Some sensitive issues of study design in bioethics

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Some almost trivial things

- Bad science and research are unethical by themselves.
- There is no way to do good research with low quality and/or inappropriate study design and methods.
- Debate and solutions in biomedical research ethics are very much reflections and reactions to possible tensions between goals and ways to reach them.

The evidence based medicine (EBM)

- EMB is the leading trend in the current Western medicine
- All medical decisions should be made on the basis of the best current evidence.
- The evidences have clearly relative character.
- The evidences have their own hierarchy.
- The best evidences are thought to come from blinded randomized studies with different arms of treatment, incl. sometimes placebo or no treatment

Research and/or therapy?

- The initial statement is that a research subject must know that she/he is in the study
- A recent case: 2 weeks ago our HREC reviewed a I phase trial proposal where research activities were misleadingly labeled as therapeutic visits

Belmont Report (1979) on practice and research

For the most part, the term "practice" refers to *interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success.* The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (2)

By contrast, the term "research' designates an *activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships).* Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

Therapeutic misconception

- The term was coined by Paul Appelbaum and his colleagues in 1982.
- They found that many people were *unaware* of the differences between participating in a study and receiving treatment in the clinical setting. They tended to believe that therapy and research were governed by the same primary goal: to advance the individual patient's best interests (Dresser, 2002)
- There is no such term in Estonian language, my own version would be rather '*uuringu vääriti mõistmine*'.

The control group or *placebo* problem

- WMA Helsinki Declaration (2004) #29: *The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods*. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote.

Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- - *Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method*; or
- - *Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm*.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

CIOMS Guidelines for biomedical research involving humans (2002)

- CIOMS -- Council for International Organizations of Medical Sciences
- CIOMS prepares also a new version of guidelines for ethical review of epidemiological studies

CIOMS *Guideline 11: Choice of control in clinical trials*

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".

Placebo may be used:

- when there is no established effective intervention;
- when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;
- when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects

Clinical equipoise

- Charles Fried coined the term ‘equipoise’ for clinical research ˇin 1974.
- Fried: **equipoise** is *state of uncertainty that must exist for a concurrently controlled trial to be justified*--all available evidence must offer NO reason for preferring one of the treatment arms over another (if so, why start a trial?) http://appliedphilosophy.org/research-ethics/research-ethics-note_more.php?id=277_0_44_0_M
- There is no such term in Estonian language, my own version would be a bit clumsy ‘*kliinilise uuringu erinevate harude võrdsus*’.
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Freedman (1987) on equipoise

"In the simplest model, testing a new treatment B on a defined patient population for which the current accepted treatment is A, *it is necessary that the clinical investigator be in a state of genuine uncertainty regarding the comparative merits of treatments A and B for population P*. If a physician knows that these treatments are not equivalent, ethics requires that the superior treatment be recommended. Following Fried, I call this state of uncertainty about the relative merits of A and B "equipoise"".

Clinical equipoise

- Sometimes it is very difficult for researcher to estimate merits of different treatments on the basis his own research data. In some cases special data-monitoring commitees are established to estimate the effect of a treatment regimen.
- A result of the successful clinical study should be break of clinical equipoise.
- The early obvious break of equipoise may serve as a basis for stopping of clinical study.

References

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