



Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Science at the heart of medicine

Trial Design and International Standards

In defense of a single ethical standard

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Interpretation of 'ethical standards'

- One candidate for a single standard might be phrased as follows
 - > *If it is unethical to carry out research with a particular design in a developed country, it is unethical to do that same research in a developing country*
- Flawed because particular circumstances can be sufficiently different
 - > Research on a preventive or therapeutic method to be used in remote rural areas with poor infrastructure could require an experimental intervention or comparator that would not be used in an industrialized country

Interpretation of 'ethical standards'

- Another candidate for a single standard in research design might be phrased as follows
 - > *All participants in research should receive the level of care they would receive in a developed country*
- Flawed because adherence to this requirement would make it impossible to do research designed to develop treatments for some diseases in remote, rural areas of developing countries
 - > Yet such research is critically important to test interventions that can benefit people in places with poor health infrastructure



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Placebos: the ‘double standard’ position

- Placebo controls are acceptable in developing countries where many people lack access to proven interventions
 - > Subjects are not made “worse off” than they would be if not enrolled in the research
 - > A costly, proven intervention would never be available to the population
- Research subjects are treated “equitably”
 - > They receive the level of care that patients in the same community receive for the same disease
 - “Local justice”

Placebos: the 'single standard' position

- The same standards used in the sponsoring industrialized country should be applied in the resource-poor country
 - If patients in a developing country who are not enrolled in a clinical trial would receive no treatment, that cannot justify withholding an effective treatment from subjects in research
 - Placebos may not be used in a control group in the poor country when an effective treatment for that condition exists in the industrialized country
 - “Global justice”

Declaration of Helsinki 2008

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
 - > The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - > Where for *compelling and scientifically sound methodological reasons* the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.

CIOMS statement of “single standard”

- In externally sponsored research “...the ethical standards applied should be no less stringent than they would be for research carried out in [the sponsoring] country”
 - Guideline 3, Ethical Review of Externally Sponsored Research
 - > Not enough clarity on what constitutes “standards”
 - But requires that ethical standards in developing countries be equal or equivalent to those in industrialized countries

UNAIDS/WHO: Ethical Guidance for HIV Prevention Trials

- Guidance Point 15: Control Groups
 - “The use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been shown to be effective in comparable populations”
 - Examples
 - An effective HIV vaccine exists but it is not known to be effective against the virus that is prevalent in the research population
 - A microbicide shown to be effective for vaginal intercourse may not be effective for rectal intercourse

UNAIDS/WHO examples of justifiable use of placebos in HIV prevention trials

- (continued)
 - > The biological conditions that prevailed during the initial trial demonstrating efficacy of a biomedical HIV prevention product are so different from the conditions in the proposed research population that the results of the initial trial are not generalizable and cannot be directly applied to the research population under consideration
 - > Effectiveness of an intervention in one population may not be reproduced in the context of another population if the success of the intervention is strongly related to behaviour....

ICH GCP E10 2.1.3 *Ethical Issues*

- In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control.... In other situations, when there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is noncoercive and patients are fully informed about available therapies and the consequences of delaying treatment.

European Group on Ethics in Science and New Technologies (2003)

- “Ethical Aspects of Clinical Research in Developing Countries”
 - > ...[R]esearch activities involving human subjects cannot exclusively be assimilated to an economic activity subject to market rules. On the contrary, in the context of solidarity, regarding health as a public good, rather than a commodity, it needs to be regulated according to fundamental principles. The general approach chosen within this Opinion is that fundamental ethical rules applied to clinical trials in industrialized countries are to be applicable everywhere.

Conclusions

- Basic value underlying the defense of a single ethical standard for research design is global justice
 - > Disparity in the economic circumstances of industrialized and poor countries is not a morally relevant factor for determining ethical standards for research design when the external sponsor is a wealthy country or a pharmaceutical company
- To endorse double standards is to conclude that financial inequalities should be a significant determinant of global justice in the design of research



“Our standards are very high. We even have high double standards.”