to all Phase I to Phase IV clinical trials
  - Do not apply to medical devices or Natural Health Products (NHPs) *

**other regulations apply*

HEALTH CANADA OVERVIEW



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Health Canada
Mandate

- Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and
- Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

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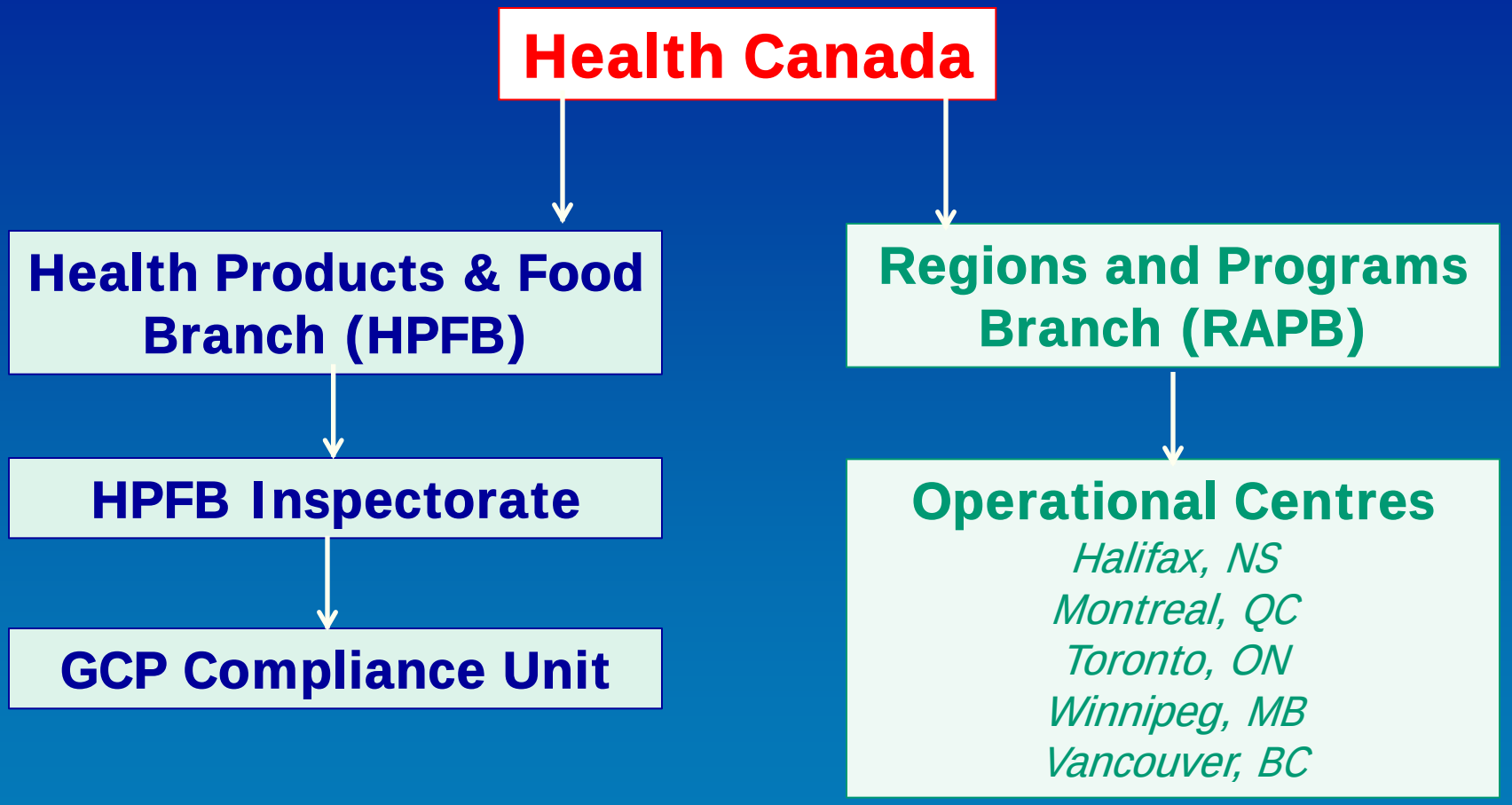
Structure *(partial)*



Operational centres (RAPB) in collaboration with the Inspectorate (HPFB) conduct Clinical Trial Inspections

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Inspectorate Objectives

- Objectives are to
  - Minimize risks associated with use of drug in clinical trials
  - Verify compliance to Division 5 of the Food and Drug Regulations (including ICH – GCP)
  - Validate the integrity of the data generated

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Inspectorate Objectives

- Continued…
  - Request corrective actions from the inspected party whenever observations are made
  - To take compliance and enforcement actions when deemed necessary

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Inspectorate Functions

- 4 core functions of Inspectorate
  - Inspection
  - Compliance Verification/Investigation
  - Establishment Licensing
  - Laboratory Functions

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INSPECTION PLANNING

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Site Selection (I)

- Conducted under the authority of section 23 of the Food and Drugs Act
- Generally one inspection is conducted in relation to one CTA
- Lists of approved CTAs are generated by Submission and Information Policy Division for the GCP Compliance Unit
- Others may be contacted during selection process for clarification or additional information

Site Selection (II)

- Factors that may influence site selection may include
  - # of trials at site
  - Status of trial at site
  - # of subjects enrolled in trial
  - Therapeutic area
  - Study population
  - Compliance history
  - ++

Site Selection (III)

- Target 2% or approximately 80 clinical trial applications per year
- Each region is assigned a # of inspections based on requirements and resource allocation
- Average of 5 days in length
- 1-2 inspectors

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Location

- Inspections may be conduced at
  - QI / Investigator Centre
  - Sponsor
  - Contract Research Organization (CRO)
  - Site Management Organization (SMO)
- Most are conducted at the QI /Investigator Centre but are a bilateral review of QI and sponsor

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Notification

- Notification (original) is sent to the QI with copy to the Sponsor
- Notification occurs a minimum of 5 days prior to the inspection
- *<u>Note:</u> Unannounced inspections may be conducted if necessary*

INSPECTION PROCESS

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7 Inspection Stages

- Preparation
- Opening Meeting
- Inspection
  - Preliminary Discussion of Observations
- Report Writing
- Exit Interview
- Final Exit Notice
- Follow Up (if needed)

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Preparation (I)

- Ensure QI (or delegate) notifies all trial and centre personnel
  - Trial: QI (Qualified Investigator), SIs, PCRA, ACRAs, ECRAs, and Pharmacist
  - Sponsor – we can help!
  - Centre notifications (unless otherwise stated):
    - Research Ethics Board
    - VP Research, Cancer Centre Manager, Clinical Trials Manager
    - Other - Biomedical Dept, Pathology, Diagnostic Imaging, Laboratories, and other areas as applicable

Preparation (II)

- Review key points of trial with trial personnel including but not limited to:
  - Timeline of the trial
  - # participants reg / rand and process
  - Amendment history
  - Safety reporting including local events
  - IMP supply process
  - Protocol compliance / non compliance
  - Tissue Banking
  - Agreements
  - Training and qualifications
- NCIC CTG will assist through the process and provide information regarding the above topics

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Preparation (III)

- Ensure SOPs and associated training up to date, including:
  - Trial oversight and communication
  - Delegation of duties
  - Informed Consent/Re-consent
  - SAE reporting (Trial requirement + Local REB Requirement)
  - Protocol Deviation Reporting Procedures
  - Records Retention
- Consider if processes have changed

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Preparation (IV)

- Pt. charts (Consents)
- Ensure GCP required documents readily available and staff are familiar with them (GCP section 8):
  - Evidence of qualification: CV, training (GCP, Div 5, trial specific training)
  - Agreements (NCIC CTG Participating Centre Agreement)
  - Participant List/Delegation of Duties information
  - Monitoring/Auditing information
  - Calibration/preventative maintenance
  - IMP

Inspection Conduct (I)

- During the inspection, DO…
  - Consider who is the appropriate site staff to coordinate the inspection
  - Be prepared, organized, and professional, provide business cards
  - Confirm/check credentials of the Inspector

Inspection Conduct (II)

- During the inspection, DO…
  - Allow use of phone/fax/ **BUT** make copies if requested
  - Listen carefully to questions
  - Answer completely, directly, and honestly
  - If needed, defer the question. Consult with colleagues and come back with the correct answer

Inspection Conduct (III)

- During the inspection, DO NOT…
  - Provide or pay for coffee/tea/meals
  - Ask personal questions or make casual conversation
  - Guess, speculate, or assume
  - Respond to questions outside of your area of expertise - get the expert!

Opening Meeting

- Ensure key study personnel are present at opening meeting
- Purpose, scope, and inspection plan will be discussed as well as
  - Inspection room
  - Work schedule
  - Availability of all records
  - Sponsor information (CRO, SMO, monitors, auditors, labs)

Inspection (I)

- Site Tour
- Interviews – QI, SI, PCRA, ACRA, ECRA, Pharmacist, + other as needed
- Qualifications
- HC authorization/correspondence
- REB approvals/correspondence
- Informed consent

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Inspection (II)

- Training
- IMP – Chain of Custody of drug and drug accountability & disposition
- Facilities
- SOPs
- Protocol compliance/non compliance
- AE/SAE reporting
- Review of source data

Discussion of Observations

- At the end of the inspection it may be possible to discuss observations noted
- Formal exit interview is conducted following report writing and review by Health Canada

Reporting (I)

- Observations are recorded and assigned per Classification of Observations Made in the Conduct of Inspections of Clinical Trials(GUIDE-0043)
- Observations are classified as
  - Critical Risk 1
  - Major Risk 2
  - Minor Risk 3

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Reporting (II)

- Definition of a Critical observation

"Observation describing a situation that results in fatal, life threatening or unsafe conditions for subjects enrolled in a clinical trial. It presents an immediate or latent undue risk to the rights, health and safety of subjects."

Reporting (III)

- Definition of a Major observation

“Observation describing a marked deviation or deficiency, other than a critical one, that may result in undue health risks to the clinical trial subjects, in other persons or could invalidate the data.”

- Definition of a Minor observation

“Observation that is classified as not critical or major, but which indicates a deficiency and/or deviation from Division 5.”

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Reporting (IV)

- Observations noted determine the overall rating for the inspection of
  - Compliant = “C”
  - Non Compliant = “NC”
- Non Compliant ratings may result if
  - One or more critical observations
  - Repetitive or multiple major observations reported
- Compliant ratings are assigned when few major or only minor observations are noted

Exit Interview

- Draft exit notice is issued which includes all observations and overall rating
- An opportunity for response and/or clarification is provided
- Corrective actions taken are evaluated

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Final Exit Notice

- Observations are listed and a response to each noted is required
- The final rating is assigned; if NC…
  - Inspection findings are discussed with the review Directorate
  - Action to be take may include suspension or cancellation of the clinical trial
- Original is sent to sponsor with copy to QI

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Follow Up
(if applicable)

- All observations noted require follow up from the Sponsor, QI/Centre, or both
- Conference call between Sponsor and QI/Centre to determine plan for follow up will be arranged
- One combined response will be submitted by Sponsor with copy to QI/Centre

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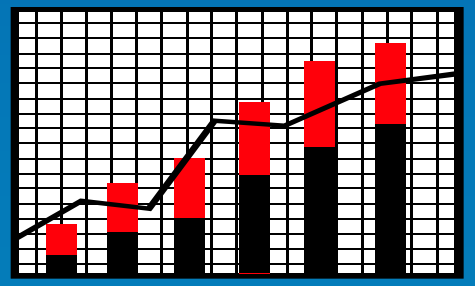
INSPECTION DATA AND COMMON FINDINGS



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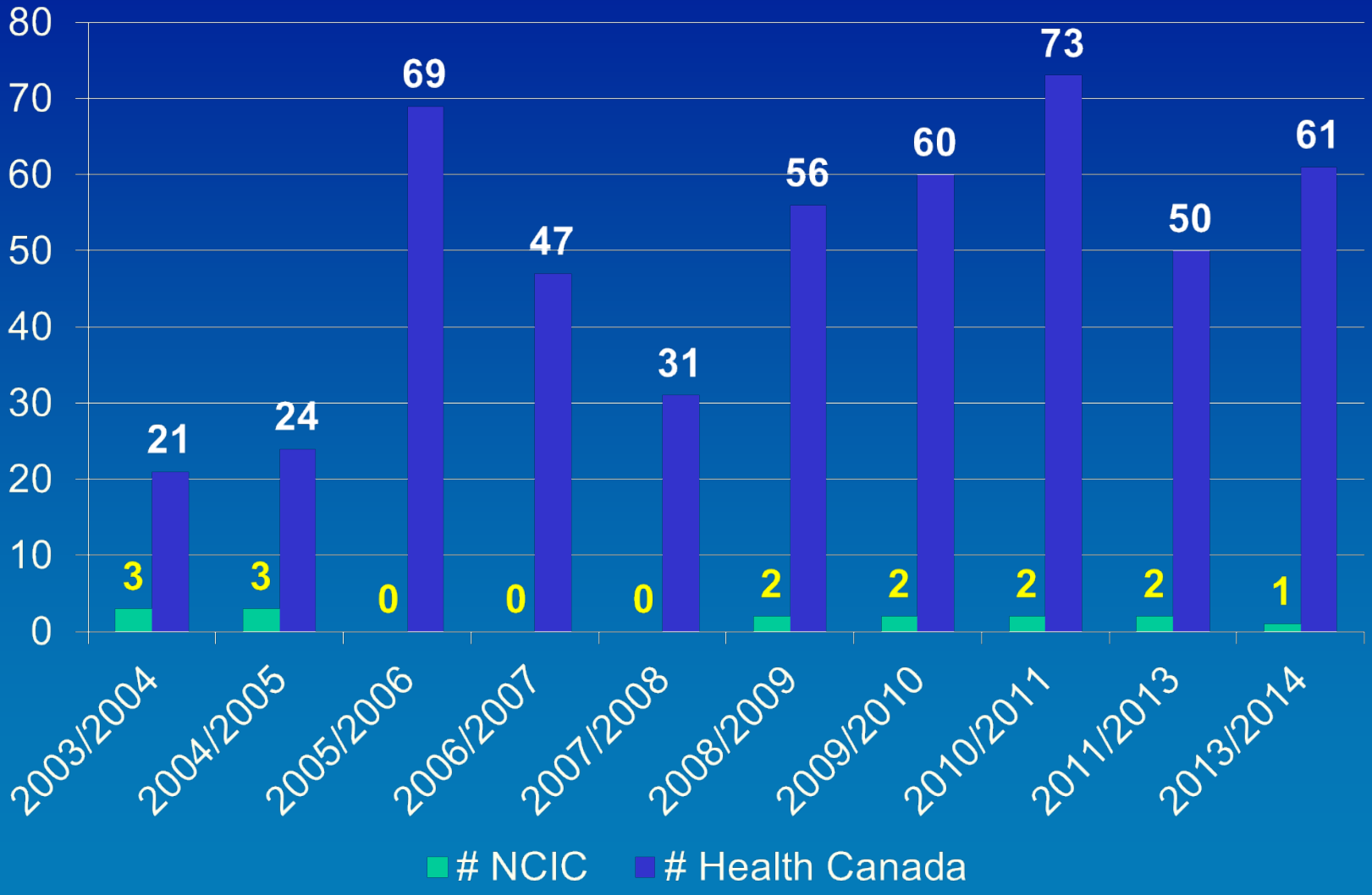
Inspection Summary

Inspection #: NCIC CTG Versus Health Canada



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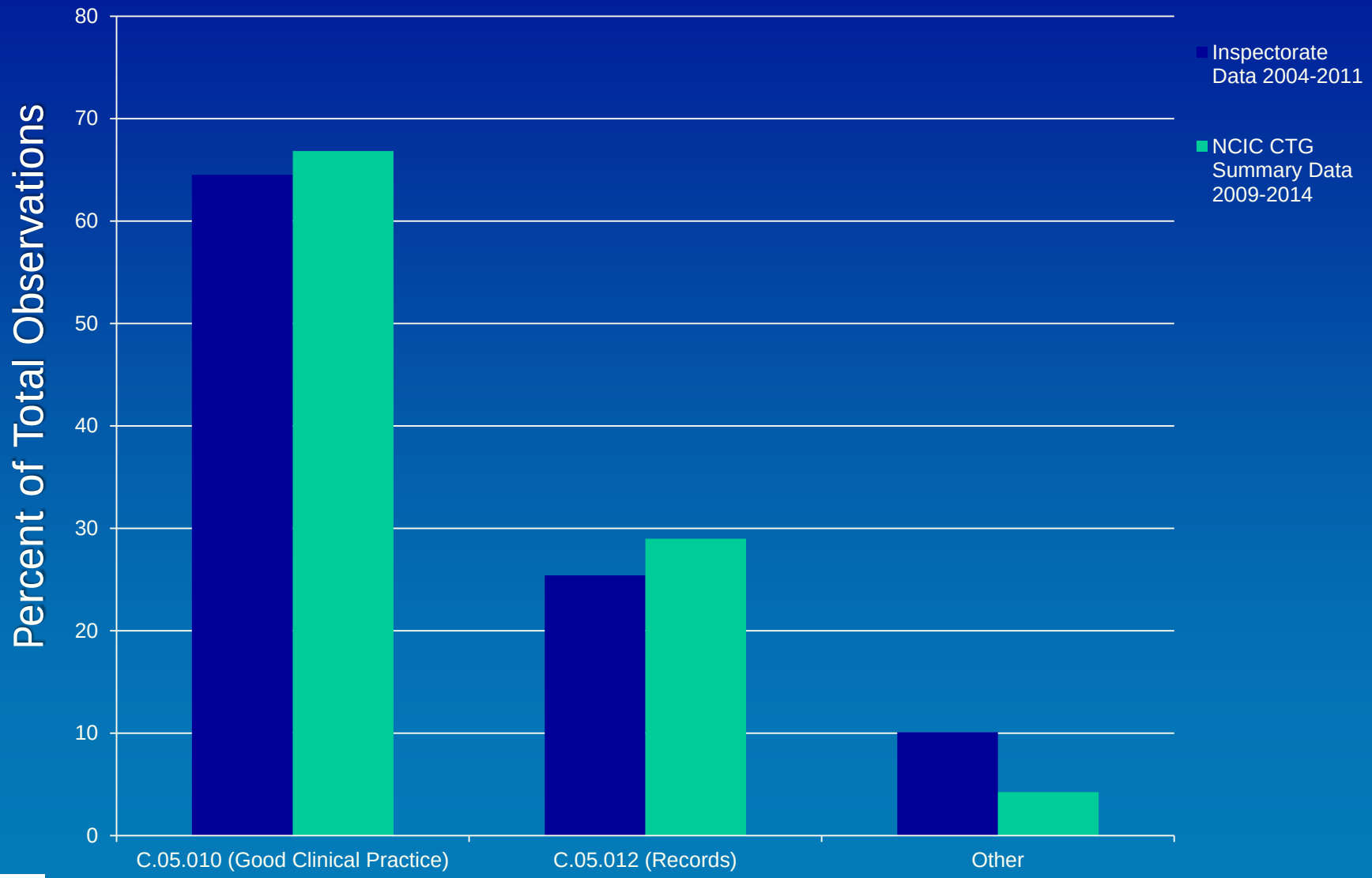
Ref Summary Report of Inspections of Clinical Trials conducted from Apr 2004 to Mar 2014

Inspection Data



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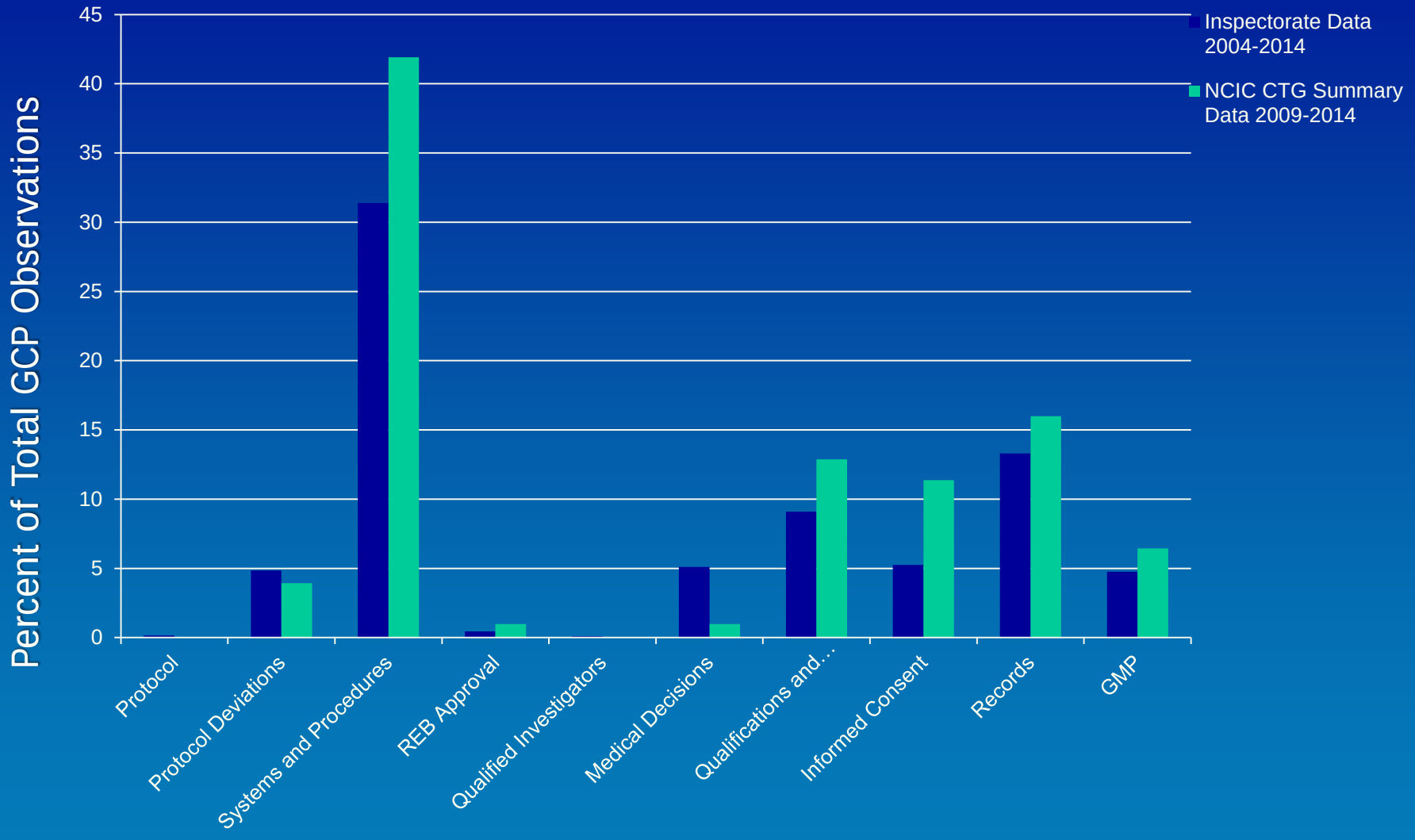
Ref Inspectorate Program Annual Inspection Summary Report

Inspection Data: GCP



Good Clinical Practice Category: Division 5, Section C

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Systems and Procedures

- Largest proportion of inspection findings (31% 2004-2014)
- Common findings (Division 5, Part C):
  - Lack of clarity regarding delegation of duties documentation and medical oversight
  - Lack of documentation regarding calibration for equipment/facilities review
  - Lack of clarity regarding records retention procedures

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Avoiding Inspection Observations (I)

- Delegation Logs
  - Review regularly for accuracy
  - Everyone listed on the delegation log must provide evidence of training related to his or her role in the trial
  - Include clinical personnel performing significant trial related tasks

Avoiding Inspection Observations (II)

- Training
  - Consider creating a training file for each individual to log relevant training
  - Be mindful of expiry dates on training certificates
  - Create a Standard Operating Procedure on training for your site/organization
  - Include Division 5 and GCP training

Avoiding Inspection Observations (III)

- Protocol Deviations
  - The investigator should not intentionally deviate from the approved protocol without prior approval from the Sponsor and REB except to remove an immediate risk to the participant
  - Consider tracking the number any type of deviations that have occurred to identify trends
  - Report protocol deviations as per your sponsors and/or institutions procedures

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N2 Quality Committee, Health Canada Inspection Survey Results for Protocol Deviations
www.n2canada.ca

Summary

- Per the Food and Drugs Act - Health Canada has an inspection program
- Goals are to ensure patient safety, compliance, and data integrity
- Please contact NCIC CTG if your centre receives an inspection notice related to NCIC CTG trials
  - And also as a resource anytime!
- Inspection data is collated and reviewed to understand compliance trends

Recommended Reading

RESOURCES

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Resources

- Health Canada
  - www.healthcanada.gc.ca/gcp
    - Includes links to GCP; Health Canada Food and Drug Regulations Division 5 – *Drugs for Clinical Trials Involving Human Subjects;* Classification of observations made during the inspection of clinical trials (GUIDE-0043); Guidance for Records Related to Clinical Trials (GUIDE-0068)
- Health Canada Pre-Inspection Package
  - https://www.ctg.queensu.ca/public/useful-links
- N2 - Network of Networks (Initiative to Streamline Clinical Trials document and other resources)
  - http://n2canada.ca/

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Thank you for your time!

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