

Considerations for International Research



Susan L. Rose, Ph.D.
Office for the Protection of Research Subjects
(OPRS)

Research in Diverse Communities

- When conducting research in a multi-cultural city like Los Angeles, many of the same considerations are required as when research is conducted internationally.
- This talk will explore what is required when conducting research in Los Angeles as well as differences when conducting research outside the United States.



Keep in mind...

- Doing research overseas does not obviate the need for ethical and regulatory protections
- Expectations may differ when research is biomedical vs social and behavioral and when it is conducted in a developed versus developing country
- The guidance needs to go beyond principles and include practical benchmarks to guide investigators
- The goal is to maximize local benefits/minimize exploitation



Top 5 Recruitment Strategies for Minority Populations

1. Partnerships with Community Based Orgs
2. Attending social and cultural events
3. Word of mouth
4. Providing Financial Incentives
5. Tailored recruitment materials



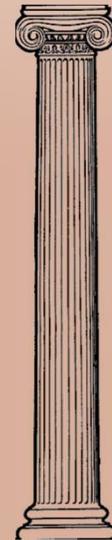
"Attributes of researchers and their strategies to recruit minority populations" (Quinn, 2012)

International Cultural and Regulatory Issues



Eight Universal Ethical Principles

1. Collaborative Partnership
2. Social Value
3. Scientific Validity
4. Fair Selection of Participants
5. Favorable Risk-Benefit Ratio
6. Peer Review
7. Informed Consent
8. Respect for Participants built in



International Research Considerations

- **What is the motivation for international research?**

- Money – And?
- Unique disease/genetics/populations

- **What is Changing in the clinical trials world?**

- Science – Access
- Genetics – IT
- Recruitment fatigue

- **What are the rules? Whose rules are they?**

- Theirs – Ours – International

- **Remember to address:**

- Respecting national norms, ministries and local morés
- Financial/Scientific payoff must accrue beyond to researcher/sponsor
- Hope, need, lack of understanding, natural resources must not be exploited



Increase in International Research

Date	US Registration (50 states)	International Registration (167 countries)
2003	1000	0
2004	13,000	0
2006	>40,000	12,000
2009	74,734	> 72,000

Since 2002, the number of active Food and Drug Administration (FDA)-regulated investigators based outside the United States has grown by 15% annually, whereas the number of U.S.-based investigators has declined by 5.5%



Federal and International Guidance



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The Belmont Report*

Ethical Principles and Guidelines for the Protection of Human Subjects of Research:

- **Respect for persons:**
 - Subjects voluntarily consent to participate
- **Beneficence:**
 - Risks of research are justified by potential benefits to the individual or society
- **Justice:**
 - Equal distribution of risk/benefits among all



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* "Ethical Principles and Guidelines for the Protection of Human Subjects Research," Belmont Conference Center April 18, 1979

The Common Rule (CFR 45 Part 46)

Major Concepts:

- Prior approval by ethics committee
- Written informed consent and documentation (voluntary, understandable, explains risk and choices)
- Equitable recruitment of research participants
- Special protection for vulnerable groups
- Continuing review of approved research (has risk changed?)



International Conference on Harmonization

FDA/Drug companies, Japan, Canada and the U.S.

Goals:

- standardize drug development and approval process internationally
- set protocol development standards
- require review by ethics committee
- set researcher responsibilities
- set sponsor responsibilities
- obviate need for repeat reviews
- set standards for manufacturing processes



Council for International Organizations of Medical Science Objectives (CIOMS)

- Facilitates and promotes international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary
- Maintains collaborative relations with the United Nations and its specialized agencies (WHO and UNESCO)
- Serves the scientific interests of the international biomedical community in general



www.cioms.ch

Declaration of Helsinki (WMA)*

Declaration of Helsinki:

"The WMA...has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research."

WMA / Helsinki placebo position:

"The WMA... hereby affirms its position that... a placebo controlled trial ...should [generally] only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available: Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a... therapeutic method, or - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.



* World Medical Association - <http://www.wma.net>



Nuremberg Code

- Developed following the Nuremberg Military Tribunal, the Code provided many of the basic principles that still govern the ethical conduct of human subjects research.
 - For example it asserts that **“the voluntary consent of the human subject is absolutely essential” to conducting medical research.**
- In order to satisfy these principles, Nuremberg Code explains the requirements:
 - capacity of participants to consent
 - voluntary participation
 - freedom from coercion
 - no penalty for withdrawal
 - full knowledge of the risks and benefits of participation

The Nuremberg Code can be found at:

<http://www.nihtraining.com/ohsr/site/guidelines/nuremberg.html>.



Points to Consider for International Trials

- Cultural-sensitivity to local site
 - Community Leader / Community Involvement
 - Paternalism
 - Language
 - Spiritual/Moral /Legal values
 - Collectivism vs. Autonomy
 - Justify placebo if used
- Potential for coercion (Socioeconomic status)
- Genetics/Homogeneity/Validity to other populations
- “Helicopter” research (data/sample collection & leaving site with no follow-up)
- Absence of infrastructure / Infrastructure enhancement
- Justification for foreign population in research
- Ethics body equivalent (Research Ethics Review Board/IRB) Approval/local oversight sought/required
- Financial/injury protection
- U.S. regulations and ethics don’t always fit local scene



Research & Sponsor Responsibilities



Researcher Responsibilities

- Protection of Human Subjects
- Scientific Validity
- Appropriate Informed Consent
- Confidentiality Protection
- Responsible for study team
- Conduct Research According to Protocol
- Compliance with Ethics Committee requirements
 - Report adverse experiences, protocol violations, participant complaints, conflicts of interest
- Post-study
 - Long-term interests of participants
- Integrity, respectful, professional, sensitive, cooperative



Sponsor Responsibilities

- Overall:
 - Ensure appropriate review, approval and supervision by an Ethics Committee
 - Monitor the research
 - Select qualified researchers
 - Provide policies and procedures to study / site
 - Commitment to follow-up for subjects in trials
- International Research:
 - Comply with the local ethical, regulatory and legal requirements
 - Ensure the local relevance of the research while involving local partners in the development stages
 - Promote research integrity



Summary of International Subject Protections

- Educate researchers about research ethics
- Ensure international researchers understand and are sensitive to the social, economic and political milieu
- Involve members of the host country in research design and conduct
- Ensure trials are of direct relevance to the health needs of the host community and that research benefits the community
- Conduct prior evaluation by a local committee to determine whether study findings can be incorporated into the healthcare system
- Provide subjects with care or treatment not otherwise available
- Address existing disparities if possible and not exploit human or material resources
- Provide justification when developed world standard of care is not provided



Resources

- International Committee on Harmonization (ICH)
Good Clinical Practice Guidelines
www.ifpma.org/ich5e.html
- Council for International Organizations of Medical Sciences (CIOMS)
International Ethical Guidelines for Biomedical Research
www.who.int/ina-ngo/ngo/ngo011.htm
- World Medical Association
<http://www.wma.net>
- Canadian Institutes of Health Research
www.nserc.ca/programs/ethics.htm
- National Council on Ethics in Human Research-Canada
www.ncehr-cnerh.org/english/mstr_frm.html
- Danish Council on Ethics
www.etiskraad.dk/english/about_the_council.html
- French National Consultative Committee on Ethics
www.ccne-ethique.org/
- National Committee for Medical Research Ethics-Norway
www.etikkom.no/E/index/htm
- U.S. Department of Health & Human Services
www.hhs.gov/ohrp/international/HSPCompilation.pdf



Articles of Interest

- Rotavirus vaccines stopped by CDC
"Global Illness and Deaths Caused by Rotavirus Disease in Children"
– <http://www.cdc.gov/ncidod/EID/vol9no5/pdfs/02-0562.pdf>
- "AZT Trials and Tribulations"
– http://findarticles.com/p/articles/mi_qo2103/is_6_28/ai_n28718837/
- Pfizer trials in Nigeria and Legal Settlement
"Finding an Abundance of Subjects and Lack of Oversight Abroad, Big Drug Companies Test Offshore to Speed Products to Market"
– http://www.washingtonpost.com/wp-dyn/content/article/2007/07/02/AR2007070201255_pf.html
- "Pfizer Reaches Settlement In Nigerian Drug-Trial Case"
– <http://www.washingtonpost.com/wp-dyn/content/article/2009/04/03/AR2009040301877.html>
- "The debate over maternal-fetal HIV transmission prevention trials in Africa, Asia, and the Caribbean: racist exploitation or exploitation of racism?"
– <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1508416>
- "The Ethics of Clinical Research in the Third World"
– <http://content.nejm.org/cgi/content/full/337/12/847>

