THE ETHICAL ISSUES IN RESEARCH INVOLVING HEALTHY VOLUNTEERS

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Presented in the 13th FERCAP International Conference
Bali, 19 November 2013
Disclosure

The speaker has no conflicts of interest.
In doing medical research, we hold the classical ethical principle that healthy volunteers should not be exposed to more-than-minimal risks.

Today, we see this the principle has been “ignored" in some way e.g., in vaccine development and in phase 1 studies of drug development.
Background (2)

- Participation of healthy volunteers in medical research → intriguing ethical issues because they get no potential therapeutic benefit.

- The purpose of this presentation is to discuss the assessment of risk in the context of medical research involving healthy volunteers.
An example

- In June 2001, a female healthy volunteer was given a methacholine challenge by inhalation. The next day she experienced dyspnea, followed by hypotension and multi organ failure and death.

- This sparked a question: to what extent of risk may a healthy volunteer be exposed to in the context of medical research?
How should we weigh a benefit?

1. Direct benefit for the patient: not applicable to healthy volunteers
2. Benefit for the society: however large the benefit, to expose a participant to anything more than minimal risk needs very careful consideration and would rarely be ethical
What do our guidelines state? (1)

- “Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.” (Declaration of Helsinki)

- “Risks to the research participants should be weighed against the benefits to both the participants and to the concerned community.” (WHO)
What do our guidelines state?

- “...in non-therapeutic research, you must keep the foreseeable risks to participants as low as possible and the potential benefits from the development of treatments and furthering of knowledge must far outweigh any such risks” (General Medical Council, UK)

- None of these guideline, however, describe clearly what degree of risk is acceptable, other than that the risk has to be very low.
What is minimal risk?

“The risks of a research are minimal if their procedures involve no foreseeable harms which are no more severe than those which one could meet in everyday life. It is accepted that daily living involves a certain amount of risk, after all.”


- What are the examples of this in daily life?
- Can we maintain this in the execution of various medical research?
What is the limitation of considering minimal risk alone as a prerequisite for research involving volunteers?

- In all research involving human subjects, risk should always be assessed together with the benefit.

- Example:
  - It is unethical to instruct a healthy person to take an antihypertensive tablet then take 15 serial venous blood samplings over the period of 24 hours (more than minimal risk!)
  - In fact, it is ethical in the context of Bioavailability/Bioequivalent study. The risk and discomfort are clearly more than minimal, but it is outweighed by the potential benefit (for the society).
Are there trials that pose more than minimal risk to healthy volunteers?

- Phase I studies in drug development
- Infection challenge experiments
- Toxicology research involving monitored drug overdosage
- Bioavailability/bioequivalent studies on “copy drugs”
What are the points to assess the risks caused by an intervention?

- What is the chance that interventions will produce harms to the participants?
- How serious is the potential harm induced by the interventions of the study?
- How long is the potential harm expected to last if it occurs?
Risk of harm: the ethical considerations (1)

Let us try to answer these questions:

- Why should research related risk be more tightly controlled and more restrictive as compared with risk in other areas in our lives?
- In contrast: Why don’t we restrict people from selling motorbikes or diving equipments?
According to Evans and Evans, the answer is:

We should distinguish between the risk someone wants to take based on his own choice and the risk it is appropriate for a professional or other public figure to invite a patient to contemplate.


What arguments can be used to support this statement?
Risk of harm: the ethical considerations (3)

1. A non-therapeutic trial offers no potential benefit to the healthy subjects
2. The potential participants may feel they ought to respond to such figures of respect and authority
3. People believe professionals have higher standards compared to a motorbike or diving equipment salesman
When can healthy volunteers be exposed to more-than-minimal risk?

1. The volunteers give a valid informed consent
2. The potential benefit of the study is large
3. There is unlikely to be a public reaction against research as a result of harm to participants

(Hope T and J McMillan, J Med Ethics, 2004;30:110-6)
How can we minimize the risk?

1. Find the least risky method

2. Establish exclusion criteria to rule out subjects having high chance to get risks

3. Carefully read the information on risk associated with the intervention

4. Choose the tests with the lowest risk or causing least discomfort
What can we recommend?

1. The volunteers give a valid informed consent
2. The potential benefit of the study clearly outweighs its risk
3. Undesirable public reactions is remote
4. The risk of death or permanent injury is extremely small
5. Every effort should be done to minimize risk and discomfort
6. Subjects should be closely monitored
Summary

- Exposing healthy volunteers to a more-than-minimal risk is not a wrong in itself
- In all cases, the risk for a volunteer should be weighed together with the potential benefit for the society
- Minimizing risk and risk-benefit assessment are very important issues in research involving healthy volunteers
- Whether there should be an upper limit on acceptable risks for healthy volunteers remains an unsettled issue of research ethics.

THANK YOU