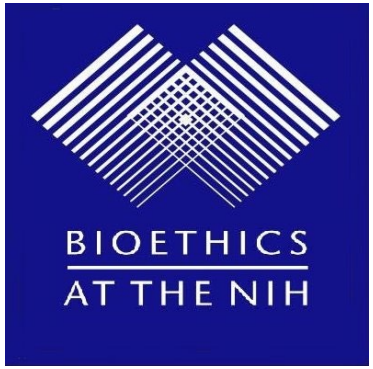


# International Research Ethics: Introduction & Standards of Care

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# 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.
- I use the terms low- and middle-income countries (LMICs) and high-income countries (HICs) to match current NIH terminology and program announcements

What are researchers' and sponsors' ethical obligations in international collaborative research*?

*Sponsored by institutions in HICs and carried out in LMICs with limited resources

# Context

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

# Key ethical challenges

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

What sparked the controversy about standards of care in international collaborative research?

# 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
- Tested against placebo

# Ethical controversy

SOUNDING BOARD

## 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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CORRESPONDENCE MAR 19, 1998
Ethics of Placebo-Controlled Trials of Zidovudine to Prevent the Perinatal Transmission of HIV in the Third World

# Ethical controversy

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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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## 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.

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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 claim

(Lurie & Wolfe 1997, Angell 1997)

- The short-course AZT trials were unethical because they did not provide the control group with the global best standard of care (076 AZT regimen)

# Key ethical argument

(Lurie & Wolfe 1997, Angell 1997)

- Researchers should provide the control group the global best standard of care because researchers should:
  - Avoid preventable harm

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(Lurie & Wolfe 1997, Angell 1997)

- Researchers should provide the control group the global best standard of care because researchers should:
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  - Not treat participants “merely as a means”

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(Lurie & Wolfe 1997, Angell 1997)

- Researchers should provide the control group the global best standard of care because researchers should:
  - Avoid preventable harm
  - Not treat participants “merely as a means”
  - Treat participants equally

# Key ethical argument

(Lurie & Wolfe 1997, Angell 1997)

- Researchers should provide the control group the global best standard of care because researchers should:
  - Avoid preventable harm
  - Not treat participants “merely as a means”
  - Treat participants equally
  - Adhere to universal ethical standards

# Declaration of Helsinki

(Declaration of Helsinki 1996)

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

(Declaration of Helsinki 2024)

## Use of Placebo

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:

- If no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- If for compelling and scientifically sound methodological reasons the use of any intervention other than the best proven one(s), the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention; and the participants who receive any intervention other than the best proven one(s), 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?

# 1) 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

# 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)

# 2) The “appropriate local care” view

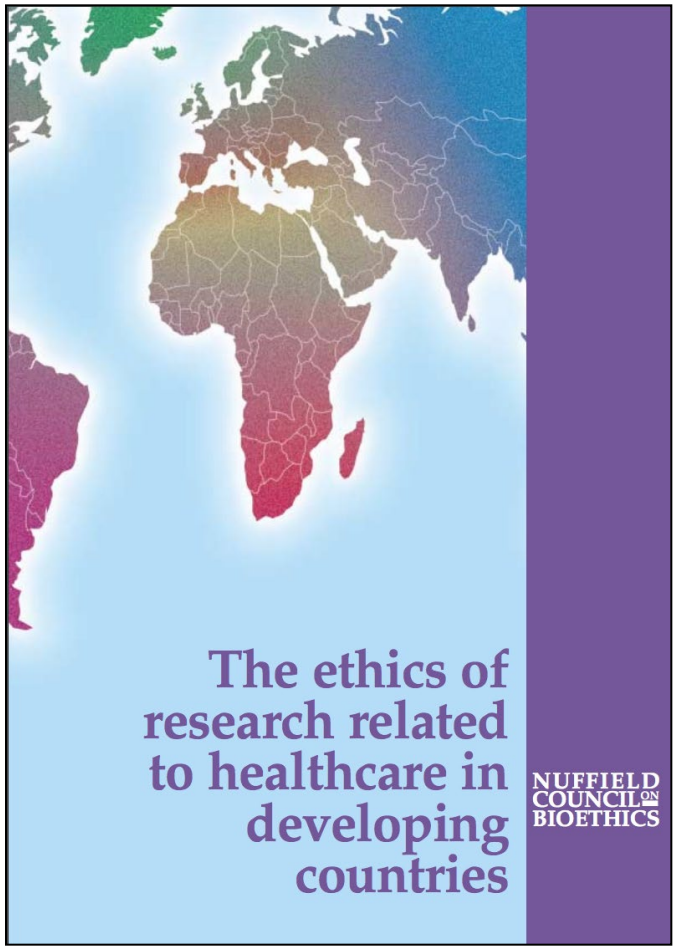
- It is permissible to provide less than the global best standard of care if participants are not deprived of treatment that they *should* otherwise receive
- Implies that researchers should provide the *de jure* local standard of care (London 2000)

# 2) The “appropriate local care” view

- What is the *de jure* standard of care?

# Defining appropriate local care

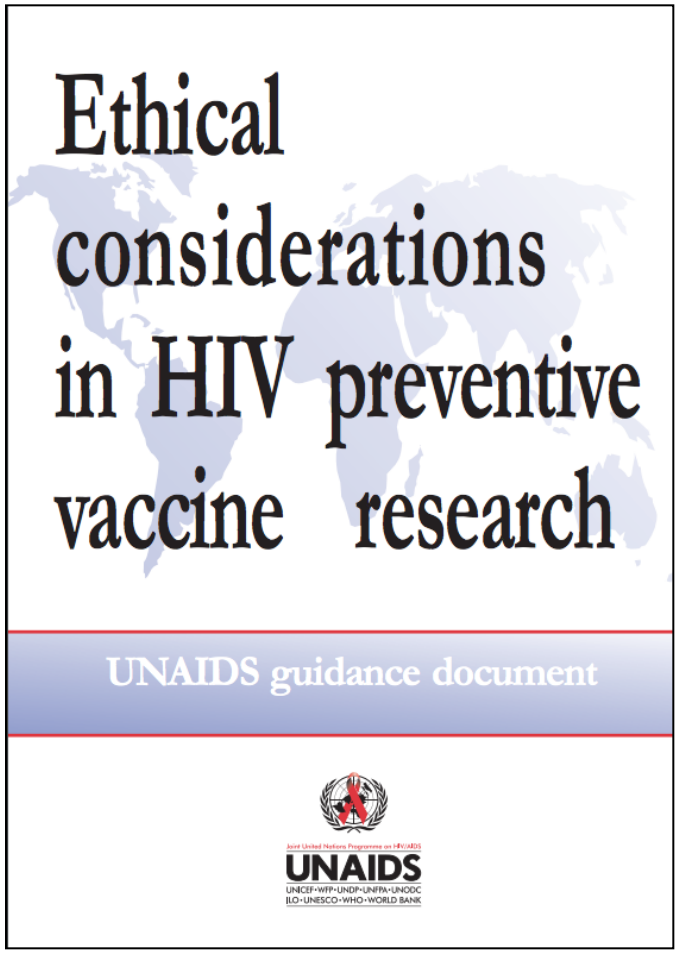
(Nuffield Council 1999)




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

# Defining appropriate local care

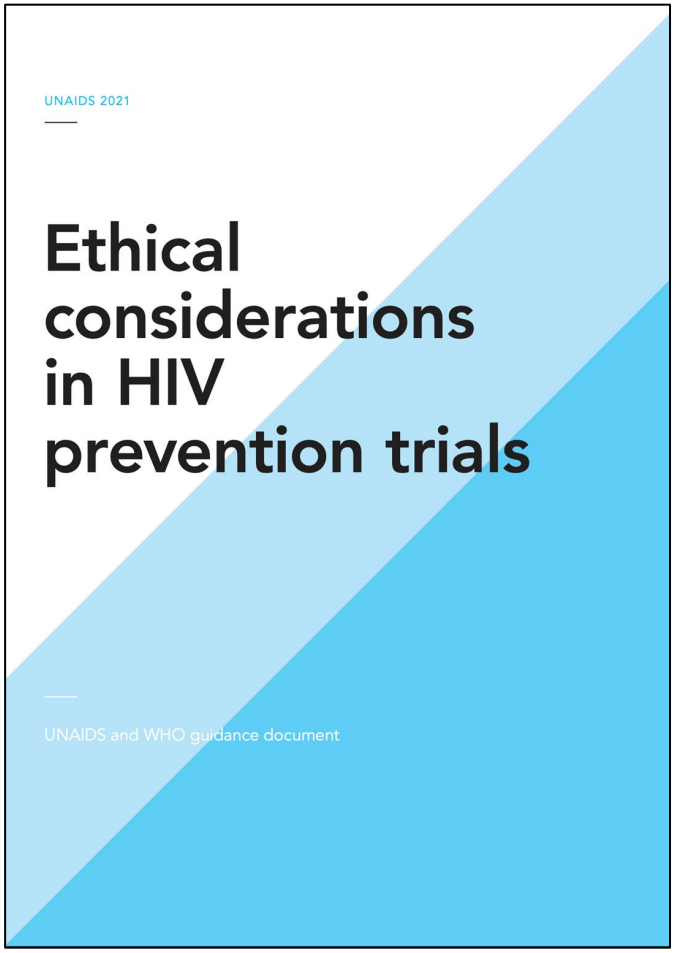
(UNAIDS 2000)




"highest level of care attainable in the host country"

# Defining appropriate local care

(UNAIDS 2021)




"package of prevention methods recommended by the WHO"

# 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 can still serve as a hypothetical ideal that is useful in determining 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 most LMICs
- Hence unlikely that it would count as appropriate local care

# Critique of “appropriate local care”

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

➢ Note the standard of care has implications for research questions and feasibility

# 3) 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

# 3) 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?


# 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 and made size of trials manageable

# 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
  - Instead, researchers should develop interventions that are expected to be non-inferior to, or equivalent with, the global best standard of care

# 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)

# 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
  - 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

- Researchers should strive to develop interventions for LMICs that are equivalent to or better than those available in HICs
  - But this may not always be feasible (e.g., large sample size of active-controlled trials)
- Research should be conducted on how to ameliorate the underlying inequalities which drive differences in care
  - But the results of this research may be uncertain and far-off


# Applied to AZT trials

- We should work to improve health in LMICs in a number of ways
- But developing new interventions for LMICs (including ones that are “second-best”) can be key in the short term
- Different efforts can go in tandem

# Conclusions

- The standard of care debate reveals different positions on what is owed to participants in international collaborative research in LMICs, as well as what should be researched and how

# Conclusions

- Three potential standards: “no loss” / de facto, appropriate / de jure, global best
- One requirement: responsiveness
- A limited conclusion: the appropriate care view, together with a responsiveness requirement, is superior to the global best view

# Appropriate and Responsive:

- 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 appropriate local standard of care; and
4) … and local communities are engaged.

# Appropriate and Responsive:

Recall the reasons for embracing the global best:

- Avoid preventable harm
- Not treat participants “merely as a means”
- Treat participants equally
- Adhere to universal ethical standards

Claim: these concerns are reasonably addressed

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