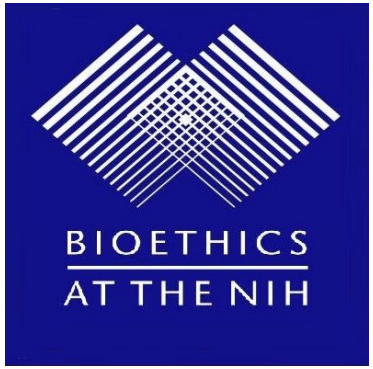

International Research Ethics: Introduction & Standards of Care

Annette Rid
Department of Bioethics, NIH Clinical Center

Disclaimer

- The views expressed in this talk are my own. They do not represent the position or policy or the NIH, DHHS, or US government.

Question for today

- What are researchers' and sponsors' obligations in international collaborative research?
  - Sponsored by high-income country (HIC) institutions
  - Carried out in low- and middle-income countries (LMICs) with limited resources

Mother-Offspring Malaria Study

- NIH-sponsored study in Tanzania
- Learn about malaria infection in early life
- Frequent clinical visits and blood draws from pregnancy or birth to 5 yrs

Photo credit: Victoria Cornelius (www.malariagen.net)

Mother-Offspring Malaria Study

- Participants treated for malaria
- Also receive prophylaxis for HIV-related infections and referral to hospice care in case of serious HIV-related illness

Photo credit: Victoria Cornelius (www.malariagen.net)

1) What are key ethical challenges raised by international collaborative research, such as the Mother-Offspring Malaria Study?

Key challenges

1) Cultural differences
2) Power differentials
3) Background injustices

Key ethical questions

1) Cultural differences: informed consent, community engagement
2) Power differentials: collaborative partnership, independent review, informed consent
3) Background injustices: responsiveness of research, standards of care, ancillary care obligations, post-study obligations

Short-course AZT trials

- Pregnant people who live with HIV transmit the disease to 15-45% of their newborns
- 076 AZT regimen lowers transmission to <5%
- But 076 could not be implemented in many LMICs because of high costs and insufficient healthcare infrastructure

Short-course AZT trials

- Researchers wanted to develop a “short course” AZT regimen that could be implemented in LMICs
- Expected to be inferior to 076
- Comparison with 076 was not expected to produce meaningful results, so tested against placebo

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.

Article

28 References **294** Citing Articles Letters

September 18, 1997
N Engl J Med 1997; 337:853-856
DOI: 10.1056/NEJM199709183371212

IT HAS BEEN ALMOST THREE YEARS SINCE THE JOURNAL [1] PUBLISHED THE results of AIDS Clinical Trials Group (ACTG) Study 076, the first randomized, controlled trial in which an intervention was proved to reduce the incidence of human immunodeficiency virus (HIV) infection. The antiretroviral drug zidovudine, administered orally to HIV-positive pregnant women in the United States and France, administered intravenously during labor, and subsequently administered to the newborn infants, reduced the incidence of HIV infection by two thirds.[2] The regimen can save the

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Ethical controversy

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

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EDITORIAL

The Ethics of Clinical Research in the Third World

Marcia Angell, M.D.

Article

17 References 278 Citing Articles Letters

AN ESSENTIAL ETHICAL CONDITION FOR A RANDOMIZED CLINICAL trial comparing two treatments for a disease is that there be no good reason for thinking one is better than the other.[1,2] Usually, investigators hope and even expect that the new treatment will be better, but there should not be solid evidence one way or the other. If there is, not only would the trial be scientifically redundant, but the investigators would be guilty of knowingly giving inferior treatment to some participants in the trial. The necessity for investigators to be in this state of equipoise[2]

September 18, 1997
N Engl J Med 1997; 337:847-849
DOI: 10.1056/NEJM199709183371209

Related Articles

CORRESPONDENCE MAR 19, 1998

Questions about a Placebo-Controlled Trial of Preventive Therapy for Tuberculosis in HIV-Infected Ugandans

Ethical controversy

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EDITORIAL

The Ethics of Clinical Research in the Third World

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Ethical Complexities of Conducting Research in Developing Countries

Harold Varmus, M.D., and David Satcher, M.D., Ph.D.

Article

6 References 155 Citing Articles Letters

ONE OF THE GREAT CHALLENGES IN MEDICAL RESEARCH IS TO conduct clinical trials in developing countries that will lead to therapies that benefit the citizens of these countries. Features of many developing countries — poverty, endemic diseases, and a low level of investment in health care systems — affect both the ease of performing trials and the selection of trials that can benefit the populations of the countries. Trials that make use of impoverished populations to test drugs for use solely in developed countries violate our most basic understanding of

October 2, 1997
N Engl J Med 1997; 337:1003-1005
DOI: 10.1056/NEJM199710023371411

Related Articles

CORRESPONDENCE MAR 19, 1998

Ethics of Placebo-Controlled Trials of Zidovudine to Prevent the Perinatal Transmission of HIV in the Third World

Key ethical concerns

(Lurie & Wolfe 1997, Angell 1997)

- Researchers should provide the control group with the global best standard of care (unless the costs are excessive)

Key ethical concerns

(Lurie & Wolfe 1997, Angell 1997)

- Researchers should provide the control group with the global best standard of care (unless the costs are excessive)
  - Beneficence, non-instrumentalization

Key ethical concerns

(Lurie & Wolfe 1997, Angell 1997)

- Researchers should provide the control group with the global best standard of care (unless the costs are excessive)
  - Beneficence, non-instrumentalization
  - Universal ethical standard

> In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

(Declaration of Helsinki 1996)

Declaration of Helsinki

(Declaration of Helsinki 2013)

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

1) Is it permissible to provide less than the global best standard of care?
2) If so, under what conditions?

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
- Implies that researchers may provide the *de facto* local standard of care (London 2000)

Critique of “no loss” view

- The *de facto* local standard of care may not be acceptable

> Annas and Grodin recently commented on the characterization and justification of placebos as a standard of care: “‘Nothing’ is a description of what happens; ‘standard of care’ is a normative standard of effective medical treatment, whether or not it is provided to a particular community.”[25]

(Lurie & Wolfe 1997)

The “appropriate local care” view

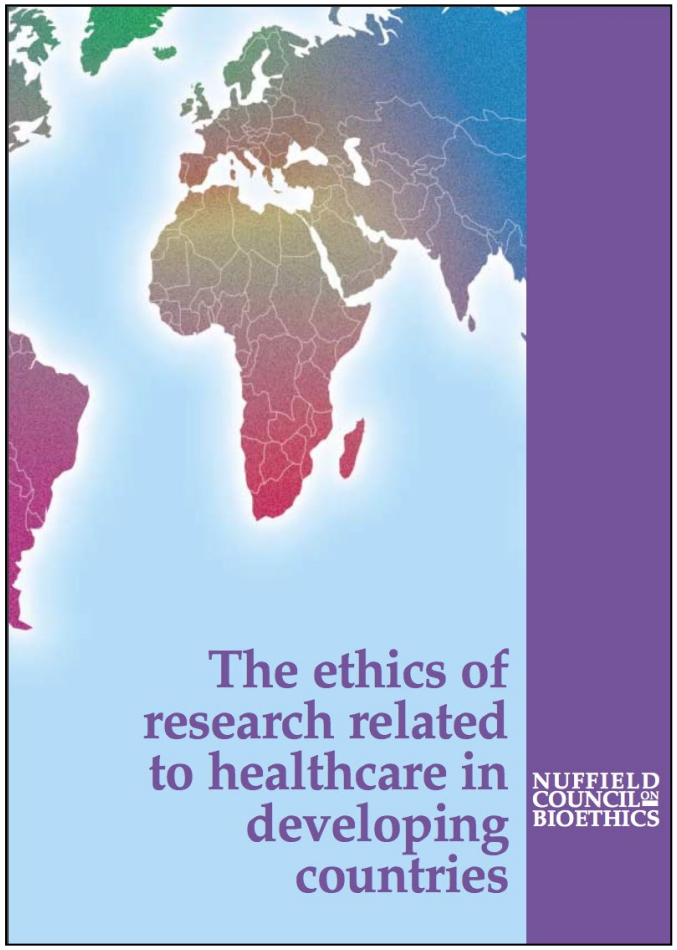
- It is permissible to provide less than the global best standard of care if participants are not deprived of treatment that they *should* otherwise receive
- Implies that researchers should provide the *de jure* local standard of care (London 2000)

Critique of “appropriate local care”

- The *de jure* standard of care is difficult to define

Defining appropriate local care

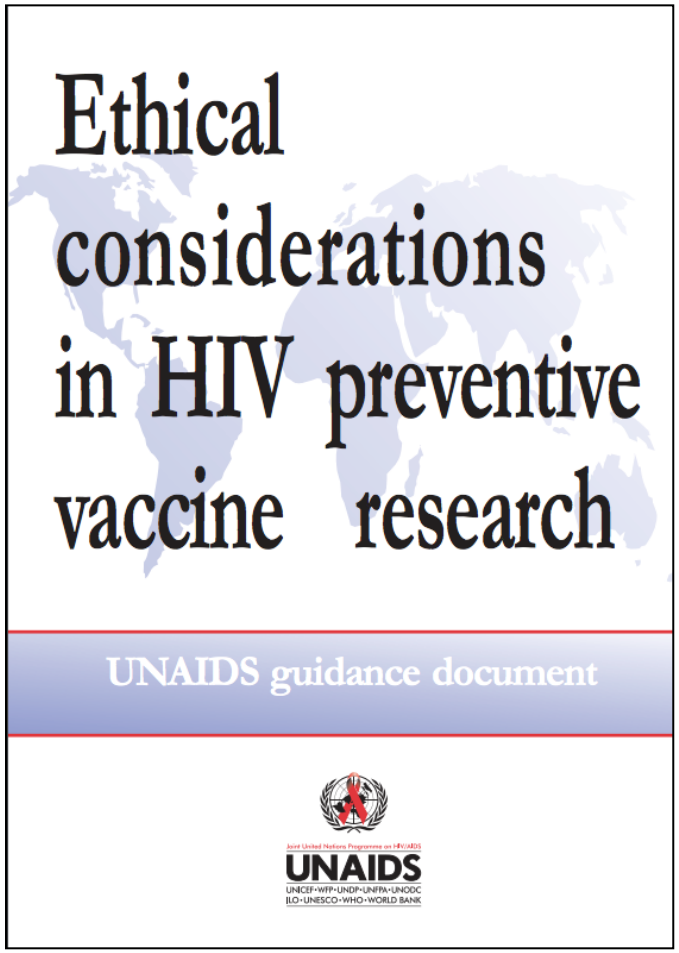
(Nuffield Council 1999)



"standard [of care] that the country endeavours to provide nationally"

Defining appropriate local care

(UNAIDS 2000)



"highest level of care attainable in the host country"

Defining appropriate local care

- A fair priority-setting process on the path to universal health coverage should define appropriate local care
- Where such a process does not exist, it should serve as an ideal to determine what appropriate local care might be

Applied to AZT trials

- Few LMICs (and few HICs…) in 1990s had a fair priority-setting process
- But the 076 AZT regimen cost more than 10x the healthcare budget per person and year in many LMICs
- Unlikely that LMICs would have included 076 in their basic healthcare packages, hence unlikely the *de jure* standard of care

Critique of “appropriate local care”

- The *de jure* standard of care is difficult to define
- The *de jure* standard of care view is not sufficient to justify providing less than the global best standard of care: there must also be a positive justification for testing against a lower standard of care

The “responsiveness” view

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

1) the research is responsive to local health needs; and
2) it is scientifically necessary to test against a lower standard of care; and
3) the local standard of care is not undercut

The “responsiveness” view

ment. The most compelling reason to use a placebo-controlled study is that it provides definitive answers to questions about the safety and value of an intervention in the setting in which the study is performed, and these answers are the point of the research. Without clear and firm answers to whether and, if so, how well an intervention works, it is impossible for a country to make a sound judgment about the appropriateness and financial feasibility of providing the intervention.

(Varmus & Satcher 1997)

Applied to AZT trials

- Trials were responsive to local health needs
  - Aimed to develop short-course 076 regimen that would be feasible to implement in LMICs
  - Answered key question for local policy-makers: Is a short course better than nothing? By how much? Is it worth investing scarce resources?
- Placebo control was scientifically necessary given variable perinatal HIV transmission

Critique of “responsiveness” view

- It is not scientifically necessary to test against a lower standard of care
- Researchers should test study interventions against the global best standard of care and use historical data to establish superiority to the local standard of care

Applied to AZT trials

- Researchers should minimize risks to participants by using historical controls where this is scientifically sound
- However, given variable perinatal HIV transmission, historical controls would have raised scientific concerns in the AZT trials

Critique of “responsiveness” view

- Research is not responsive to local health needs when it develops interventions that are expected to be inferior to the global best standard of care
- Researchers should test study interventions against the global best standard of care in order to establish non-inferiority to, or equivalence with, the global best standard

Critique of “responsiveness” view

ASKING THE WRONG RESEARCH QUESTION

has been identified. The researchers conducting the placebo-controlled trials assert that such trials represent the only appropriate research design, implying that they answer the question, “Is the shorter regimen better than nothing?” We take the more optimistic view that, given the findings of ACTG 076 and other clinical information, researchers are quite capable of designing a shorter antiretroviral regimen that is approximately as effective as the ACTG 076 regimen. The proposal for the Harvard study in Thailand

(Lurie & Wolfe 1997)

Applied to AZT trials

- Researchers should strive to develop interventions for LMICs that are equivalent to or better than those available in HICs
- But if this is not feasible, developing “second-best” interventions can be key to improving health and/or saving lives in LMICs

Critique of “responsiveness” view

- Developing simpler, cheaper and inferior interventions is not the right approach to improving health in LMICs
- Instead, we should work on lowering drug prices, invest in health infrastructure in LMICs, develop more equitable ways of incentivizing innovation etc.

Critique of “responsiveness” view

economic necessity. Similarly, wanting to develop a treatment regime that is easier to administer in a developing world context is *not* a scientific reason, it is an economic reason. I remain sceptical that the approach to such problems should lie in more research. Rather, it suggests that we should address the economic inequities that underlie much of the rhetoric, because it is these economic inequities that are making more likely the lower standards of care trials in developing countries. If we really want to “improve medical care for the world’s poor”, as Lie *et al* will have it, perhaps we should spend more time thinking about ensuring access to *existing* drugs as opposed to using this as a rationale for developing additional drugs. I have discussed this at length

(Schüklenk 2004)

Applied to AZT trials

- We should work to improve health in LMICs beyond conducting research
- But developing new interventions for LMICs (including ones that are “second-best”) can be key to improving health and/or saving lives in LMICs in the short term
- Research and non-research activities to improve health in LMICs can go in tandem

Conclusions

- The standard of care debate reveals fundamental disagreements about researchers' obligations of beneficence towards participants and the social and scientific value of research
- Note these disagreements can be relevant beyond the ethics of international collaborative research

Conclusions

- The *de facto* standard of care in international collaborative research is not defensible
- The *de jure* standard of care is preferable
- However, the *de jure* standard of care is difficult to define and not sufficient to justify providing less than the global best standard of care

Conclusions

- The *de jure* standard of care should form part of the responsiveness view on international collaborative research, with two qualifications:
  - Should engage communities given need to evaluate local research priorities
  - Can be appropriate to withhold *de jure* standard of care depending on risks to participants involved

Modified responsiveness view

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

1) the research is responsive to local health needs; and
2) it is scientifically necessary to test against a lower standard of care; and
3) participants receive (as a default) the *de jure* local standard of care

Over to Dr. Millum!

- The responsiveness view may not be the only way to justify providing less than the global best standard of care
- This might also be justifiable when the research is *not* responsive to local health needs, but host communities receive a fair level of other benefits (e.g., investments in healthcare infrastructure)