Ethical issues in international collaborative research

Reidar K. Lie, M.D., Ph.D.

Department of Clinical Bioethics,
NIH

Disclaimer

- The opinions expressed are the author's own. They do not reflect any position or policy of the National Institutes of Health, Public Health Service, or Department of Health and Human Services

Special concerns

- Different regulations
  - Children
  - Emergency Research
  - Informed consent requirements
- Different scientific judgments
  - Acellular pertussis vaccine trials
- Different ‘values’
  - Individual informed consent

Different economic conditions

- Level of care controversy
  - Should there be a requirement to provide all participants, regardless of location and availability of treatments, the same level of care during the trial
- Obligation to provide proven treatment after conclusion of trial?
  - To participants? To general community?

Previous Declaration of Helsinki

- In any medical study, every patient – including those of a control group, if any – should assured of the best proven diagnostic and therapeutic method

Current Helsinki

- Should be assured best current therapy
  - Essentially the same as best proven therapy
- Also guarantee of therapy to study participants after successful trial
- Responsiveness to needs of country

Helsinki “clarification”

- Placebo controlled trials permitted
  - For compelling and scientifically sound methodological reasons
  - OR
  - When not causing serious or irreversible harm

Essential disagreement

- Defenders: Sometimes a different standard of care is essential to identify useful results
- Criticizers: Useful results can be obtained from equivalence trials. No need to do trials with a local standard of care to obtain useful results

“Current” 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

Necessary conditions for placebo use

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

Basic agreement

- NBAC
- Nuffield Council
- EGE
- CIOMS
- UNAIDS Guidance Document for HIV vaccine trials

Benefit to research participants: Current Helsinki

- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by that study
- This is also reflected in other guidelines
- General agreement

Basic justification

- It is morally wrong to take away medication from a person who is benefiting from it
- Those who happen to be randomized to the control group has some claim to receive the intervention which is identified as beneficial in the study
- Ordinarily, the health care system in the country would supply the necessary intervention
- This has become problematic in the face of increasingly costly treatments

Some problems

- Drug may not be approved by regulatory authorities after some time of the study
- May be necessary to do an additional trial
- Possibly of interest to continue long term follow up
  - Vaccine study for example, duration of protection
  - Level of viral load in HIV vaccine study

General agreement

- In spite of special cases and difficulties, there IS an obligation to provide treatment to trial participants who benefit
- Issue is: WHO has this obligation, and HOW does one have to address this issue before the trial starts

Solutions?

- Research sponsor supplies the drug as part of the trial costs?
  - Would bankrupt publicly funded research
  - Would create disincentives for commercial research
- No condition regarding post-trial access is necessary before the research is started
  - It seems wrong that one should not give SOME thought to this

Plan as a precondition?

- One should only do research if there is a plan for supplying the drug afterwards
  - Country, existence of a fund, etc
- How firm does the plan have to be? Do you have to have the actual funds or is it enough with a political commitment?

Availability to general community

- CIOMS: As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to the inhabitants of the underdeveloped community in which the research was carried out. Exceptions to this general requirement should be justified, and agreed to by all concerned parties before the research is begun

Weaker requirement

- Current Helsinki: Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research

Weaker, NBAC

- Research proposals submitted for IRB approval should include an explanation of how successful interventions will become available to some or all of the host country populations…Where investigators do not believe that successful interventions will become available to the host country populations, they should explain to the relevant IRB why the research is nonetheless responsive to the health needs of the country and presents a reasonable risk/benefit ratio

Apparent agreement

- Before one approves a trial one should establish that there is a reasonable chance that the trial intervention will become reasonably available to the community at the conclusion of the trial
- It is unethical to approve a trial if one is confident that the trial results will not be useful for the host country

Three cases

- HIV treatment trial in South Africa
- Blood pressure trial in India
- Malarone prevention trial in Indonesia

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

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 cheaper to do it there
- Drug will be sold almost exclusively in Western Europe and North America

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

Three positions

- We only need to be concerned about safety, risks and benefits to the participants in trial. If that is favorable, the trial should be approved
- Only approve research if there is a chance that the trial results will be useful for the host country or that there is a guarantee of reasonable availability
- All benefits, present and future, need to be considered

Problems

- Against 1) At a very basic level it seems wrong to take away interventions a person is benefiting from
- Against 2) Focus on availability as an absolute requirement ignores realities of access, and denies communities real health benefits
- Against 3) Ignores realities of political decision-making

Fair benefits framework

- All benefits and risks need to be evaluated
  - Benefits and risks to research participants
  - Benefits to general community during trial
  - Benefits after the completion of the trial
- Community involvement
  - Involvement at all level of decision making
  - Uncoerced
- Transparency in decision making

Challenge

- We are perhaps focusing on the wrong issue.
- Focus more energy on specifying concretely how we should understand appropriate benefits of research, and responsiveness to health needs
- Identify criteria for decision making for RECs which are
  - Open to scrutiny
  - Realistic

Current reality

- US based Quintiles (CRO) has recruited 6400 patients for clinical trials in India in psychiatry, infectious diseases and oncology since 1997
- There are now dozens of CROs which have set up operations in India, compared with three in 2001
- Centerwatch: India has about 30 m people with heard disease, 25 m with type II diabetes, and 10 m with psychiatric disorders. Abundances of these rich world diseases is regarded as a prize attribute for companies looking to test drugs destined for Western Consumers
- Source: Financial Times

Responsiveness to health needs

- There should be a national health policy plan
  - In line for example with a country's obligations under the Covenant on Social, Economic and Cultural Rights (if they have ratified this Covenant)
- A condition for approval of a trial is that it is shown to be in accordance with this national health policy plan

Fair benefits

- If company saves US$ 200 million when they do their trials in India, would it not be reasonable that India receives US$100 million over and beyond the investment in the trial itself?