International Research: Preparing for Your Upcoming Scientific Safari

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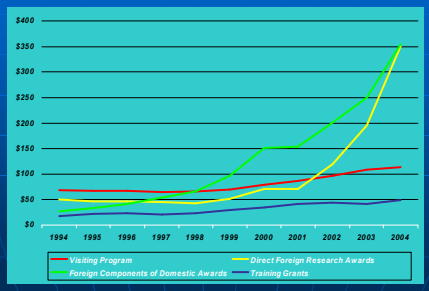
May 2, 2013

Session Overview

- Growth in international research
- Regulatory considerations
- Declaration of Helsinki
- Global tour:
  - Canada
  - European Union
  - India
- Discussion

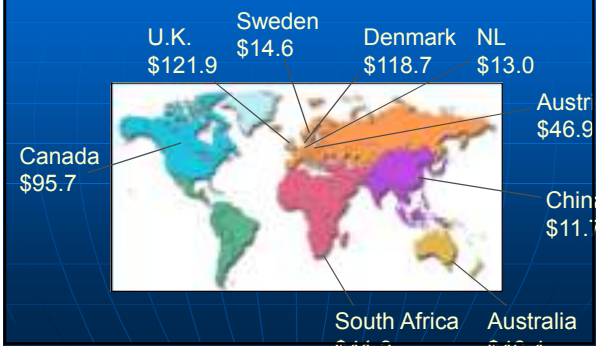
NIH International Research Expenditures

FY1994-2004 (Dollars in Millions)



Source: Fogarty International Center, Nov. 2005

Largest Recipients of NIH Awards:
Millions $ in FY2004



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Regulatory Considerations

The same regulations that apply to US research also apply to other countries for research funded by US governmental agencies.

45 CFR 46.101:

"(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research."

Knowledge of Local Research Context

45 CFR 46.107:

"The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including…sensitivity to such issues as community attitudes…The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice."

How to Obtain Knowledge of Local Research Context

- Information in research protocol
- Knowledgeable IRB members
- Local students from the country of interest
- CIA World Factbook: https://www.cia.gov/library/publications/the-world-factbook/index.html
- In-country resources – representatives can serve as consultants to the US IRB
  - National ethics committee
  - IRB
  - Governmental authority
- International Compilation of Human Research Standards

International Compilation of Human Research Standards

- Lists over 1,000 laws, regulations, and guidelines in 104 countries
- URL: http://www.hhs.gov/ohrp/international/intlcompilation/intlcomp2013.pdf.pdf

Organization of Listings

Country	Key Organi-zations	Legislation	Regula-tions	Guidelines
General				
Drugs and Devices				
Research Injury				
Privacy/Data Protection				
Human Biological Materials				
Genetic Research				
Embryos, Stem Cells, and Cloning				

Korea

Drugs and Devices	Pharmaceutical Affairs Act (No. 10324) Articles 10 and 31-34 (2010)	Enforcement Rule of Pharmaceutical Affairs Act No. 1, Articles 12, 22, 24, 29, 31-34, 49, 62, 75, 76, and 94 (2010)	
Privacy/Data Protection	1. Act on the Protection of Personal Information Maintained by Public Agencies No. 10012 (2010) 2. Medical Affairs Act No. 10387 (2010)		

Korea (cont.)

Genetic Research	Bioethics and Safety Act No. 9932, (2010)	Presidential Order of Regulation for Bioethics and Safety No. 22075 (2010)	Guidelines for Bioethics and Safety Act No. 18 (2010)
Embryos, Stem Cells, and Cloning	Bioethics and Safety Act No. 9932, Articles 2, 18-21, 38, 41, and 45 (2010)	Presidential Order of Regulation for Bioethics and Safety No. 22075 (2010)	Guidelines for Bioethics and Safety Act No. 18 (2010)

Most recent addition:
Listing of Standards on Research Injury

- 53 standards on research injury around the world

Standards on Research Injury:
North America

- United States – Common Rule Sec. 116:

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

- Canada – Tri-Council Policy Statement:

Information for informed consent includes:
(j) information about any payments, including incentives for participants, reimbursement for participation-related expenses and compensation for injury;

Standards on Research Injury:
ICH-GCP-E6

- International Conference on Harmonization GCP-E6:

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

Standards on Research Injury: *CIOMS*

- Council for International Organizations of Medical Sciences:

Guideline 19: Right of injured subjects to treatment and compensation

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability, or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.

Standards on Research Injury: *Europe*

- European Union – Clinical Trials Directive

Article 3.2: A clinical trial may be undertaken only if:
(f) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

Article 6.3: The Ethics Committee shall consider:
(h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;
(i) any insurance or indemnity to cover the liability of the investigator and sponsor;

- Council of Europe

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Declaration of Helsinki

- Most widely recognized presentation of the ethical basis of human subjects research in the world
- Originally adopted in 1964
- Numerous updates:
  - 1975
  - 1983
  - 1989
  - 1996
  - 2000
  - 2002
  - 2004
  - 2008

Controversy #1: Waiver of Informed Consent

- "no competent individual may be enrolled in a research study unless he or she freely agrees" – Paragraph 22, 2008 version
- Concerns:
  - What about exempt research on previously collected biological specimens or data?
  - What about population surveys?
  - What about other research that cannot be conducted without a waiver of informed consent?

Controversy #2: Post-Study Access

- At the conclusion of the study, subjects are entitled to "share any benefits that result" from the research – Paragraph 33, 2008 version
- Concerns:
  - What if the study intervention is found to be ineffective or harmful?
  - What if the country does not approve the study drug for its national drug formulary?
  - Does this represent undue influence?

Controversy #3: Standard of Care for Control Group

- "in any medical study, every patient – including those of a control group, if any – should be assured of the best current diagnostic and therapeutic method" – Paragraph 29, 2000 version
- Concerns:
  - What about placebo control groups?
  - "best current" method – available anywhere in the world, or just in the country where the research is conducted?
- "the Declaration of Helsinki has lost its moral authority with regard to this controversy" – RL Lie, *Journal of Medical Ethics*, 2003

New Version of DOH

- DOH is approaching its 50th anniversary and the World Medical Association is undertaking another round of consultations
- April 6, 2013: WMA released draft DOH update featuring:
  - Better protection for vulnerable groups
  - Addresses the issue of compensation
  - More precise and specific requirements regarding post-study arrangements
  - More transparency in the functioning of research ethics committees
  - More systematic approach to the use of placebos, but no weakening in the ethics of placebo use
  - Better readability by restructuring the document with sub-headings
- Document can be viewed at: http://www.wma.net/en/20activities/10ethics/10helsinki/15publicconsult/index.html

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Case Study #1: Canada

Key Organizations

- Panel on Research Ethics: http://www.pre.ethics.gc.ca/eng/index/
- Health Canada, Therapeutic Products Directorate: http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/tpd-dpt/index-eng.php

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans

Joint policy of Canada's three federal research agencies:

- Canadian Institutes of Health Research (CIHR)
- Natural Sciences and Engineering Research Council (NSERC)
- Social Sciences and Humanities Research Council (SSHRC)

TCPS Ethics Framework: Core Principles

- Founded on respect for human dignity
- Research to be conducted in a manner sensitive to the inherent worth of all human beings
- Expressed through three core principles:
  - Respect for Persons
  - Concern for Welfare
  - Justice

TCPS Versions

- First published in 1998, updated in 2010.
- What's new in 2010 edition:
  - three chapters
    - Multi-Jurisdictional Research (Chapter 8)
    - Research Involving First Nations, Inuit and Métis Peoples of Canada (Chapter 9)
    - Qualitative Research (Chapter 10)
  - clinical trial registration
  - research ethics review during publicly declared emergencies
  - institutional responsibilities associated with security of information
  - reporting incidental findings
  - research directives
  - document structure
  - index and glossary

Case Study #2: European Union

- EU consists of 27 countries:

- Lead drug regulatory agency is the European Medicines Agency, located in London

Three Big Changes in the Works….

1. Clinical Trials Directive
2. EMA Data Transparency Initiative
3. Data Protection Regulation

1. Clinical Trials Directive 2001/20/EC

- Directive was enacted in 2001 to provide a framework to harmonize drug clinical trials throughout the EU: http://pharmacos.eudra.org/F2/eudralex/vol-1/new_v1/Dir2001-20_en.pdf
- All 27 countries were supposed to transpose the Directive into their own laws by 2003
- Only Denmark, Germany, and Italy came close to meeting this deadline

Result: Clinical Trials Took a Nosedive

- Patients, researchers, and industry criticized the Directive for its "disproportionate regulatory requirements."
- Between 2007 and 2011, the number of clinical trials conducted in the EU fell by 25%.
- Trials sponsored by academic centers were especially hard-hit because of the Directive's insurance requirements.

Clinical Trials Directive: Round Two

2012: EU issued its draft "Regulation on clinical trials on medicinal products for human use repealing Directive 2001/20/EC:" http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

Key Changes:

1. Identify low-intervention clinical trials in which the Investigational Medical Product is used in accord with the prior labeling requirements, or is used as a standard-of-care treatment.
2. Simplify safety reporting
3. Adopt the level of monitoring to the type of trial
4. Simplify drug labeling
5. Consolidate rules on drug manufacturing and importation

What About IRB Review?

- The proposed Clinical Trials Directive does *not* include any requirement for IRB review
- Only states that applications should be evaluated by a "reasonable number of persons who collectively have the necessary qualifications and experience."
- European Group on Ethics in Science and New Technologies: "deeply concerned" about the omission
- German Medical Association: the proposal undermines the "protection of study subjects, scientific quality, and public trust in clinical research."

And more…

2. EMA Transparency Initiative: Releasing Subject-Level Data to the Public

Not a Total Surprise…

- 2004: EMA establishes eudraCT, a clinical trials database to compile information on EU drug trials
- 2011: EMA launches clinicaltrialsregister.eu, making clinical trials information publicly available and searchable
- November 2012: EMA announces that it will require that participant-level clinical trials data used to support the authorization of a medicine be made publicly available

Source: April 10, 2013 presentation by Mark Barnes, ROPES & GRAY LLP

Rationale of Data Release

– Decrease possibility of selective reporting
– Allow for study replication
– Give clinical trials participants greater confidence that their contribution will be used to further medical knowledge
– Increase efficiency of research by allowing secondary analyses of data sets
– Provide patients and their advocates a greater ability to analyze relevant data

Unresolved Issues

1. De-identification: Which identifiers must be removed to be considered "de-identified"? How to reconcile with HIPAA?
2. Which groups will do the de-identification?
3. Subject consent: Subjects will need to be informed of release of de-identified data.
4. Will IRBs be less likely to approve studies on sensitive diseases because of data-release requirements?
5. What about intellectual property rights of pharmaceutical companies?

Implementation Timeline

- January-April 2013 – Advisory groups meet
- June 2013 – Draft policy completed
- July-September 2013 – Comment period
- November 2013 – Final policy published
- January 2014 – Policy takes effect

Potential Far-Reaching Implications

- "the EMA's initiative challenges other interested parties to evaluate their current policies and consider changes. For example, if clinical trial data are available from the EMA, should they be comparably available from the FDA and other regulatory agencies?" – Robert Steinbrook, *AMA-Internal Medicine*, March 11, 2013

3. Just when you thought you had it pretty much figured out…

The EU is working on a new Data Protection Regulation that would impose rigorous requirements on research efforts:
http://ec.europa.eu/justice/data-protection/law/index_en.htm

Current draft features:

- Broad definition of "personal" data – not just "private" data
- A proposed "right to be forgotten"
- 2% fine on firms for data breaches

Case Study #3: India

- Office of Drugs Controller General of India (DCGI) has few inspectors and provides little oversight
- India has a large generic drug industry -- 10 million people around the world with HIV-AIDS reportedly rely on Indian generic medications

Key Regulatory Standards

- Drugs Controller General of India: Good Clinical Practices for Clinical Research in India (2001)
- India Council for Medical Research: Ethical Guidelines for Biomedical Research on Human Participants (2006)

Concerns About Regulatory Oversight

- Numerous media reports about deaths among persons participating in trials
- NBC News expose on the role of CROs: "How Poor Indians are Recruited for Clinical Drug Trials"
- May 2012: Indian parliamentary Committee on Health and Family Welfare released a report highly critical of the Central Drugs Standard Control Organization (CDSCO)

ABC Newsline: Indian Drug Trials Exploiting the Poor

New Regulations

On January 30, 2013, the Government of India published 3 new sets of requirements for clinical trials:

- G.S.R. 53(E) dated 30.1.2013: delineates requirements for treatment and/or compensation for any clinical trial-related injury or death -- http://www.cdsco.nic.in/gsr%2053(e)%20dated%2030.01.2013.pdf
- G.S.R. 63(E) dated 1.2.2013: describes additional requirements for clinical trials -- http://www.cdsco.nic.in/GSR%2063(E)%20dated01%20.02.2013.pdf
- G.S.R No. 72(E) Dated 8.2.2013: outlines the role of Research Ethics Committees -- http://www.cdsco.nic.in/G.S.R%2072(E)%20dated%2008.02.2013.pdf

Compensation for Research Injury

The rules specify that any injury due to following reasons shall be considered as a clinical trial-related injury:

"(a) adverse effect of investigational product(s),
(b) violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator,
(c) failure of investigational product to provide intended therapeutic effect,
(d) use of a placebo in a placebo-controlled trial,
(e) adverse effects due to concomitant medication excluding standard care, necessitated as part of the approved protocol,
(f) for injury to a child in-utero because of the participation of parent in clinical trial,
(g) any clinical procedures involved in the study."

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Common Challenges in International Research

1. Coordinating IRB review processes – lead IRB?
2. Delays in getting approvals
3. Language barriers
4. Difficulty in properly interpreting in-country standards, e.g., defining the age of majority in Kenya
5. Logistical challenges, e.g., power failures
6. Personnel and salary issues
7. Export of data and biospecimens

Question: IRB Review of Non-English Materials

- "What are best practices for an IRB review of consent forms, survey instruments, or other materials that are in a non-English language for which it is not easy to find a suitable translator?"
- Considerations:
  - Ask PI to recommend translator
  - Google Translate is available for 60 languages
  - If you do a back-translation, do not expect a word-for-word match

Question: Assuring the Safety of Researchers

- "What are the IRB's obligations for assessing and/or assuring the safety of the researchers in the foreign country where the study is taking place?"
- Considerations:
  - No regulatory requirements
  - Institutional policies apply, use common sense – e.g., not recommended for grad student to do a survey of political prisoners in West Africa
  - Visit State Department Travel Advisory page: http://travel.state.gov/travel/cis_pa_tw/cis_pa_tw_1168.html

Your Turn to Ask that Burning Question, Share War Stories….

Thank you!