Regulatory Standards & Contracts

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Objectives

- Clinical trial regulations and guidelines
- Canadian regulatory standards
- International considerations
- Contracts

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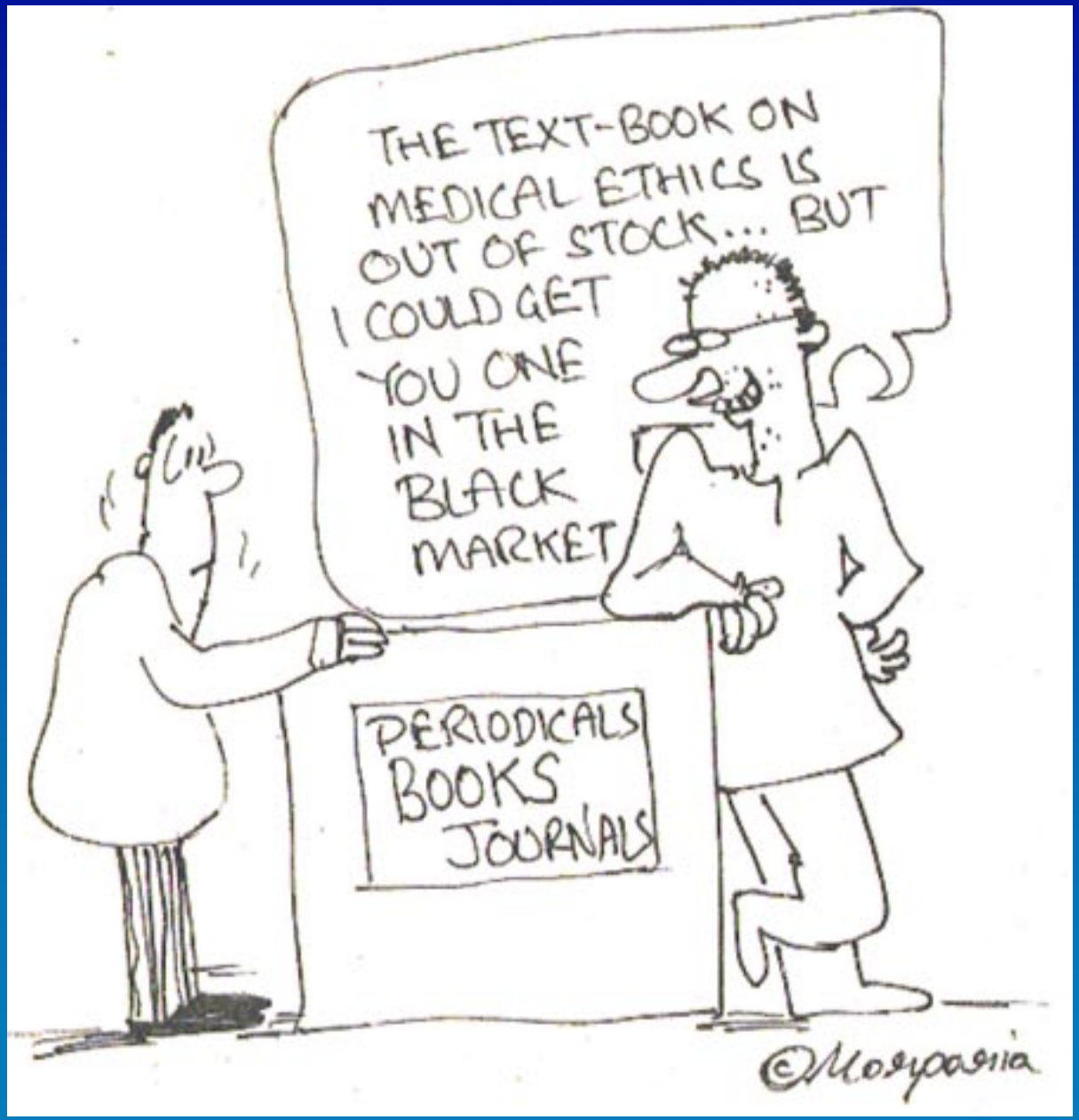

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Clinical Trial Regulations and Guidelines

HISTORY

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Nuremburg Code

- 1946 -1949 Nuremburg Trials, World War II International military tribunal
- Nazi's who conduct "medical science" experiments
- 1947 Judgment included a set of ethical standards for medical research = Nuremburg Code
- Detailed 10 standards physicians must conform to when conducting research with human subjects

Declaration of Helsinki

- Medical progress is based on research which rests in part on human subject experimentation
  - Well-being of research subjects must take precedence over all other interests
- Purpose of medical research is to improve treatments and understanding of disease
- Medical research involves risks and burdens
- Medical Research must therefore be subject to ethical standards

Declaration of Helsinki

Protocol

- Written protocol is required
  - Design and procedures clearly described
- Research must be scientifically sound and based on a thorough knowledge of scientific literature and other relevant information
- Protocol should contain statement of ethical considerations involved and state compliance with the Declaration of Helsinki

Declaration of Helsinki

Ethics Review

- Ethics review required for:
  - protocol (initially and continually)
  - serious adverse events
  - potential conflicts of interest
  - incentives for subjects
- Research Ethics Board (REB) should be independent of investigator

Declaration of Helsinki

Subjects

- Subjects must be volunteers and informed participants
- Well-being of human subject comes before interests of science and society
- Some populations need special protections
- Protect privacy and confidentiality of subjects

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Declaration of Helsinki

Informed Consent

- Informed consent must address:
  - Research aims and methods, sources of funding, any possible conflicts of interest, benefits and risks, right to refuse and withdraw, identifiable human material/data (collection, analysis, storage, re-use)
- Consent should be obtained in writing
- Subject incompetent—legally authorized representative can provide consent
- Caution recommended if subject has an dependent relationship with the investigator

Declaration of Helsinki

Publications

- Accurate
- Publish negative and positive results
- Declare funding sources, institutional affiliations and any conflicts of interest
- Studies not conducted in accordance with the Declaration of Helsinki should not be accepted for publication

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Declaration of Helsinki

Medical Care and Research

- Combine only if research justified for potential prevention, diagnostic or therapeutic value and will not adversely affect patient/subject health
- New intervention tested against best current intervention except when:
  - Use of placebo/no Rx is acceptable (no current/ proven intervention exists)
  - Use of placebo is necessary to determine safety/efficacy of intervention and no risk of serious/irreversible harm from placebo

Declaration of Helsinki

Medical Care and Research

- Consent considerations:
  - Include aspects of care related to research
  - Patients are entitled to be informed about outcome of the study at its conclusion

Tri-Council Policy Statement (TCPS)

- Policy statement for Canadian Granting Agencies:
  - CIHR-Canadian Institute for Health Research (formerly MRC)
  - NSERC-Natural Sciences & Engineering Research Council
  - SSHRC (Social Sciences and Humanities Research Council)
- Granting agencies will only fund individuals and institutions which certify compliance
- Not currently force of law in Canada

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TCPS

Guiding principles, respect for:

- Human dignity
- Free & informed consent
- Vulnerable persons
- Privacy and confidentiality
- Justice and inclusiveness
- Balancing harms and benefits

ICH – GCP

- 1996 International Conference on Harmonization, Good Clinical Practice (ICH-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

ICH – GCP

- Applies to regulatory agencies / pharmaceutical companies of ICH regions (Japan, US, and EU)
- Follow when conducting a trial
  - Intended for regulatory submission
  - Any trial under a Clinical Trials Application (CTA) in Canada
- ICH-GCP applies to all trials

ICH – GCP

- ICH Topic E6 basic structure
  1. Glossary
  2. Principles
  3. Research Ethics Boards (REBs)
  4. Investigator Responsibilities
  5. Sponsor Responsibilities
  6. Protocol/Amendments
  7. Investigator Brochure
  8. Essential Documents

ICH – GCP

Principles

- Conducted in accordance with the ethical principles that have their origin in the DOH
- Foreseeable risks and inconveniences should be weighed against the anticipated benefit for the subject and society
- Rights, safety, and well-being of trial subjects are the most important considerations

ICH – GCP

Principles

- Available nonclinical and clinical information on an investigational medicinal product (IMP) should be adequate to support the proposed clinical trial
- Clinical trials should be scientifically sound and described in a clear, detailed protocol
- A trial should be conducted per protocol following institutional research ethics board (REB) approval/favourable opinion

ICH – GCP

Principles

- Medical care given to, and medical decisions made on behalf of subjects, should always be the responsibility of a qualified physician or, when appropriate, a qualified dentist
- Clinical trial personnel should be qualified by education, training, and experience
- Freely given informed consent should be obtained from each subject prior to participation

ICH – GCP

Principles

- Clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
- Confidentiality should be ensured
- IMP should be manufactured, handled, and stored in accordance with good manufacturing practices (GMP)
- Systems with procedures that assure the quality of every aspect of the trial should be implemented

Research Ethics Board (REB)

- Responsibilities
  - Ensure rights, safety, and well-being of all subjects (emphasis on vulnerable populations)
  - Obtain
    - Protocol / amendments
    - Informed consent and updates
    - Recruitment procedures
    - Investigator Brochure or Product Monograph
    - Safety information
    - Payments and compensation
    - Qualified Investigator CV ++ other documents

REB

- Responsibilities
  - Review and approve / favourable opinion
  - Conduct continuing review at minimum annually
  - Ensure informed consent requirements have been met depending on trial type
- Composition, Functions, and Operations
  - Consist of a reasonable number of members who collectively have appropriate qualifications and experience
    - At least 5 members
    - At least one member whose primary area of interest is in a non-scientific area

REB

- Procedures
  - Detailing composition and authority (e.g. signing)
  - Scheduling of meetings and conducting reviews
  - Providing expedited review and approval / favourable opinion of minor changes in ongoing trials
  - Ensuring that no subject is enrolled prior to approval / favourable opinion
  - Specifying that deviations, adverse drug reactions, and new information be reported
  - Maintaining records

Investigator Responsibilities

- Qualifications and agreements
- Adequate resources
- Delegation of Duties
- Medical care of trial subjects
- Communication with REB
- Compliance with protocol
- Investigational Medicinal Product (IMP)
- Randomization / unblinding

Investigator Responsibilities

- Informed consent of trial subjects
- Records and reports
- Progress reports
- Safety reporting
- Premature termination or suspension
- Final report

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Sponsor Responsibilities

- Quality assurance and quality control
- Contract Research Organization (CRO)
- Medical expertise
- Trial design
- Trial management, data handling, and record keeping
- Investigator selection / responsibilities

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Sponsor Responsibilities

- Financing
- Notification / submission to regulatory authority(ies)
- Confirmation of local REB approval / favourable opinion
- Information on IMP e.g. labeling
- Record access
- Safety information, adverse drug reaction reporting

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Sponsor Responsibilities

- Monitoring & auditing
  - Central and on-site
- Noncompliance
- Premature termination or suspension
- Clinical trial / study reports

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Health Canada Food and Drug Regulations

CANADIAN REGULATORY STANDARDS

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Health Canada

- Health Products and Food Branch of Health Canada (HPFB):
  - Clinical Trials Regulations for Drugs
    - Therapeutic Products Directorate (TPD)
    - Biologics and Genetic Therapies Directorate (BGTD)
      - Blood and blood products; cells, tissues, and organs; gene therapies; radiopharmaceuticals
  - Marketed Health Products
  - Natural Health Products
  - Medical Devices

Health Canada

- Canadian 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

Health Canada

Key Points for Sponsors

- CTAs will be filed for trials which involve unmarketed agents, or marketed agents, where one or more of the following is different from the Health Canada Notice of Compliance (NOC):
  - Indication(s) and clinical use
  - Target patient populations(s)
  - Route(s) of administration
  - Dosage regimen(s)

Health Canada

Key Points for Sponsors

- CTAs are not required to be filed for clinical trials involving marketed agents where the investigation is to be conducted within the parameters of the approved NOC.
- For example, clinical trials involving Patient Reported Outcomes (PRO's), and surgical trials typically do not require a CTA

Health Canada

Key Points for Sponsors

- Example….Metformin
- Phase III randomized trial of metformin versus placebo on recurrence and survival in early stage breast cancer
- Use not covered in Product Monograph for Metformin therefore a Clinical Trial Application (CTA) was filed with Health Canada

Health Canada

Key Points for Sponsors

- CTA submissions include
  - Protocol, consent, drug information, investigator brochure, ++ required forms
- 30 day review period by Health Canada

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Health Canada

Key Points for Sponsors

- Health Canada will issue either…
  - No Objection Letter (NOL) = trial can proceed
  - Or Clairfax = additional information must be submitted to Health Canada
- Complete guidance from Health Canada is available detailing the CTA submission process and required documentation
- Pre CTA meetings with Health Canada can be arranged

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Health Canada

Key Points for Sponsors

- 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 inspect sponsors and/or sites participating on clinical trials

Considerations

INTERNATIONAL

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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

- Applicable to studies conducted in Canada where trial is conducted 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 as a well-controlled trial
    - Intention to change labeling as a result of trial results
    - Indication / dose etc… involves a significant increase in risk

US Food and Drug Administration

- Regulations and processes to consider when filing a US IND
  - CFR Title 21, Section 312
  - Requirements for labeling, safety reporting, investigators, REB review, etc…
  - Completion of FDA 1572 by Qualified Investigator
  - Completion of Financial Disclosure form

US Food and Drug Administration

- Other factors to considers…
  - IND is drug specific
  - Once an IND is in place, trials are filed to the IND
  - FDA have 30 days to comment but no formal approval is given
    - Note: May issue a clinical hold
  - Versus Canada….each trial has a unique CTA and NOL and the drug is filed under a Drug Master File (DMF)

European Union

- Regulations governing clinical trials in the EU are provided in Directive 2001/20/EC
- Addresses GCP implementation in clinical trials with select nuances
- Partnerships require legal representatives in the EU
- Should be defined in trial contracts

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European Union

- Responsibilities include…
  - Regulatory submission
  - Oversight including audit / monitoring
  - Safety reporting
  - Aspects of drug including relevant GMP requirements

Summary

REGULATORY ROAD MAP

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What Regulations and Guidelines Apply to Which Trials in Canada?

- Declaration of Helsinki / International Conference on Harmonization Good Clinical Practice
  - Yes, these ethical principles apply to all trials
- Tri Council Policy Statement (TCPS)?
  - Yes if funded by Canadian agency

What Regulations and Guidelines Apply to Which Trials in Canada?

- Health Canada Clinical Trials Application (CTA)? - Yes if new indication including…
  - Licensed drug but not in an approved disease or stage
  - Licensed drug but in a new schedule or dose
  - Licensed drug but in a new combination
- Office for Human Research Protection rules? - Yes if drug or funding is provided via NIH
- US FDA? - Yes if a US Investigational New Drug (IND) is filed

What Regulations and Guidelines Apply to Which Trials in Canada?

	DOH ICH-GCP	Local REB	TCPS	Health Canada CTA	OHRP	US FDA
All Human Trials	X	X				
Canadian agency funding	X	X	X			
+ new indication	X	X		X		
US government funding	X	X			X	
Under US IND	X	X				X

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