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Clinical Trial Regulations and Guidelines

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Quality in Clinical Trials

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Agenda

- Overview of clinical trial regulations and guidelines
  - History
  - Current state
  - What this means for you as an investigator

Objectives

- Introduction to Clinical Trial Regulations and Guidelines
- Understand investigator responsibility according to applicable Regulations and Guidelines

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 :
  - 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 2014
- Key principles
  - Respect for Persons
  - Concerns for Welfare
  - Justice
- Includes, but not limited to:
  - Informed consent
  - REB
  - Privacy
  - Genetic research
  - Research involving First Nations, Inuit and Metis peoples

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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 effect 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)
  - E.g. clinical use, dose / formulation, route of administration or target patient population
- CTA submissions include
  - Drug information, protocol, consent, product monograph/ Investigator's 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 for consultation of trial design

Canadian Food and Drug Regulations

- Clinical Trials Require:
  - Compliance with ICH–GCP (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, REB refusals or significant events
  - Health Canada may inspect sponsors and/or sites participating on clinical trials

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 Prolongation

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

E15: Definitions in Pharmacogenetics/ Pharmacogenomics

E16: Qualification of Genomic Biomarkers

E17: Multi-Regional Clinical Trials

E18: Genomic Sampling

ICH harmonisation for better health

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ICH Good Clinical Practice

- **Overview**

1. Glossary
2. Principles
3. REB responsibilities
4. Investigator responsibilities
5. **Sponsor** responsibilities
6. Protocol and amendments
7. Investigator's 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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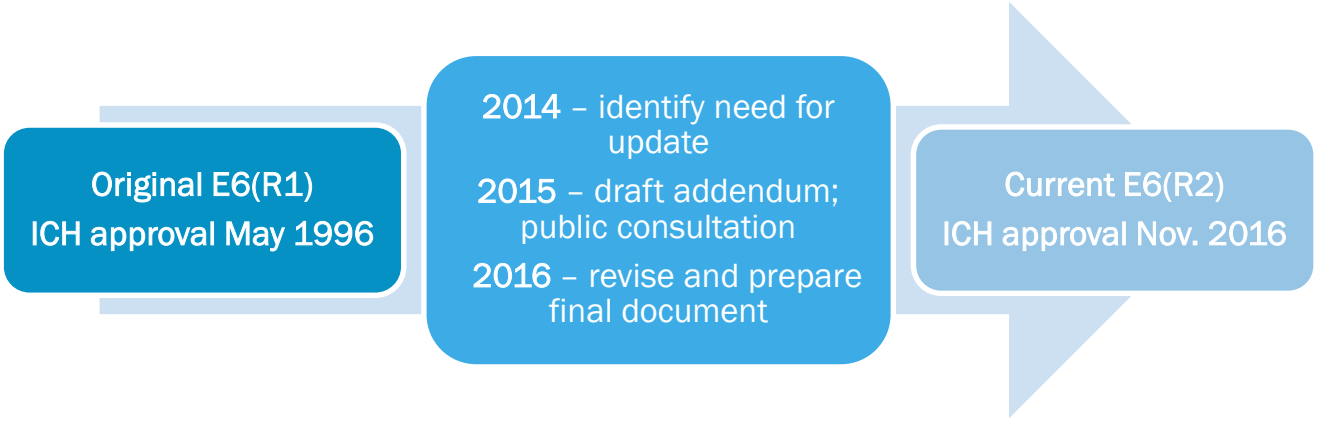
Process for ICH E6(R2) change



- **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-GCP E6(R2) Investigator Responsibilities

ICH-GCP E6: Investigator Responsibilities

- 4.1 Qualifications and agreements
- 4.2 Adequate resources
- 4.3 Medical Care of Trial Subjects
- 4.4 Communication with IRB/IEC/REB
- 4.5 Compliance with Protocol
- 4.6 Investigational Product(s)
- 4.7 Randomization Procedures and Unblinding
- 4.8 Informed Consent of Trial Subjects
- 4.9 Records and Reports
- 4.10 Progress Reports
- 4.11 Safety Reporting
- 4.12 Premature Termination or Suspension of a Trial
- 4.13 Final report(s) by Investigator

Investigator Responsibilities

- Demonstrate potential to accrue required number of participants
- Adequate number of qualified staff and facilities
- Responsible for all trial-related medical decisions and to ensure adequate medical care provided
- Communication to the Research Ethics Board (REB) and ensuring written and dated approval for protocol, consents, recruitment materials and any other written information provided to participants

Investigator Responsibilities

- Conduct trial in compliance with the protocol and report any deviations
- Accountability and records of Investigational Medicinal Products (can delegate responsibility, but maintain oversight)
- Correct storage and use of IMP and ensuring compliance by participants
- Maintain adequate and accurate source documents and trial records that are:
  - Attributable
  - Legible
  - Contemporaneous
  - Original
  - Accurate
  - Complete

Investigator Responsibilities

- Changes or corrections to CRFs:
  - Should be dated, initialed, and explained
  - Should not obscure the original entry (i.e. an audit trail)
  - Retain records of changes and corrections

- Participant trial-related and medical records must be available for review by monitors, auditors, REB, and the regulatory authority

Investigator Responsibilities

- All Serious Adverse Events (SAEs) must be reported immediately, unless otherwise indicated
- Comply with regulatory reporting requirements to regulatory authorities and REBs
- Submit final trial reports to REB and sponsor

Investigator Responsibilities: Informed Consent

- Written informed consent must be completed prior to any trial-related activities
- Important new information during the life of the trial must be communicated to participants in a timely manner
- Language must be non-technical and easily understood. Investigators and staff must not coerce or influence a person to participate on a clinical trial
- Informed consent discussions should be documented
- Participants must receive a copy of the signed informed consent document

Investigator Responsibilities: Informed Consent

- If the participant is unable to read or understand the document language, an impartial witness or interpreter can assist

- Based on various regulations there are require elements to consent documents, here are some examples:
  - Purpose of the trial
  - Trial treatment and assignment to treatments
  - Trial procedures
  - Participant responsibilities
  - Aspects of the trial that are experimental
  - Alternative treatments
  - Compensation for injury
  - Description of risk/benefit
  - Expenses/Payment
  - Etc!

Investigator Versus Sponsor Responsibilities

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