Applicability of US Regulations to Canadian Research

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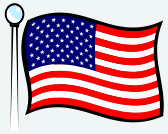
MK's Conventions:

1. US Regulation 
   name, purpose, guidance documents
2. Assurance 
   accompanying US form / attestation
3. Applicability in Canada 
   & any comparable Canadian standards

Note:

Any US requirements are in addition to applicable Canadian requirements.

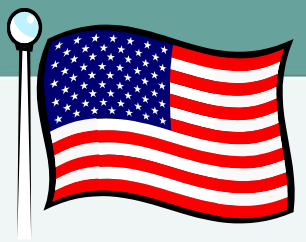
Pertinent US Regulations

- HIPAA
- 21 CFR Parts 11, 50, 54, 56, 312, 812

  ** focus on 21 CFR 312.120*
- 45 CFR Part 46

CFR = Code of Federal Regulations

HIPAA

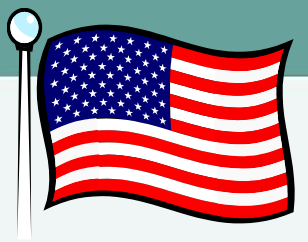


Health Insurance Portability & Accountability Act

- Enforced by US Office for Civil Rights.
- Privacy Rule protects privacy of individually identifiable health information;
- Security Rule sets standards for security of electronic protected health information;
- Patient Safety Rule protects identifiable information used to analyze patient safety events and improve patient safety.

HIPAA Applicability

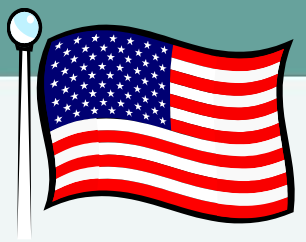
- US only; doesn't apply in Canada
- Comparable Canadian standards include:
  - PIPEDA - *Personal Information Protection and Electronic Documents Act* (national) and "substantially similar" provincial legislation governing personal information & personal health information,
  - TCPS 2 Chapter 5.



21 CFR

Title 21 governs food and drugs for the US:

- Food and Drug Administration (FDA),
- Drug Enforcement Administration,
- Office of National Drug Control Policy.



21 CFR: Notable Parts

11 Electronic Records; Electronic Signatures

50 Protection of Human Subjects

54 Financial Disclosure by Clinical Investigators

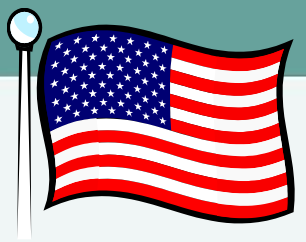
56 Institutional Review Boards (clinical trials)

300 series re: pharmaceuticals, including

312 Investigational New Drug Application

800 series re: medical devices, including

812 Investigational Device Exemptions



21 CFR Part 11

Electronic Records; Electronic Signatures

- Relatively brief (5 pages).
- Sets out criteria under which electronic records and electronic signatures are considered to be trustworthy, reliable and generally equivalent to paper records and handwritten signatures.

- FDA Guidance: "Computerized Systems Used In Clinical Investigations" (2007)
- FDA Guidance: "Part 11, Electronic Records; Electronic Signatures — Scope and Application" (2003)

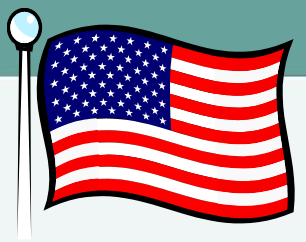
Part 11 Assurance

- Sponsors ask sites to provide assurance that computerized systems used in clinical investigations are compliant:
  - Part 11 Representation Form for Investigator Site Computerized Systems (study-specific),
  - E-Signature Certification (master letter is ok).

Part 11 Applicability

- Applies to US-regulated studies.
- Sites should identify electronic systems (e.g., health records) to be used and ask institutional experts and/or vendors to confirm compliance.
- Ask institutional rep to send a letter to the FDA confirming that electronic signatures are the legally binding equivalent of traditional handwritten signatures.
- No comparable Canadian standards,

  though Health Canada refers to Pharmaceutical Inspection Cooperation Scheme (PIC/S) Guidance: Practices for Computerised Systems in Regulated "GXP" Environments.



21 CFR Part 50

Protection of Human Subjects

- Protects rights and safety of subjects involved in investigations filed with the FDA.
- Outlines requirements for informed consent and additional safeguards for children in clinical investigations.

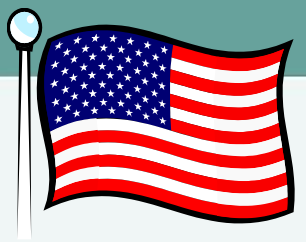
➢ FDA Guidance: *various*

Part 50 Assurance

- Form FDA 1572: Statement of Investigator requires PI to attest, “I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to informed consent in 21 CFR Part 50… are met.”

Part 50 Applicability

- Applies to foreign (non-US) sites included under an Investigational New Drug Application (IND) and device studies.
- Comparable Canadian standards include:
  - ICH-GCP E6 4.8 (drug & NHP trials),
  - Division 5 Regulations C.05.010 (drug trials),
  - TCPS 2 Chapter 3.



21 CFR Part 54

Financial Disclosure by Clinical Investigators

- Attempts to minimize bias by identifying situations where clinical investigators have a financial interest in the outcome of a study because of the way payment is arranged (e.g., royalties) or because investigators have a proprietary interest in the product (e.g., a patent) or an equity interest in the study sponsor.

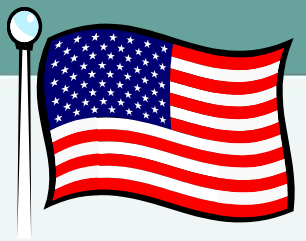
➢ FDA Guidance: "Financial Disclosure by Clinical Investigators" (2013)

Part 54 Assurance

- Sponsors must collect relevant financial information from investigators (PI and sub-investigators) – no prescribed format.
- Investigators must provide this info before they participate in the study and must submit updates to the sponsor if relevant changes occur during the study and for one year after its completion.

Part 54 Applicability

- Applies to investigators whose data will be included in a US marketing application for a drug, biological product or device.
- Comparable Canadian standards include:
  - TCPS 2 Chapter 7D (disclosure to REB),
  - Tri-Agency Framework: Responsible Conduct of Research,
  - No comparable Health Canada requirement… yet.



21 CFR Part 56

Institutional Review Boards (IRB = REB)

- Outlines standards for the composition, operation and responsibility of IRBs that review clinical trials used to support marketing applications for FDA-regulated products.
- US IRBs must register at a site maintained by the DHHS (optional for foreign REBs).

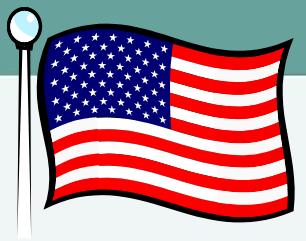
➢ FDA Guidance: *various*

Part 56 Assurance

- Form FDA 1572: Statement of Investigator requires PI to attest, “I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.”

Part 56 Applicability

- Applies to sites that are included under an IND (unless the sponsor obtains a Waiver of IRB Requirements) and device studies.
- Comparable Canadian standards include:
  - ICH GCP E6 Chapter 3,
  - TCPS 2, particularly Chapter 6,
  - Division 5 Regulations C.05.001,
  - NHP Regulations Part 4 Article 63.



21 CFR Part 312

Investigational New Drug Application

- Contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the FDA of investigational new drug applications (INDs).
- INDs can include many studies & many sites.

➢ FDA Guidance: *various*

Part 312 Assurance

- Form FDA 1572 Statement of Investigator
  - Must be signed by the PI if his/her site is included under an IND.
  - Page 1 contains site information,
  - Page 2 contains a list of commitments by the PI to conduct the study in accordance with 21 CFR Parts 50, 56 and 312.

➢ FDA Guidance: "Frequently Asked Questions Statement of Investigator (Form FDA 1572)" (2010)

Part 312 Applicability

- Applies to clinical trials used to support marketing applications for FDA-regulated products. However…
- Some exceptions apply to foreign (i.e., non-US) sites:

  312.120 Foreign clinical studies not conducted under an IND.

Inclusion of Sites under an IND

- US sites must be listed under the IND and must comply with 21 CFR 312. They must sign a Form 1572 and assure their IRB complies with 21 CFR Part 56.
- Inclusion of foreign sites is optional for sponsors. They can use foreign data to support a marketing application either way.

➢ FDA Guidance: "FDA Acceptance of Foreign Clinical Studies not Conducted under an IND Frequently Asked Questions" (2012)

Frequently Asked Questions
Statement of Investigator (Form FDA 1572)

Q #14: "Must foreign clinical study sites in a multinational study that includes domestic sites be conducted under an IND?"

A: "No. A multi-national study may include domestic sites under the IND and foreign sites not under the IND…"

Inclusion of Foreign Sites under an IND

- Foreign sites included under the IND must comply with 21 CFR Part 312 and the PI must sign the FDA Form1572.
- The 1572 commits the PI to using an IRB that complies with 21 CFR Part 56. As many foreign IRBs do not, the sponsor should request a Waiver of IRB Requirements.

➢ FDA Guidance: "Waiver of IRB Requirements for Drug and Biological Studies" (2006)

Exclusion of Foreign Sites from the IND

- Foreign sites excluded from the IND need only comply with 21 CFR 312.120.
- The PI does not need to sign a Form 1572, but the sponsor may request an alternate assurance stating that the study will be conducted in accordance with domestic laws, ICH GCP E6, the protocol, etc. and will permit onsite inspection by the FDA.

Reasons to Request Exclusion:

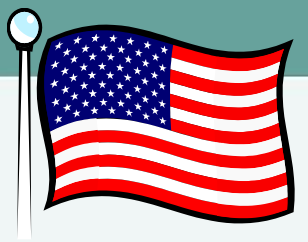
1. Inclusion is unnecessary under US law.
2. Commits the site to compliance with foreign regulations you may not have the expertise to assess or implement.
3. Additional opportunity for non-compliance (more regulations > more opportunity).
4. Canadian standards are high & sufficient.
5. Canada is a sovereign nation! 
6. Form 1572 can be an administrative pain for sites and sponsors.

Strategies for Exclusion from the IND:

- Brush up on the regulations and guidance documents.
- Ensure research teams, contracts & grants dept., quality advisor, legal dept. etc. are on board – collaboration is key.
- Ask sponsors early & often to exclude you.
- Prepare standard emails & templates.
- Be prepared to argue (nicely).
- Be patient and persistent!

Reasons Sponsors May Want a 1572:

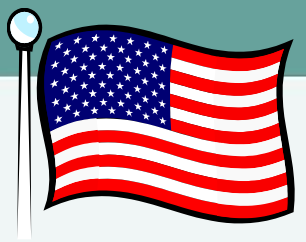
1. Handy way to obtain site information.
   - *Offer to complete an alternative form.*
2. SOP or habit.
   - *Discuss with their regulatory department.*
3. Site is already listed under the IND.
   - *Ask for evidence;*
   - *Ask sponsor/CRO to request a Waiver of IRB Requirements;*
   - *Document your request for the Waiver.*



21 CFR 812

Investigational Device Exemptions

- Provides procedures for the conduct of clinical investigations of devices.
- Requirements vary for “significant risk” (SR) devices vs. “non-significant risk” (NSR) devices. SR studies must be approved by the IRB and the FDA. NSR studies don’t require an IDE submission.



21 CFR 812

Investigational Device Exemptions

- Requires compliance with 21 CFR Parts 50, 54 & 56.

- FDA Guidance: "Frequently Asked Questions About Medical Devices" (2006)
- FDA Guidance: "Significant Risk and Nonsignificant Risk Medical Device Studies" (2006)

Part 812 Assurance

Investigator must provide the sponsor with a statement confirming commitment to:

i. Conduct the investigation in accordance with the agreement, regulations, etc.

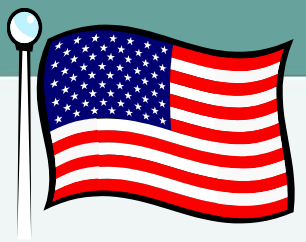
ii. Supervise all testing of the device involving human subjects; and

iii. Ensure requirements for obtaining informed consent are met.

Part 812 Applicability

- Applies to U.S. regulated device studies, including those at foreign sites.
- Comparable Canadian standards include:
  - Medical Devices Regulations Part 3.

Alert: 21 CFR Part 812 is much more stringent than Canadian requirements re: the conduct of device trials.



45 CFR Part 46

Protection of Human Subjects aka

"The Common Rule"

- Applies to human subjects research conducted or supported by an U.S. federal department or agency, including:
  - National Institute of Health,
  - Department of Defense,
  - Centers for Disease Control & Prevention.

45 CFR Part 46 Assurance

- The institution (not the investigator) signs a Federal Wide Assurance committing to compliance with specified ethical codes (Belmont Report, Declaration of Helsinki), procedural standards (inc. ICH GCP E6 & TCPS 2) and 45 CFR Part 46.
- The institution's IRB/REB must register with the Office for Human Research Protections (OHRP).

45 Part 46 Applicability

"For HHS-conducted or-supported research, all institutions holding an OHRP-approved FWA and engaged in such research must comply with the requirements of 45 CFR part 46. That compliance is required regardless of whether the institution marked one or more other procedural standards on the FWA form for international (non-US) institutions as a standard to which the institution committed itself to comply."

- Department of Health & Human Services

Federal Register Vol. 71, No. 130 (2006)

"Equivalent Protections"

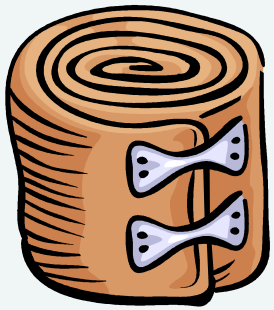
45 CFR 46.101(h) includes an "equivalent protections" provision. However, to date, no foreign standards have been deemed equivalent.

- OHRP Guidance: http://www.hhs.gov/ohrp/international

"OHRP works to ensure that human subjects outside of the United States who participate in research projects conducted or funded by DHHS receive the same level of protections as research participants inside the United States. To that end, the OHRP International Activities program offers consultation services, disseminates pertinent reports, and provides research ethics training."

Wrap-Up & Words of Advice

- Be aware of the Canadian and US Regulations that apply to your research;
- Avoid committing to compliance with unnecessary Regulations;
- Don't be shy to raise the issue with your sponsor / CRO;
- Focus on ensuring compliance with necessary standards.



Questions?

Thank You

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