Ethical Issues, Community Perspective and Standards of Care for Clinical Research on Women & Children in Africa

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ICASA
Dakar, Senegal
3 December 2008
Ethical Concerns

- Women in clinical research
  - Protectionism versus Access
    - Risk of exposing fetus to risk of teratogenicity
    - Continued lack of knowledge regarding effects of drugs on maternal-placental-fetal unit

- Children
  - Informed consent and childhood assent
  - Avoidance of coercion
  - Expand treatment options to this neglected and vulnerable population
Ethical debates pertaining to clinical research in RLS

- Standard of care that should be used in research in RLS
- The “reasonable availability” of interventions that are proven to be useful during the course of clinical trials
- Quality of informed consent

Emanuel et al. JID 2004;189:930-37.
The challenge of defining “Standard of Care”

- In 1997 an editorial was written criticizing the use of placebo in PMTCT trials nearly 3 years after the publication of ACTG 076.

  Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries

  - Use of placebo was rationalized by the premise that the current available standard of care was no treatment in these countries.
  - NEJM study published a placebo-controlled trial comparing 3 regimens for TB prophylaxis in PPD-positive HIV-infected patients.

What to do?

- **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 methods.”

- **UNAIDS**
  - “Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country…” (Guidance point 16)

- **Third option**
  - All are offered care that is no worse than what they *should* have received had the study not been done
The challenge of determining “should have received” as a standard

- Risk moralizing standard
  - Potential for exploitation of participants
- WHO Performance Assessment
  - Ranked Performance Assessment of 191 Health systems
    - Characterizes how well countries are reaching healthcare goals given resources
Standard of care based on what patients “should have received”

- **Advantages**
  - Allows testing of promising new interventions when a superior, but unaffordable, intervention exists
  - Forbids studies the deny what patients “should receive”

- **Problems**
  - Does not address injustice of inequalities in care
  - May be distorted by idiosyncrasies of health allocation in comparable countries

- Ethical review boards may require higher standards in particular studies
Use of Placebo Justified

- When there are no approved, effective treatments for the condition, OR
- If there is a disagreement about whether standard treatment is better than placebo, OR
- When the additional risk posed by the use of placebo is minor and withholding the current standard therapy would not lead to serious or permanent harm, OR
- If the study is anticipated to result in widespread or major benefits and the receipt of placebo by individuals poses minimal risk.
Foundations of Human Subjects Regulation & Biomedical Ethics

- The Nuremberg Code (1947)
  - 10 points including the principles of informed consent, absence of coercion, beneficence towards participants, and properly formulated scientific designs

- Declaration of Helsinki (1964)
  - “Every patient should be assured of the best proven diagnostic and therapeutic method”

- The Belmont Report (1979)
  - Respect for persons
    - Participation in research is voluntary and requires informed consent
  - Beneficence
    - Subjects must be protected from harm and potential benefits must be balanced against risks
  - Justice
    - Equitable selection of research subjects
Vulnerable populations

- The Belmont Report also established special protections for vulnerable populations/persons with diminished autonomy
  - Designed to protect the rights and welfare of these subjects
  - Including impoverished individuals, limited education, HIV/AIDS, pregnant women, children, prisoners
CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects

- Pregnant women, Human Fetuses & Neonates (45 CFR 46, Subpart B)
  - Certain conditions must be met
    - Any risk is the “least possible”
    - If greater than minimal risk, research must hold out the prospect of direct benefit for the woman or the fetus
  
- Special informed consent criteria apply:
  - Risk is no greater than minimal, benefit to mom, benefit to mom and baby, or no direct benefit to mom or baby, mom’s consent required
  - Risk no greater than minimal, benefit to baby only, mom and dad should consent if possible (appropriate)
CIOMS Guidelines (cont’d)

- Children (45 CFR 46, Subpart D)
  - Children defined as persons who have not attained legal age for consent to treatments or procedures involved in the research
  - Special informed consent procedures apply:
    - Assent of children (usually older than 7 years) and permission of parents (one or both)
  - Research involving children must be no greater than minimal risk if there is no prospect of direct benefit to the children taking part
  - For the IRB to approve research with greater than minimal risk to the child participant there must be prospect for direct benefit
  - For research with greater than minimal risk to the child participant with no prospect of direct benefits, the risk can only represent a minor increase over minimal risk and the research must be likely to yield (important) generalizable knowledge about the disorder or condition
Why are HIV/AIDS patients a special population?

- Stigma and discrimination
- Resource constraints
- Sensitive issues regarding transmission
- Impact of educational and cultural context
Policy supporting research agenda: Pediatric Drug Dosing

- Two legislative initiatives, the FDA Modernization Act in 1997 and the Best Pharmaceuticals for Children Act in 2002 authorized an incentive program for manufacturers who conducted pediatric clinical trials in response to an FDA written request.
- The Pediatric Research Equity Act in 2003 codified the authority of the FDA to require pediatric studies of certain drugs and biological agents.
Sharing research & knowledge

- New research requires innovative approaches to gathering, managing and sharing of information

- Global Partnerships
  - More rapid generation of research findings
  - Consensus on standards for research
  - Research capacity strengthening
Collaborative partnerships & Global leadership

- WHO, UNAIDS, World Bank, GFATM and other multilateral and international partners working together
- Partners include governments, civil society, private sector, NGOs, communities, PLWHA, etc.
  - Helps minimize the possibility of exploitation by ensuring that the local community is involved in determining whether research is acceptable and responsive to the community’s health problems
  - Partnerships ensure that proposed research is acceptable and relevant to the host country
  - Collaborations increase likelihood that study results will influence local health-care policy
Community initiatives

- Civil society helped propel HIV/AIDS onto the international agenda
- Involvement of PLWHA at each step of the process
- Help build awareness and strengthen public support for clinical and research agendas
- Helps break down stigma surrounding disease and participation in research
- Use research findings to influence policy-making and influence allocation of scarce health-care resources
Industry Collaboration

October 2008:
- The U.N. Secretary-General Ban Ki-moon met with senior executives at 17 pharmaceutical and diagnostic firms
  - U.N. Secretary-General subsequently said that major pharmaceutical firms promised to invest more on researching treatments for the AIDS virus and diagnostic procedures for poorer regions. The companies also agreed to invest more in prevention, including vaccines and pre- and post-exposure prophylaxis...
  - In addition, companies agreed to "invest further in research and development of new HIV-related medicines adapted to resource-limited settings..."
Human Rights

- “All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood.” (Article 1 of the United Nations Universal Declaration of Human Rights)
- Recognizing patients’ rights in face of gender, stigma
Human Rights and the Millennium Development Goals

By 2015:

1. Eradicate extreme poverty and hunger
2. Achieve universal primary education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development

- Human rights remain at the heart of efforts to achieve human development.
### Human Rights & MDGs

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<th>Millennium Development Goals</th>
<th>Key Related Human Rights Standards</th>
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| **Goal 1**  
_Eradicate extreme poverty and hunger_ | Universal Declaration of Human Rights, article 25(1); ICESCR article 11 |
| **Goal 2**  
_Achieve universal primary education_ | Universal Declaration of Human Rights article 25(1); ICESCR articles 13 and 14; CRC article 28(1)(a); CEDAW article 10; CERD article 5(e)(v) |
| **Goal 3**  
_Promote gender equality and empower women_ | Universal Declaration of Human Rights article 2; CEDAW; ICESCR article 3; CRC article 2 |
| **Goal 4**  
_Reduce child mortality_ | Universal Declaration of Human Rights article 25; CRC articles 6, 24(2)(a); ICESCR article 12(2)(a) |
| **Goal 5**  
_Improve maternal health_ | Universal Declaration of Human Rights article 25; CEDAW articles 10(h), 11(f), 12, 14(b); ICESCR article 12; CRC article 24(2)(d); CERD article 5(e)(iv) |
| **Goal 6**  
_Combat HIV/AIDS, malaria and other diseases_ | Universal Declaration of Human Rights article 25; ICESCR article 12, CRC article 24; CEDAW article 12; CERD article 5(e)(iv) |
| **Goal 7**  
_Ensure environmental sustainability_ | Universal Declaration of Human Rights article 25(1); ICESCR articles 11(1) and 12; CEDAW article 14(2)(h); CRC article 24; CERD article 5(e)(iii) |
| **Goal 8**  
_Develop a global partnership for development_ | Charter articles 1(3), 55 and 56; Universal Declaration of Human Rights articles 22 and 28; ICESCR articles 2(1), 11(1), 15(4), 22 and 23; CRC articles 4, 24(4) and 28(3) |
Human Rights “Lens”

- Using a human rights lens to address clinical and research agendas
- Human rights focus on the relationship between the duties of the state and the rights of the individual
  - Identify groups whose rights have been neglected or ignored
- By using a human rights “lens” can help researchers design appropriate and informed policy responses
  - Including exclusion of groups based on their inability to access health processes (e.g., extreme poverty, rural, marginalized areas)
Future Directions

- Women
  - Variability of pharmacokinetics as a result of ethnic or racial phenotype
  - Optimizing Infant feeding

- Children
  - Improving options for pediatric ARV formulations
    - 81% of drugs listed in the 1991 PDR contained language disclaiming use in children or restricting to certain age groups
  - Optimal timing of ART initiation for children
    - CHER trial showed benefit in very young infants
      - Are current guidelines appropriate for older children?
  - OI treatment and management
  - HBV coinfection outcomes and options for treatment