Ethical Issues in Clinical Trials in Developing Countries

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Key Ethical Issues

- Risk-Benefit Assessment
  - What type of risks are acceptable?
  - What type of benefits can justify risk?

- Informed Consent
  - The impact of context
  - Cultural variables

- Process Issues
  - The role of local decision-making
Risks must be “reasonable in relation to anticipated benefits”

- In general, no absolute upper limit
- But limits for “vulnerable populations”
  - U.S. FDA regs: children
  - CIOMS guidelines: individuals “who are politically powerless and members of communities unfamiliar with modern medical concepts”
Risk and the Concept of Clinical Equipoise

- Clinical equipoise: “an honest, professional disagreement” among experts about the relative merits of competing interventions (Freedman)
- Premise: it is unethical to give subjects interventions known to be inferior
- Placebos are acceptable only when
  - No standard treatment exists
  - Standard treatment involves intolerable risks
- Consistent with concept of “reasonable risk”?
Case Study

Studies of AZT to reduce maternal-fetal HIV transmission (Africa, Thailand, Dominican Republic)

- Background: AZT had already been proven to reduce transmission rate from 25% to about 8%
  - Standard of care in wealthy countries: give AZT orally during the last trimester, intravenously during labor and delivery, and to the infant during first 6 weeks
  - Too expensive for developing countries

- Research goal: develop short-course treatment targeted around time of delivery

- Research design: compare short-course treatment against placebo
Arguments against the Studies

- Unethical to enroll participants in a study and knowingly deprive them of treatment known to work
- Compared to Tuskegee study
- Double standards/exploitation
Arguments in Favor of the Studies

- Participants were not made worse off
- If “best proven treatment” had to be used in the control group, the studies might never have been conducted
- The issue of concern to these countries was whether the short course was superior to no treatment – not whether it was superior to the full regimen
- The placebo-controlled studies were effective: They showed a 51% reduction in perinatal HIV transmission rates
Competing Perspectives

**Declaration of Helsinki**

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic method.

**CIOMS Guidelines**

If an aim of research into health care is to improve current forms of treatment, there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting.
“Clarification” to Declaration of Helsinki
A placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for **compelling scientifically sound methodological reasons** its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or 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.

CIOMS Guidelines
Also permits placebos when **an established intervention is not generally available or affordable in the country** and the study is designed to develop an affordable intervention specifically for the region.
Ambiguities

Declaration of Helsinki
- What is a “compelling and scientifically sound methodological reason” that makes it “necessary” to use a placebo?
  - Why not use historical controls?
  - Does ability to do a smaller, quicker trial count?

CIOMS Guidelines
- What if intervention will also be used in wealthy countries?
- Does logic of CIOMS guidelines create obligation for sponsor to make drug available to host country at an affordable price?
Benefits

- General standard: risks weighed against potential benefits (1) to subjects, *if any*; and (2) to society

- Exceptions for vulnerable populations
  - Potential direct benefits to subjects not always necessary
  - But generalized societal benefits not sufficient
  - Must be potential benefits to the specific vulnerable population
    - Use vulnerable population only when necessary
    - Justified by long-term best interests of population as a whole
Case Study

GlaxoSmithKline, in partnership with UNICEF, UNDP, the World Bank, and WHO, proposed studies in Thailand to document the efficacy of Malarone in pregnant women with acute malaria.

Background: Resistance has grown to existing treatments for malaria in Southeast Asian countries.

Malarone already approved for treatment of malaria, but safety in pregnancy not established.
The Concern: Post-Trial Access

- Malarone is currently too expensive to be used in developing countries
- GSK would donate the drugs for use in the studies
- But what would happen after the studies were over?
Access and Benefits

- The Malarone studies would have provided a potential direct benefit to the participants in the studies.
- But long-term benefits would be primarily for foreign travelers in countries with malaria, not for local residents.
Guidelines

Declaration of Helsinki

- Paragraph 30: At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

- “Clarification”: The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.
CIOMS Guidelines

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- The research is responsive to the health needs and the priorities of the population and community in which it is to be carried out; and

- Any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.
Issues

- What does “reasonably available” mean?
- Can alternative benefits to the community be provided (e.g., support of health care infrastructure)?
- Can direct benefits to study participants take the place of long-term benefits of the local population?
- Who decides?
Process Concerns

- Importance of local ethics review
- But capacity for such review often lacking
  - Oversight systems just beginning
  - Lack of resources
  - Conflicts of interest
- Does informed consent process provide adequate safeguards?
Case Study

- Study to test Tenofovir as pre-exposure prophylaxis for HIV among sex workers in Cambodia
- Concerns
  - Insurance for complications
  - Post-trial access
  - Suspicion about safety (“if it’s so safe, why aren’t you studying it in the U.S.?“)
  - Suspicion about intentionally misleading counseling
  - Lack of community involvement in planning process
- Trial halted by Cambodian government
Initiatives

- Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) recognition process
- AAHRPP accreditation
- Institutional partnerships
- Pilot public education project in Thailand and Philippines