International Research: Introduction and Standards of Care

Joseph Millum, Ph.D.

Clinical Center Department of Bioethics/Fogarty International Center

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The views expressed are my own and do not represent the views of the NIH, DHHS, or any other US government agency

Short-course AZT trials

- Without treatment 15 - 30% of newborn children of HIV-positive mothers are HIV-positive
- 076 regimen reduces this by two-thirds
- Could not be implemented in many low- or middle-income countries
  - High cost
  - Lack of healthcare infrastructure

Short-course AZT trials

- Researchers wanted to develop a “short course” AZT regimen that could be implemented
- Expected to be worse than 076 regimen
- Comparison to 076 regimen was expected not to produce meaningful results

Ethical controversy

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

Peter Lurie, M.D., M.P.H., and Sidney M. Wolfe, M.D.

N Engl J Med 1997; 337:853-856 | September 18, 1997 | DO

f double standards

Defense of short course AZT trials

- Active controlled trial not expected to produce meaningful results
- Urgent need for intervention:
  - 076 regimen could not be implemented
  - HIV prevalence very high in host countries

International research of concern

- Sponsored by high-income country institutions
- Carried out in low- and middle-income countries
  - Resource-limited settings
  - Vulnerable participants
  - Lack of access to good quality healthcare outside of clinical research

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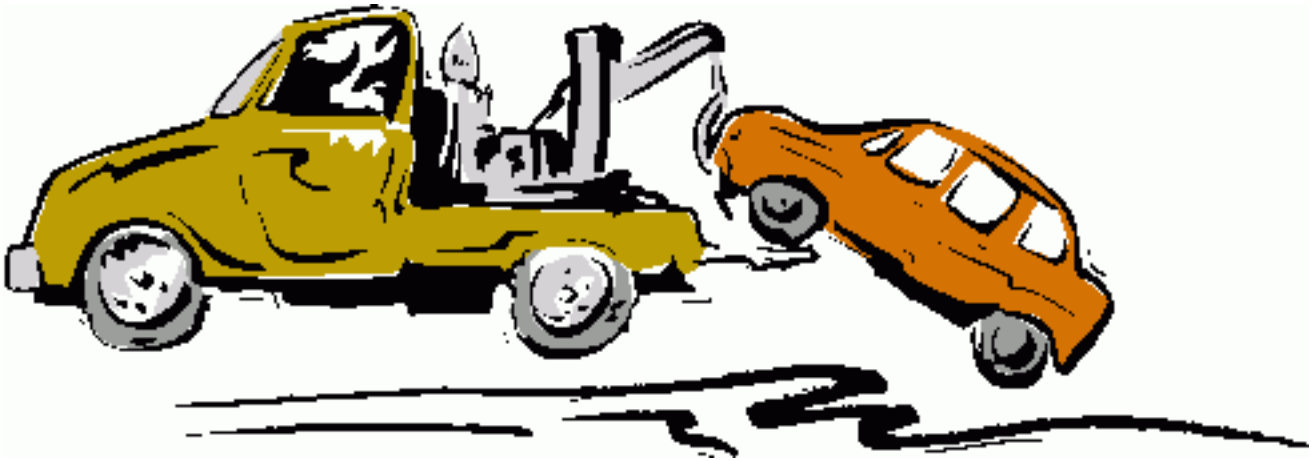
vascular disease, it will be important to test drugs and devices on a global scale. However, among the ongoing phase 3 clinical trials that we examined that were sponsored by U.S.-based companies in developing countries, none were trials of diseases such as tuberculosis that disproportionately affect the populations of these countries. In contrast, we found a variety of trials in developing countries for conditions such as allergic rhinitis and overactive bladder. Developing countries will also not realize the benefits of trials if

A (fictional) study

- Placebo-controlled trial of new anti-hypertensive
- Enrolling treatment-naïve patients diagnosed with hypertension in urban clinics in India
- Free physical examination, education, monitoring
- 50/50 randomization to experimental drug or placebo
- No plans to market drug in India

Exploitation

- A exploits B when A takes unfair advantage of B's situation



How to avoid exploitation

- Ensure that the distribution of benefits and burdens is fair

The standard of care debate

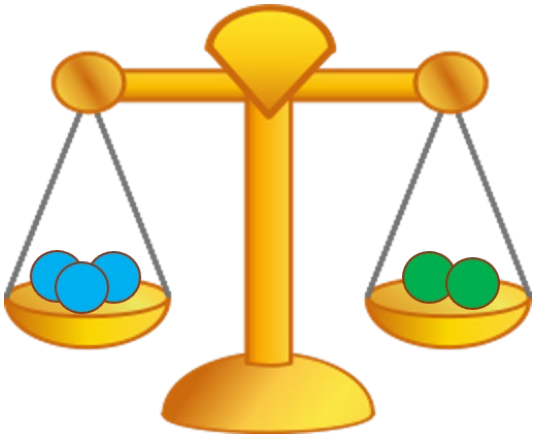
- Concerns what care should be provided in the different arms of a trial
- This determines what interventions the trial compares
- The interesting clinical question is usually whether an experimental intervention is better than the best proven intervention

Standards of care

- Local standard of care
  - De facto
  - De jure
- Global best standard of care

Risk/benefit analysis

1. Minimize risks consistent with the goals of the research
2. Risks should not exceed a threshold
3. Risks to participants should be balanced by the benefits to participants and the social value of the knowledge gained

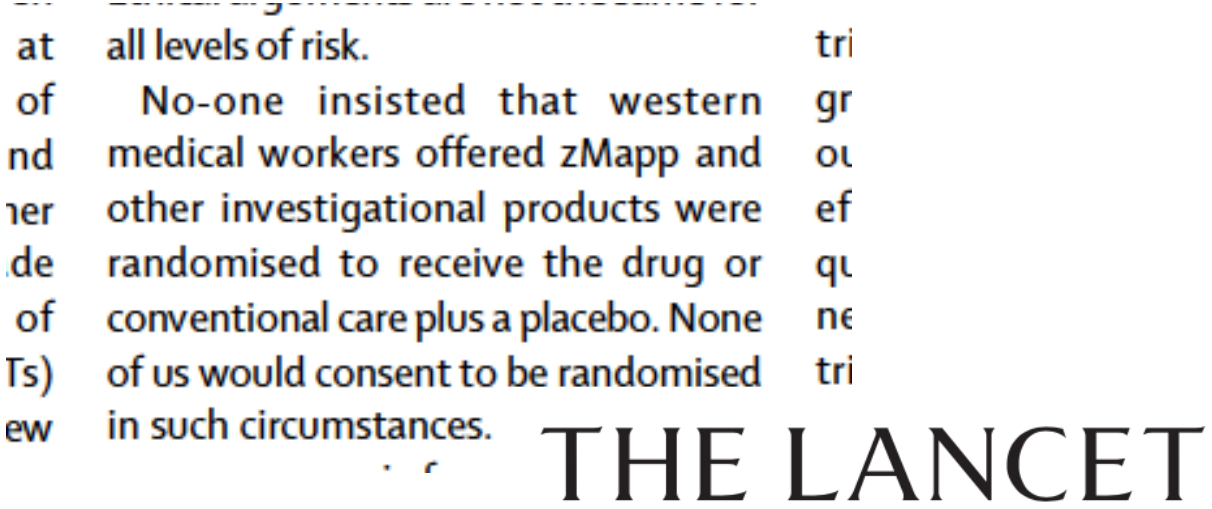


The “no loss” view

- It is permissible to provide less than the global best standard of care if participants are not deprived of treatment that they would otherwise receive

The “no double standards” view

- It is permissible to provide less than the global best standard of care if the same trial would be permissible in a developed country



at all levels of risk.

No-one insisted that western medical workers offered zMapp and other investigational products were randomised to receive the drug or conventional care plus a placebo. None of us would consent to be randomised in such circumstances.

THE LANCET

Adebamowo et al. 2014

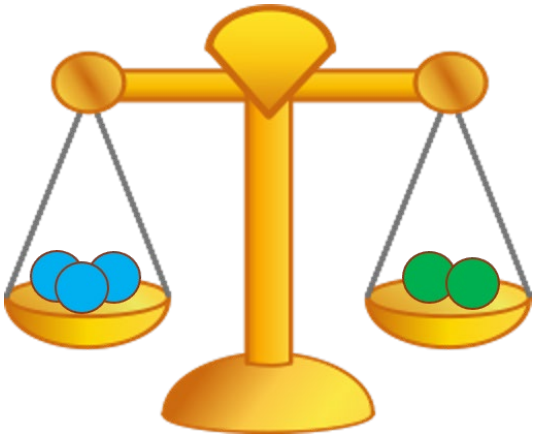
The “responsiveness” view

- It is permissible to provide less than the global best standard of care if:

1. Lower standard of care scientifically necessary
2. Participants not deprived of treatment they would otherwise have received
3. Research is responsive to the needs of the host communities

Risk/benefit analysis

1. Minimize risks consistent with the goals of the research
2. Risks should not exceed a threshold
3. Risks to participants should be balanced by the benefits to participants and the local social value of the knowledge gained



Outstanding questions

- Who ought to benefit from the research?
- What sorts of benefits should people receive?
- What should happen after the trial?
- Who is responsible for providing benefits?

Summary

- International research conducted in resource-limited settings raises complex ethical questions
  - Exploitation of poor participants and host communities
  - Risks of providing less than the best standard of care
- These ethical considerations are intertwined