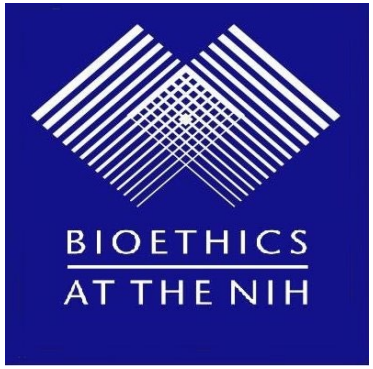


International Research Ethics: Introduction & Standards of Care

Annette Rid
Department of Bioethics, NIH Clinical Center

The views expressed are my own and do not represent the views of the NIH, PHS or DHHS

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)

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
3) Background injustices: responsiveness of research, standards of care, ancillary care obligations, post-study obligations

Short-course AZT trials

- 15-45% of newborn children of HIV-positive mothers are HIV-positive
- 076 AZT regimen reduces this to <5%
- But 076 could not be implemented in many LMICs because of high costs and lack of 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

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 Refere

I T
res
co
human i
adminis
adminis
infants.

EDITORIAL

The Ethics of Clinical Research in the Third World

Marcia Angell, M.D.

Articl

17 Refe

A
even e
one wa
the inv
partici

SOUNDING BOARD

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)
  - 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

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

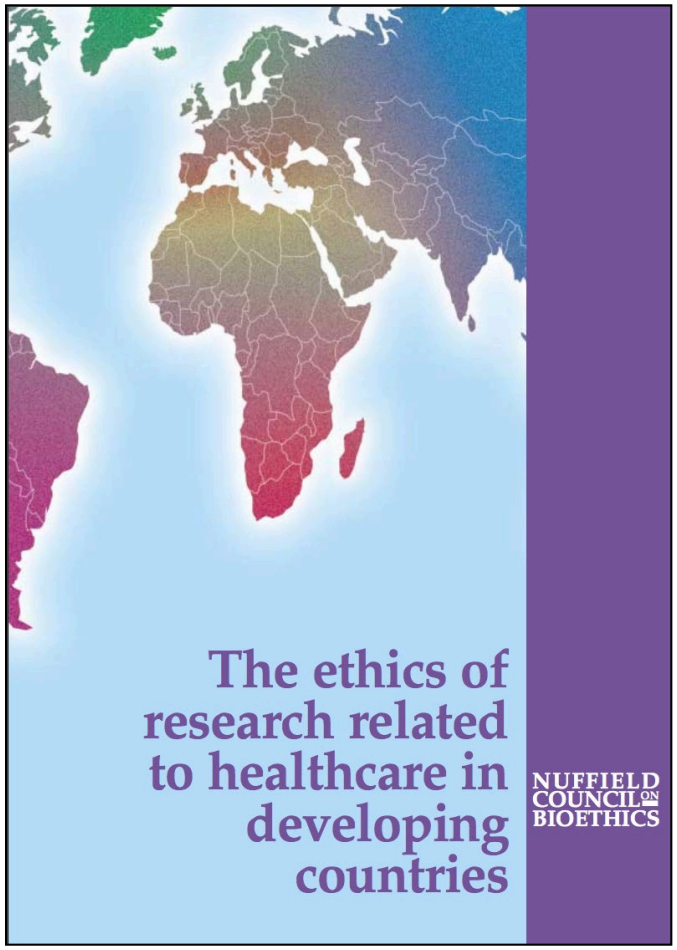
- It is permissible to provide less than the global best standard of care if participants are not deprived of treatment that they *should* otherwise receive
- Implies that researchers should provide the *de jure* local standard of care

Critique of “appropriate local care”

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

Defining appropriate local care

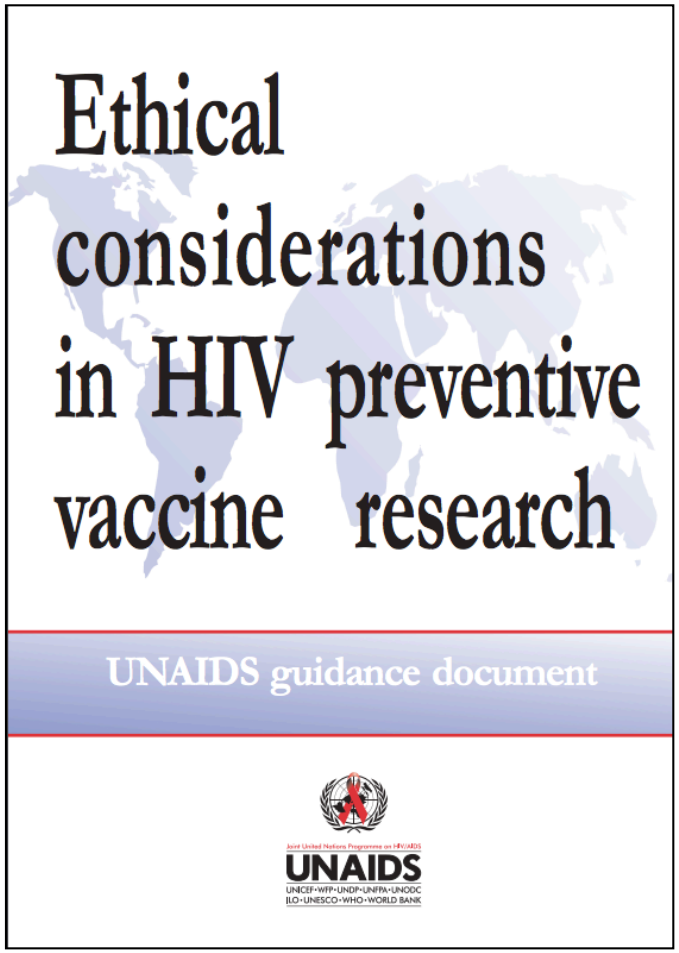
(Nuffield Council 1999)



"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 is

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)

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

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

mistic 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 states the research question clearly: "Can we reduce the duration of prophylactic [zidovudine] treatment without increasing the risk of perinatal transmission of HIV, that is, without compromising the demonstrated efficacy of the standard ACTG 076 [zidovudine] regimen?"[13] We believe that such equivalency studies of alternative antiretroviral regimens will provide even more useful results than placebo-controlled trials, without the deaths of hundreds of newborns that are inevitable if placebo groups are used.

(Lurie & Wolfe 1997)

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)

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 that these disagreements are relevant for the ethics of conducting research everywhere, not just in LMICs

My own 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

My own view

- Community engagement about when these conditions are met is critical, as judgments about responsiveness and the *de jure* local standard of care are highly contextual and subject to reasonable disagreement