International Issues in the Bioethics of Research

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Fogarty International Center

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Overview

- FIC Activities in international research ethics
- The challenge of defining international standards in research ethics
- Capacity Building in research ethics

The Challenge of Defining International Standards

International Standards

"Human subjects in any part of the world should be protected by an irreducible set of ethical standards."

Marcia Angell,
NEJM, 1988

International Standards

"It is time to develop standards of research that preclude the kinds of double standards evident in these trials."

Lurie P, Wolfe S
NEJM, 1997

International Standards

- Debate about standards has focused primarily on *guidelines*
  - Disagreement on language and justifications
  - Divergence on substantive issues
  - Different goals/constituencies
  - Different status
  - Different claims of authority

International Standards

- Guidelines can't foresee the full spectrum of factors and contextual features that might influence
  - an investigator's decisions/actions
  - IRB's decisions
- Can't tell IRBs *what to do* in any given case
- Guidelines—and over-zealous concern with "compliance" in particular—may make people less willing to accept that they are dealing with complex human judgements

International Standards

- Guidelines, alone, cannot guarantee ethical conduct in research
  - In cases of disagreement between host country and "remote" (i.e., U.S.) IRBs, U.S. IRBs are still bound to follow the Common Rule.
  - The guidelines/regulations do not assist in resolving these disagreements

International Standards

- Other relevant targets for standards?
  - Standard of care in clinical trials
  - Research ethics review procedures
  - Institutional accountability practices
  - IRB training/education

A new look at international research ethics

Solomon R Benatar, Peter A Singer

Editorial by Lansang

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The normal "standard of care" against which new interventions are tested in medical research has not been formally defined. It is usually taken to mean the "best proved treatment" for any condition under investigation in a trial. We reject the arbitrariness of this notion of the standard of care and offer a more comprehensive alternative. Use of this new standard invokes a new approach to international research ethics that focuses on reducing inequalities in global health.

The debate on what constitutes a fair and reasonable standard of care for subjects in developing countries who participate in clinical trials has been rekindled by critics of studies on the transmission of HIV.[1–3] They argued that placebo controlled trials of new regimens to prevent the vertical transmission of HIV were unethical because they included a placebo arm rather than "the best proven treatment" available in developed countries. Some commentators considered the criticisms to be unfounded[4–6] and associated with imperialistic attitudes.[7]

The debate made it clear that the high standards of research aspired to have not been adequately defined. It was also marred by simplistic notions of ethics. Although there was justified concern that pressure from the US Food and Drug Administration could "dilute" the Declaration of Helsinki, critics also presumed that whether a trial was ethical could simply be deduced from the text of a declaration. But declarations—such as the Declaration of Helsinki, governing international research ethics—are like constitutions, needing interpretation. Determining what is ethical goes beyond merely following prescriptions and requires moral reasoning: consideration of all relevant aspects of the case in its context, weighing and balancing competing moral requirements, and developing justifiable conclusions.

Although more mature insight is gradually emerging into the complexity associated with the ethics of research in developing countries, the debate remains incomplete for several reasons.[8–12] Firstly, there has been a failure to define adequately the "standard of care." Secondly, it has been incorrectly assumed that the standard set by developed countries can be considered the norm. Thirdly, few commentators on research ethics have taken into consideration the injustice of 90% of all medical research being undertaken on those diseases that cause 10% of the global burden of disease.[13]

Box 1: Expanded concept for standard of care

- Provision of the same access to research, expenditure on the total care of each subject, and therapeutic drugs shown to be most effective in other locations
- Provision of the same "hotel" facilities, access to technology, general medical care, and other external influencing factors during the trial that were associated with and contributed to the "best proven" use of the drugs elsewhere
- Provision of the same follow up facilities for subjects after completion of the study and the same access to ongoing care
- Research undertaken by a team of the same culture and language group as the subjects, so that the same degree of effective communication, trust, and genuine informed consent is achieved through a legitimate informed decision making process
- Care provided by a research team with equivalent qualifications, training, and expertise

Summary points

- The standard of care for subjects participating in clinical trials is not well defined
- Excessive reliance has been placed on international declarations to define what is ethical, but declarations, like constitutions, need to be interpreted
- International researchers must develop a deeper understanding of the context within which their research is being conducted
- An expanded concept for standard of care is offered that takes account of the context of the trial and is sensitive to the social, economic, and political milieu
- National and international bodies concerned with research ethics need to confront the greatest ethical challenge—the enormous inequities in global health

How do we define "standard of care" for research subjects?

Equal standards of medical care during research, reflecting equal respect for the dignity of subjects, could be taken to mean any one or a combination of several requirements (box 1). It is arbitrary and not justifiable to select only one of these—for example, which drugs are used—to compare the standard of care in developed and developing countries.

In the context of the disputed studies on HIV transmission, the vehement emphasis on the "best proven drugs" eclipsed considerations of whether the drug regimen could be safely applied in different settings. Little attention was paid to the fact that there were many differences between pregnant women in developing countries and those in countries where the "best proven" treatment had been established. Pregnant women in developing countries present to antenatal clinics much later in pregnancy than the women in the original studies; they are often anaemic and malnourished, and they live within a context in which breast feeding has different implications for newborn infants. Moreover, advice not to breast feed would contradict years of intensive education by the World Health Organization.

TDR/PRD/ETHICS/2000.1

Operational Guidelines for Ethics Committees That Review Biomedical Research

World Health Organization
Geneva
2000

WHO Health Research Systems Initiative

- Performance of Health Research Systems
- 7 domains including…
- "Ethics"
  - Need conceptual framework that can reflect the real determinants of ethical conduct
  - Need approach to structure cross-country comparisons

WHO Health Research Systems Initiative

- Survey (191 WHO member countries)
- Basic description of research ethics review
  - Numbers of committees?
  - Training levels of members?
  - Turnover of members?
  - Funding, resources and workload?
  - National guidelines?

WHO Health Research Systems Initiative

- Case studies (selected countries)
- Members' attitudes and opinions
  - Expectations/perceptions of fair treatment?
  - Perceptions of authority?
  - Perceptions of independence?
  - Perceptions of institutional support?
  - Perception of researchers' willingness to accept decisions?
  - Trust in system?

WHO Health Research Systems Initiative

- In-depth exploration of experiences of REC/IRB members, investigators, research administrators, MOH, etc.
  - Obstacles to ethical conduct
  - Facilitators of ethical conduct
- Description of policy environment

WHO Health Research Systems Initiative

- Development context
  - Political freedoms
  - Social opportunities
  - Economic facilities
  - Transparency guarantees
  - Protective Security

Equivalent Protections

- U.S. Federal Government Working Group
  - Clarify the meaning of equivalent protections (45 CFR 46.101(h))
  - Make recommendations to OHRP re.
    - What could be achieved by implementation
    - What's a stake
    - How to do it

Capacity Building in International Research Ethics

Capacity Building

- Relevant disparities between sponsoring and host countries
  - Social, economic and political circumstances
  - Research funding (10/90 gap)
  - National laws, regulations, guidelines
  - Institutional policies and procedures
  - Human capital
  - Educational/training opportunities

Beyond Helsinki: a vision for global health ethics

Singer PA, Benatar SR. BMJ 2001; 322: 747-748.

- Improving ethical behaviour depends on strengthening capacity
- North-South partnerships
- South-South partnerships
- Systems of regional training centres for ethics

Capacity Building

- OHRP
- PRIM&R/ARENA (IRB 101)
- NIH Clinical Center Dep't of Clinical Bioethics
- NIH Short Courses
- NIH Overhead (8%) on direct foreign awards
- WHO/TDR/SIDCER

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NIAID

NINR

NHLBI

International Bioethics Education and Career Development Award

NIH Collaborating Partners

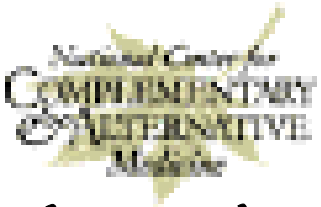
NICHD

NIA

NIAMS

NIMH
National Institute of Mental Health

NIGMS



NCCAM

NIDA

The FIC Mission

"To promote and support scientific research and training internationally to reduce disparities in global health."

Fogarty International Center

FIC fulfills its mission by:

Advancing research and research training that prepares current and future health scientists to meet global health challenges.

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Science for Global Health

Research Training Mechanisms

- Long-term training
  - pre- and post-doctoral training in U.S. institutions (duration: minimum 9 months)
- Short-term training
  - focused workshops and technology transfer (duration: several days to several weeks)
- Research performed preferentially in-country

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Science for Global Health

Program Objectives

- Train leaders in science and public health
- Establish centers of excellence in home countries
- Promote long-term collaborations between U.S. and foreign institutions
- Facilitate outstanding scientific research focused on problems of developing countries
- Facilitate trainees assuming positions of responsibility, authority, and influence

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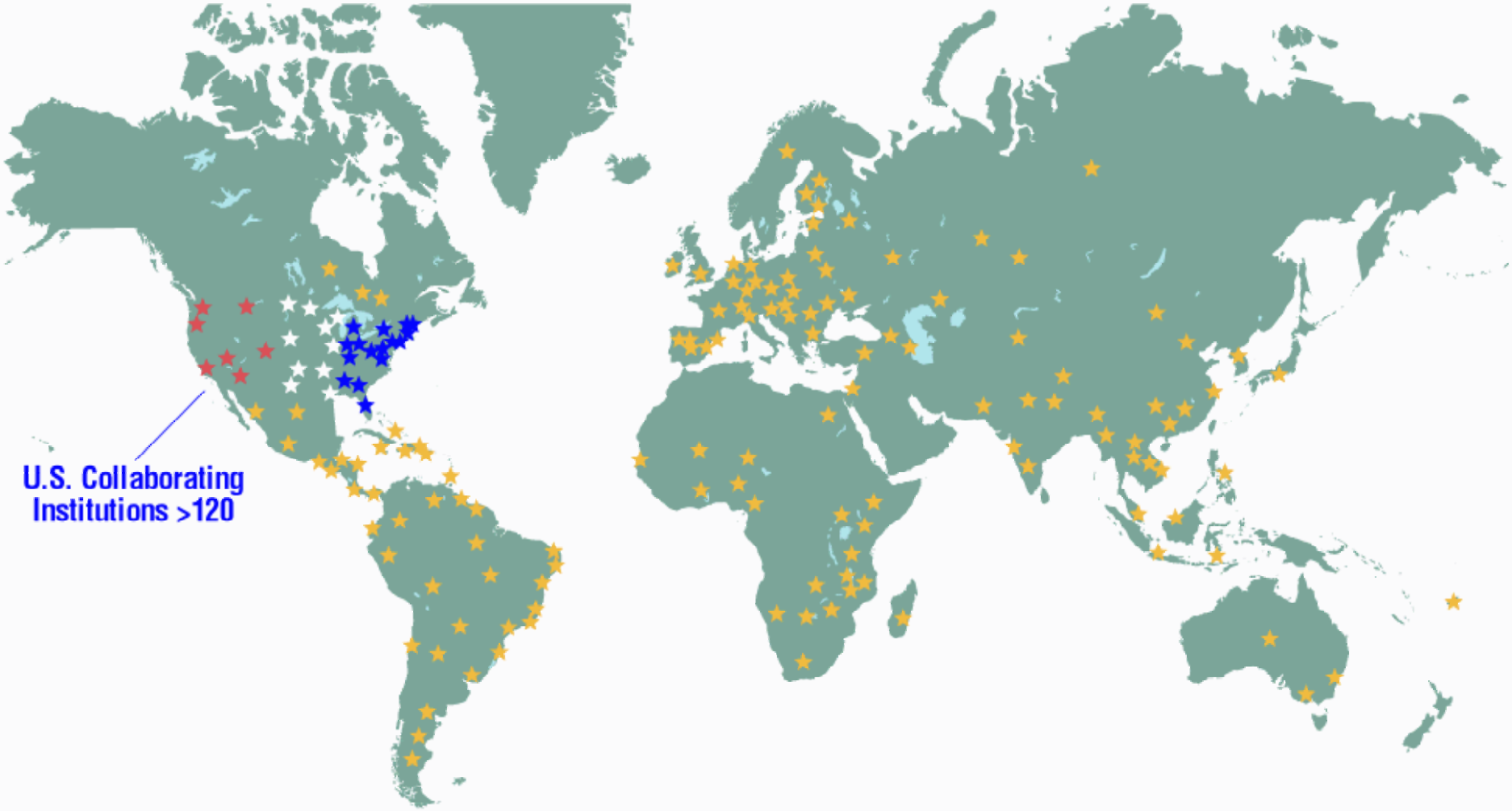
Science for Global Health

Major Training and Research Sites



Fogarty International Bioethics Education and Career Development Award

Objectives:

- Improve quality of training in existing programs
- Stimulate development of new programs
- Establish networks of developing-country bioethicists
- Contribute to emerging regional capacity

Fogarty International Bioethics Education and Career Development Award

- FIC/NIH Training Programs
  - U.S. (3)
  - Canada
  - Australia
  - Philippines
  - Bangladesh
  - India
  - Pakistan
  - China
  - S. Africa (X2)
  - Chile
  - Argentina

For More Information:

International Bioethics Initiatives

http://www.nih.gov/fic/programs/bioethics.html

http://www.nih.gov/fi
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