International research: Trial design issues and outsourcing

Reidar K. Lie, MD, PhD
Department of Bioethics, NIH

Disclaimer

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Current Helsinki

- 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

Helsinki, continued

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

RCT design requirement

- Control group in a clinical trial should always receive state of the art intervention, except when removal of intervention causes only temporary or no serious harm

The perinatal HIV transmission studies

- It had been shown that a long course of AZT treatment reduced transmission from around 30% to less than 10%
- This intervention was expensive and logistically difficult in resource poor settings
- Urgent need to develop a more suitable intervention
- A number of short course trials initiated. All but one tested against placebo
- It was argued that the design was scientifically necessary

CIOMS

- Placebos permitted
  - If scientifically necessary for trivial conditions
    - Hair loss
    - Nasal congestion
  - If scientifically necessary and if causing temporary harm or non serious harm
    - Migraine headaches
    - Minor elevations of blood pressure

CIOMS

- An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable.

CIOMS, II

- Also, the scientific and ethical review committees must be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population. In these circumstances an ethical review committee can approve a clinical trial in which the comparator is other than an established effective intervention, such as placebo or no treatment or a local remedy

Examples

- Test a simplified diagnostic method to monitor effect of HIV treatment to take the place of viral load measurements
- Test interventions that will prevent HIV infection during breastfeeding, without bottle feeding
- Examples such as these show that exceptions are necessary

3 conditions for exception

- 1. The results of the trial will be relevant to the study population/country in which the study is carried out *or*
- There is a reasonable likelihood that the new intervention will be implemented
- 2. No alternative designs are possible
- 3. Participants are not denied treatment they would ordinarily receive

Declaration of Helsinki

- Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

Responsiveness requirement

- Research in resource poor settings should only be conducted if the results of the research
  - Product developed
  - Knowledge gained
- Is useful for that setting

Fair benefits framework

- A number of examples show that one may want to think of benefits more broadly
  - Benefits of getting access to research interventions
  - Benefits of medical care provided by trial personell
  - Benefits of infrastructure and capacity to do high quality research
- Not only benefits of products developed or knowledge gained from trial itself

HIV treatment trial in SA

- Pharmaceutical company wants to do a treatment trial of a new promising drug combination
- Ethics committee requires that those who benefit receive the drug combination as long as they benefit afterwards
- Company says no: it is too costly, partly because they have to buy rival company drugs
- Activist community wants the trial

Malarone trial in Indonesia

- Trial to establish the effect of malarone on prevention of malaria
- Proposed for a malaria endemic region of Indonesia.
- Placebo controlled trial. Observe number of malaria cases in the two groups
- Number of safety measures in place
- Community wants it because of health benefits

Blood pressure trial in India

- Pharmaceutical company wants to do a trial of a new blood pressure drug in India. A new version of an existing drug whose safety profile is well established
- They want to do it India because it is $200 m cheaper to do it there
- Drug will be sold almost exclusively in Western Europe and North America

HAVRIX trial in Thailand

- Trial to test out a new vaccine against hepatitis A in 20.000 school children in Thailand
- Hepatitis A common among children, but rarely a serious disease
- Not a public health priority in Thailand
- Trial can easily be done in high prevalence settings in the US
- Main beneficiaries are travelers and military
- Thai authorities would prefer to do a dengue vaccine trial, but no good candidates available, and country needs vaccine trial infrastructure

Surfaxin trial

- A company wants to test out a new surfaxin, wanting to test it against placebo (smaller trial, quicker results)
- Not approved in the US, because effective surfactants already on market
- Company wants to go to a South American country arguing that
  - It is not available outside of trial
  - Trial participants benefit because half of them receive active surfactant

Four questions to ask

- Is the trial part of a strategy to improve research capacity in the country?
- Is the product developed or knowledge gained of use to the country?
- Do participants receive state of the art interventions?
- Are participants better off than non-participants
  - In terms of interventions provided as part of the study design?
  - In terms of additional care provided during the trial

Havrix trial

- Is the trial part of a strategy to improve research capacity in the country? YES
- Is the product developed or knowledge gained of use to the country? NO
- Do participants receive state of the art interventions? YES
- Are participants better off than non-participants
  - In terms of interventions provided as part of the study design? YES
  - In terms of additional care provided during the trial YES

Surfaxin trial

- Is the trial part of a strategy to improve research capacity in the country? NO
- Is the product developed or knowledge gained of use to the country? NO
- Do participants receive state of the art interventions? NO
- Are participants better off than non-participants
  - In terms of interventions provided as part of the study design? YES
  - In terms of additional care provided during the trial YES

Malarone trial

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  - In terms of interventions provided as part of the study design? YES
  - In terms of additional care provided during the trial YES