Canadian Cancer Trials Group

Regulatory Standards and Contracts

New Investigator Clinical Trial Course
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Disclosure Statement

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Nothing to disclose.

Objectives

- Provide an overview of the regulations and guidelines necessary in the conduct of clinical trials
- Understand the differences between Investigator and Sponsor roles
- Understand the requirements for clinical trial conduct in Canada as well as International considerations
- Provide examples of research contracts and discuss the Investigator perspective

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Regulations and Guidelines

Timeline

- 1906 US Pure Food and Drug Act & 1920 Canada Food and Drug Act were first passed
- 1946 Nuremburg Trials or international military tribunals post World War II which resulted in the establishment of the Nuremburg Code in 1948
- 1960 Thalidomide led to Amendments to both US and Canadian Food and Drug Acts
- 1964 Declaration of Helsinki
- 1932 - 1972 Tuskegee Syphilis Study
- 1979 Belmont Report is established

Timeline

- 1981 US Department Health and Human Service (DHHS) revised regulations to include Title 45 (public welfare), Part 46 (protection of human subjects), and FDA revised to include Title 21 (food and drugs), Part 50 (protection of human subjects) and 56 (REB) & 1985 Canadian Food and Drugs Act revised
- 1996 International Council on Harmonization established Good Clinical Practice Guidelines
- 2001 Canadian Food and Drugs Act revised to include Part C Division 5 Food and Drug Regulations and GCP

Timeline

As noted throughout history, unregulated clinical research has lead…

- to compromised safety, rights, and well being of subjects,
- unreliable data, and
- public mistrust

Compliance Today

Health Canada Inspection database
https://www.canada.ca/en/health-canada/services/inspecting-monitoring-drug-health-products/drug-health-product-inspections.html

- Results online via database and summary reports published
- >1000 inspections across domains (e.g. GCP – Clinical Trials, GMP)
- As example, in 2014-2015, 51 clinical trial sites were inspected and 41 were compliant
- 457 observations of which 11 were critical (2%), 292 were major, and 154 were minor

Compliance Today

FDA Debarment List

http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm

- FDA audits 1-5% of trials
- Primarily driven by complaints registered
- 2% misconduct; 10-20% irregularities

Compliance Today

2006 Anil Potti, at Duke University and others file patent applications on the idea of using gene-expression data to predict sensitivity to cancer drugs. Potti is first author on a paper in *Nature Medicine*1.

2007 Potti is last author on a paper in the *Journal of Clinical Oncology* (*JCO*)2. Duke begins three clinical trials to test Potti's predictors in patients with breast or lung cancer.

2009 Keith Baggerly and Kevin Coombes, statisticians UT/MDACC publish a paper stating that they could not replicate Potti's claims. Duke suspends the trials and asks a review panel to investigate.

2009 Potti places data underlying the *JCO* paper online. Baggerly identifies differences in raw data.

2010 *The Cancer Letter* reveals that Potti made false claims about his CV. Trials are suspended and an investigation begins. Harold Varmus, director of the National Cancer Institute in Bethesda, Maryland, asks the Institute of Medicine to review Duke's trials.

2010 *JCO* paper is retracted. Duke closes the trials permanently. Potti resigns.

2011 *Nature Medicine* and other paper is retracted.

Which regulations & guidelines apply?

Criteria	Regulations & Guidelines
All research involving human subjects	Nuremburg Code Declaration of Helsinki ICH Good Clinical Practice Local Requirements (e.g. REB)
Human research funded by Canadian federal granting agencies (e.g. CIHR)	Tri Council Policy Statement (TCPS)
Clinical Trials Involving Drugs	Canada – Food and Drugs Act US – FDA Regulations
Clinical Trials Involving Natural Health Products	NHP Regulations
Clinical Trials Involved Medical Devices	Medical Device Regulations
Human research funded by US federal funds (e.g. NIH)	US Federal Regulations (e.g. OHRP)

Nuremburg Code

- 10 standards physicians must conform to when carrying out experiments on human subjects
- Key principles include but are not limited to…
  - Informed consent
  - Research must be necessary and based on prior animal experimentation
  - Risk is proportionate to importance
  - No unnecessary physical/mental suffering
  - Freedom to withdraw at any time

Declaration of Helsinki

- Medical progress is based on research, research improves treatments and understanding of disease but involves risks and burdens, and therefore must be subject to ethical standards
- Key principles include but are not limited to…
  - Content of protocol
  - Consent of the informed consent form
  - Independent ethics review
  - Well being of subject overrides science and society
  - Participation is voluntary and informed
  - Informed Consent requirements
  - Protection of privacy and confidentiality of subjects
  - Publication requirements

Tri Council Policy Statement

- Joint policy of Canada's three federal research agencies – the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council of Canada (SSHRC)
- 1st TCPS came out in 1998
- Revised to TCPS 2 in December 2010
- Key principles
  - Respect for Persons
  - Concerns for Welfare
  - and Justice
- Includes informed consent, REB, privacy and more…

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH)

Good Clinical Practice

ICH
harmonisation for better health

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International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (**ICH**)

Efficacy Guidelines

ICH Guidelines relevant to clinical trial conduct

E1: Clinical Safety for Drugs used in Long-Term Treatment

E2A-E2F: Pharmacovigilance

E3: Clinical Study Reports

E4 Dose Response Studies

E5: Ethnic Factors

E6: Good Clinical Practice

E7: Clinical Trials in Geriatric Population

E8: Considerations for Clinical Trials

E9: Statistical Principles for Clinical Trials

E10: Choice of Control Group in Clinical Trials

E11: Clinical Trials in Pediatric Populations

E12: Clinical Evaluation by Therapeutic Category

E14: Clinical Evaluation of QT/QTC Interval Prolongation

E15: Definitions in Pharmacogenetics/ Pharmacogenomics

E16: Qualification of Genomic Biomarkers

E17: Multi-Regional Clinical Trials

E18: Genomic Sampling

ICH Good Clinical Practice

Overview

1. Glossary
2. Principles
3. **REB** responsibilities
4. **Investigator** responsibilities
5. **Sponsor** responsibilities
6. Protocol and amendments
7. Investigator Brochure
8. Essential Documents

Principles

1. *Ethical principles*
2. *Benefits/risk*
3. *Rights/safety most important*
4. *Drug info supports trial*
5. *Trial scientifically sound, protocol*
6. *Protocol REB approved*
7. *Medical care by a qualified MD*
8. *Qualified individuals conduct trials*
9. *Free informed consent*
10. *Data accuracy*
11. *Confidentiality*
12. *Drugs: GMP/protocol*
13. *Quality assurance*

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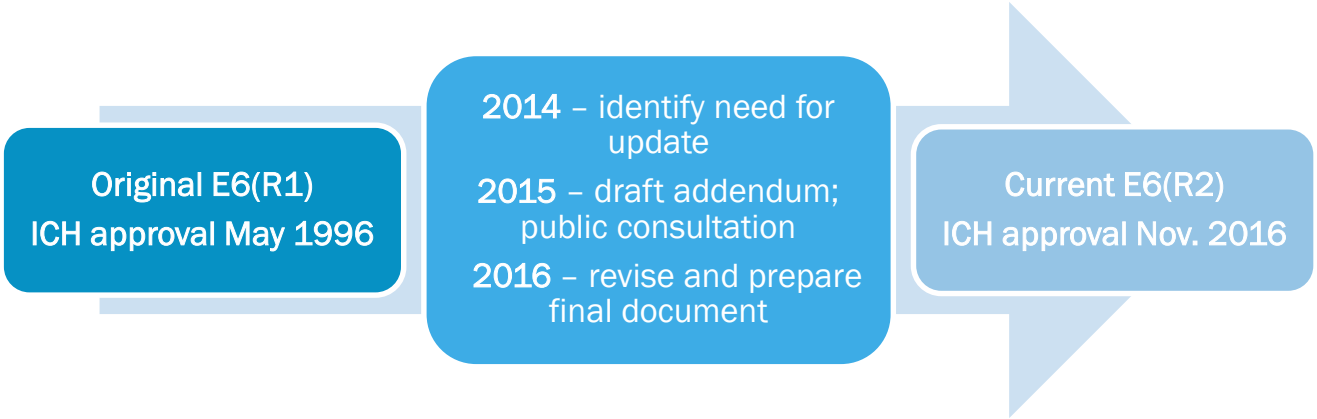
ICH harmonisation for better health

Process for ICH E6(R1) change



Perceived problem: Since 1996 clinical trials have evolved substantially, with increase in globalization, study complexity and technological capabilities

Objective: Encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, reporting while continuing to ensure human subject protection and reliability of results

Integrated Addendum to ICH E6(R1): GCP E6(R2)

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ICH harmonisation for better health

Integrated Addendum GCP E6(R2)

Investigator Responsibilities (4.0)

- Supervise clinical trial staff delegated trial-related duties (4.2.5)
- Ensure trial staff are qualified to perform trial-related duties/functions; implement procedures to ensure integrity of trial-related duties/ functions performed and data generated (4.2.6)

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Responsibilities of Investigators Versus Sponsors

Investigator Versus Sponsor

Investigator

- Adequate resources & qualifications
- Contracts
- Informed Consent
- Randomizing/Unblinding
- Medical care of trial subjects
- Compliance with Protocol
- Communication with REB
- Investigational Medicinal Product (IMP)
- Records and reports including Investigator Site File
- Local safety reporting

Sponsor

- Trial design
- Contracts and financing
- Medical expertise
- Protocol development
- Trial management, data handling, and record keeping including Trial Master File
- Investigator selection and oversight responsibilities
- Notification / submission to regulatory authority
- Quality assurance and quality control
- Noncompliance
- Premature termination or suspension
- Clinical trial / study reports
- Data Safety Monitoring
- Final Report
- Contract Research Organization (CRO; e.g drug distribution)
- Inspection Coordination

Investigator Versus Sponsor

- Medical care of trial subjects
- Ensure protocol compliance
- Research team conducting the trial is essential to successful conduct
- Involves training, appropriate delegation, and also oversight
- Documenting key steps and decisions within the subjects time on trial is also essential
- Being aware of significant changes

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Conduct of Clinical Trials in Canada

Canadian Food and Drug Regulations

- 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
  - Includes GCP (C.05.010)
  - Applies to all Phase I to Phase IV clinical trials

Canadian Food and Drug Regulations

- Marketed agents used outside of their approved use in Canada require a Clinical Trial Application (CTA)
  - eg clinical use, dose / formulation, route of administration or target patient population
- CTA submissions include
  - Drug information, protocol, consent, product monograph/ investigator brochure, safety information, ++ required forms
- 30 day review period by Health Canada

Canadian Food and Drug Regulations

- Health Canada will issue either…
  - No Objection Letter (NOL) = trial can proceed
  - Or Clairfax = additional information must be submitted to Health Canada
- Pre CTA meetings with Health Canada can be arranged

Canadian Food and Drug Regulations

- Clinical Trials Require…
  - Compliance with ICH – GCP Topic E6
  - Submission and approval of changes to the protocol / consent
  - Drug labeled specifically for the trial
  - Reporting of serious adverse events
  - Submission of safety data upon request
  - Notification of premature trial discontinuation or significant events
  - Health Canada may inspection sponsors and/or sites participating on clinical trials

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International Considerations

US Federal Regulations

- US Code of Federal Regulations (CFR); Title 45, Part 46, Protection of Human Subjects
- Governs research funded by the US National Institutes of Health (NIH) or agencies (e.g. Oncology – NCI)
- OHRP (US Office of Human Research Protection) ensures compliance with the code

US Food and Drug Administration (FDA)

- Applicable to studies conducted in Canada where trial is being directly under a US IND
- IND required in US when…
  - IMP is not marketed or
  - IMP is marketed but one of the following conditions exist
    - Intention to submit trial to FDA
    - Intention to change labeling as a result of trial results
    - Indication / dose and involves a significant increase in risk

US Food and Drug Administration (FDA)

- Processes to consider when filing a US IND
  - IND is drug specific and once in place trials are filed to the IND
  - FDA has 30 days to comment but no formal approval is given
  - Canada - each trial has a unique CTA and NOL and the drug is filed under a Drug Master File (DMF)
  - Completion of FDA 1572 & Financial Disclosure form
  - Pre CTA type meeting called a SPA

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Contracts

Contract Requirements

- Good Clinical Practice 1.17 Contract:

  A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Contract Requirements

GCP	Contract/Agreement	Investigator / Site Files	Sponsor Files
8.2.4	Financial Aspects of Trial To document financial agreement between Site and Sponsor	Yes	Yes
8.2.5	Insurance Statement To document that compensation to subject(s) for trial-related injury will be available	Yes	Yes
8.2.6	Signed Agreements between Involved Parties To document agreements	Yes	Yes

Contract Requirements

- Legal Entity
  - Determine legal entity of sponsor, Investigator centre, Institution
  - CCTG legal entity is Queens University
- Signing Authority
  - Determine who is authorized to sign
  - CCTG signatory is Director of Industry Partnerships at Queen's University

Common Contracts

- Bilateral Confidential Disclosure and Limited Use Agreement (CDA)
  - Agreement between sponsor and company
  - Signatories intend to hold discussions and exchange information
- Clinical Trials Agreement (CTA) and Collaboration Agreements
  - Agreement between sponsor and partners
  - Signatories intend to conduct a clinical research study according to a protocol
  - Roles and Responsibilities are detailed

Key Roles & Responsibilities

- Protocol and protocol amendments
- Case Report Forms
- Informed Consent Form
- Investigational Medicinal Product
- Correspondence with Health Authorities
- Serious Adverse Event Reporting
- Safety Monitoring
- Research Ethics Board Approvals/Ethics
- Audit and Monitoring
- Site and Investigator Selection
- Trial and Investigator Centre Initiation
- Investigator Meetings
- Data Management
- Trial Close Out
- Statistical Analysis and Report
- Communication
- Other (ie Trial Master File retention)

Common Contracts

- Participating Centre Agreement (PCA)
  - Agreement between sponsor and Investigator centre
  - Signatories intend to conduct a clinical research and responsibilities are specified
  - CCTG has PCA with each Investigator centre that covers all research conducted
  - Renewable every 5 years
  - If Trial Specific PCAs are required this can cause delays in trial activation and accrual

Common Contracts

- Tumor Tissue Data Repository (TTDR), Clinical Trial Tissue Access Agreement
  - Agreement between sponsor and Investigator
  - Contract to access tissue samples collected for the clinical trial
  - Investigator applies to CCTG to conduct a research project related to the database/tissue and an agreement is signed
- Data Sharing Agreement
  - Agreement between sponsor and Investigator
  - Results of a study have been published
  - Investigator applies to CCTG to conduct additional research project on the database and an agreement is signed
  - CCTG provides a partial anonymized database to the Investigator for the project

Investigator Perspective

- CCTG sponsored trial in which centre and Investigator participates
  - Participating Centre Agreement already in place
  - Centre/Investigator activates the trial or access tissue/data post trial
  - CCTG manages all other contracting
- Pharmaceutical sponsored trial in which Investigator participates
  - Agreement between Investigator Institution and pharma partner
  - Details responsibilities of Investigator team in delivering the trial from an Institutional perspective
- Investigator initiated clinical trial
  - Investigator has clinical trial agreement with pharma partner to provide agent and funding
  - Investigator has submitted CTA to Health Canada
  - Investigator now responsible for delivering to pharma partner and regulatory authority from both the Investigator and Sponsor levels

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Thank You

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A national programme of the Canadian Cancer Society

NCI National Clinical Trials Network
a National Cancer Institute program

Canadian Cancer Society | Société canadienne du cancer

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