Research Skills: Ethical Issues

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What is Ethics?

- Ethics is concerned with theories and concepts which explain and justify what is right and good.
- Applied it aims to tell us how we ought to act in a given situation and to provide us strong reasons to do so.

Roots of Medical Ethics

Deontological (study of duties) Ethics:

(since Hippocrates, referring to physicians)

Stresses:

- data privacy and confidentiality
- care for the beneficence of the patient only
- to do the sick no harm (non-maleficence)
- gratefullness to teachers and willingness to share knowledge and experience

→ **attitude and action orientated**

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Roots of Medical Ethics

Principle-based ethics(Belmont Report):

- four prima facie principles:
  - autonomy and respect for the dignity of the patient or healthy volunteer,e.g. Informed Consent, ‘man must not be a means to an end’
  - beneficence

Roots of Medical Ethics

- non-maleficence
- justice → to act in a fair and equitable manner as far as the distribution of research risks or burdens and benefits are concerned.

There is no hierarchical order

→ **action-orientated**

Roots of Medical Ethics

Utilitarian Ethics (J. Bentham, S. Mills):

Our actions should maximize utility, i.e. happiness or preferences satisfaction for the greatest number of people, and minimize pain, suffering and harm.

Roots of Medical Ethics

Utilitarian Ethics:

e.g. requirement to use the most efficient research design which allows for highest validity with a minimum of research subjects.

→ **Outcome-orientated**

Ethical Issues in Clinical Research

Major issue

- ***The ethical aporia*:**
  It is unethical to administer a medicine of unproven benefit and unknown safety.
  But to find out whether a medicine has beneficial effects and acceptable safety, one has to test this very medicine on humans.

Ethical issues in Clinical Research

- Whereas in patient care the physician is solely devoted to the good and beneficence of the patient, clinical research requires a different role:

  the physician has to act *as* ***an investigator*** following the strict procedures of a trial protocol

  → conflict of professional roles.

Declaration of Helsinki (Seoul 2008)

- The health of my patient will be my first consideration.
- A physician shall act in the patient's best interest when providing medical care (A4.)
- In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests (A6.)

In clinical research, the aim to answer the hypotheses in an efficient, reliable and valid manner may cause a role conflict and present a conflict of interest.

Methods for the resolution of these ethical issues

- extensive preclinical testing
- requirement of a detailed trial protocol
- authorization by competent drug authority
- review by research ethics committee

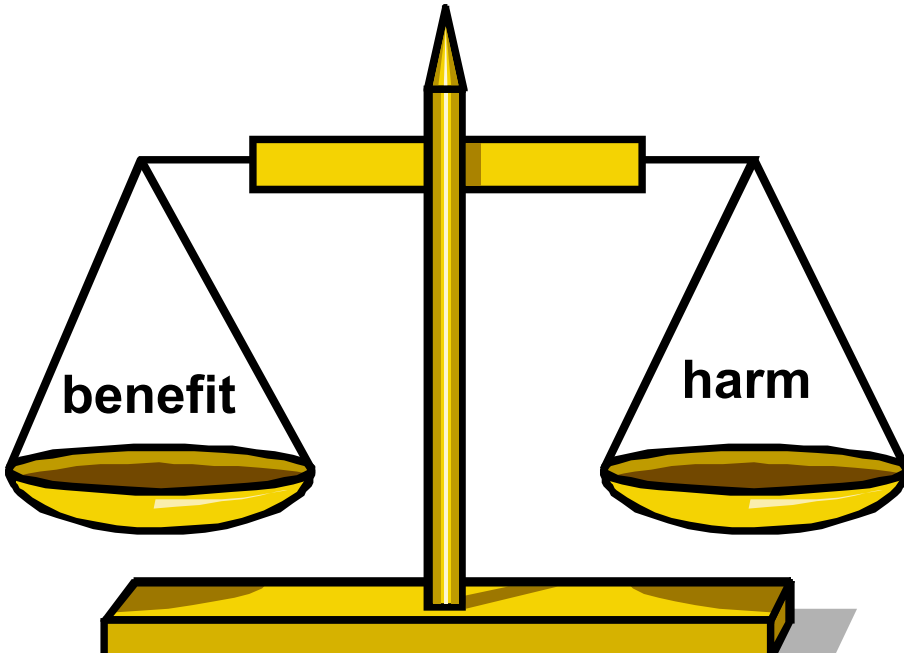
Methods for the resolution of these ethical issues

- safety monitoring, interim analyses and data monitoring committees
- informed consent
- unalienable right to withdraw IC at any time
- compensation in case of harm
- GCP- conformity

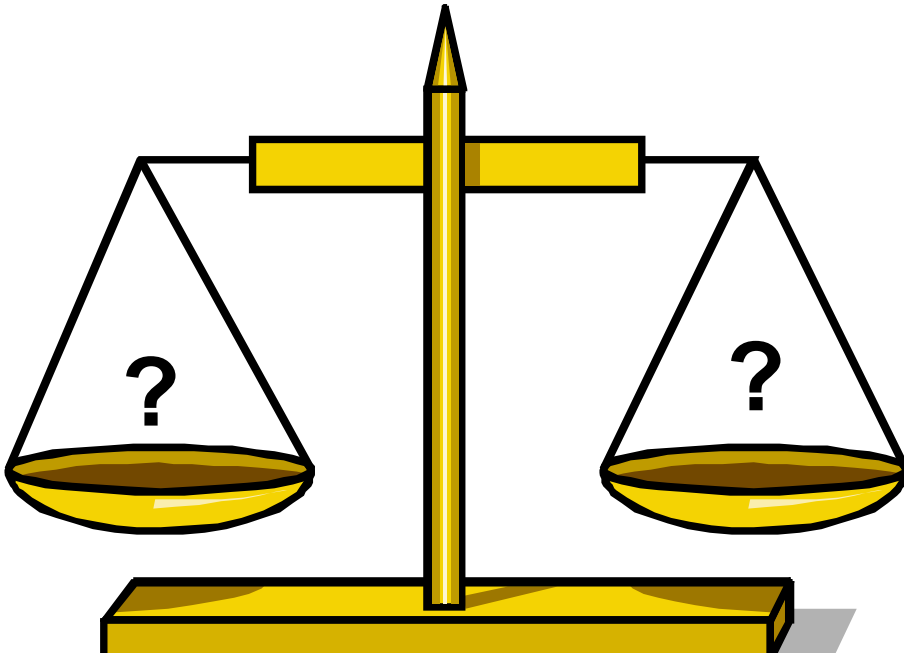
Ethical Deficiencies of Clinical Trials in Europe

- inadequate procedures to achieve ‘informed consent’, focusing on formalities
- limited access to trial medication after end of trial
- inadequate compensation for harm, e.g. the patients in the Tegenero-Phase I-Study (TGN1412)
- privatization of the results, although patients and healthy volunteers risked their well-being to support the development of new treatments.
- inadequate oversight of CTs in many EU member states.

Clinical Trials: Individual Ethical Issues



Epidemiology: Individual Ethical Issues?



Data privacy & confidentiality issues prevail

Three 'Ethical' Issues in Epidemiology

- delinking subject identifiers from their information
- modifications to subject IC requirements
- modifications to EC review

Ethics Issues in Pharmacoepidemiological Research. In Strom, Kimmel, Hennessey, eds. Pharmacoepidemiology, 5. El Khoury AC et al. Bioethical Issues e, John Wiley, 2012

Data Privacy and Confidentiality

- Privacy refers to security and personal space including personal information and handling of waste materials from a person.
- Confidentiality is the right to limit the transfer of information to control the secondary use of information by others.

➡ **Right of informational self-determination**

Complete Anonymisation → no ethical or legal problem

In PV/PE data often have to be updated or quality controlled

➡ Informed consent is required

Although the directive 95/46/EU allows for the processing of health data 'for the purposes of preventive medicine … the provision of care or treatment, or the management of health care services' [Art. 8(3)] without individual IC, **most EU member states ask for consent.**

CIOMS Ethical Guidelines for Epidemiological Studies (2009)

„For all epidemiological research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law.“

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In Epi to achieve IC is often difficult

- as the person may not be available (death, discharged from hospital etc.)
- when using PE databases large populations would have to be asked for IC
- strict requirement of IC may lead to selection bias and reduced response rates -> no valid results

Although people have a right to know the profile of harm of their medicines, current regulations of data confidentiality and perceptions of ethics are a serious drawback.

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Ethical Review of Epi-Research

PRO

- a detailed research plan has to be prepared → quality control
- data privacy issues will not be neglected
- international guidelines, e.g. CIOMS support this.

Ethical Review of PV/PE-Research

CONTRA

- Lack of qualified epidemiologists in ECs
- Time consuming
  - a CCS in CH had to be submitted to the ECs of all cantons where it was done.
  - a safety NIS in 7 European countries needed between 1 month and 1 year to get the ECs approvals needed.
  - no harmonized procedures in the EU

Case-Study

Objective:

To find out whether administration of estrogens to adolescent girls results in cancer in later life

Research Design:

Linkage of the National Cancer Registry, the National Death Cause Registry and medical records.

M Hansson. BMJ 2010, 340: 1172

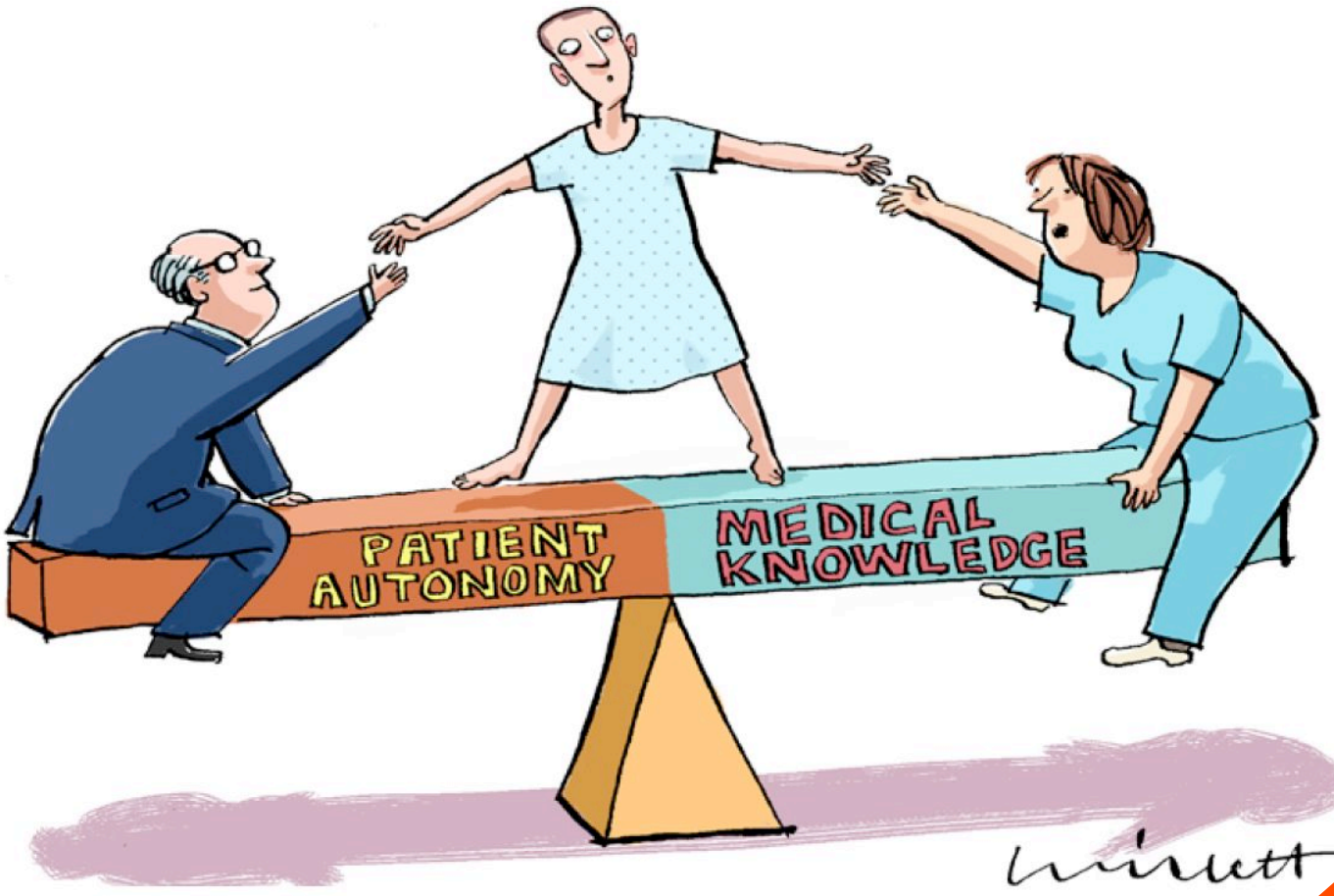
Informed Consent Required

PRO	CONTRA
– Respect for women's informational autonomy	– Might cause unjustified concern and worry – Rejections ➢ selection bias ➢ reduced power ➢ valid results may not be obtainable ➢ exposed may never learn about adverse effects/ reactions ➢ medical knowledge – How to get IC of the dead? – Right to not know

→ The competent EC rejected the application and asked for IC

In epidemiological research there is typically no health risk and no individual benefit. There is rather – if at all – the risk of violating a person's civil rights like privacy.

Thus the ECs have to consider the 'right to know' of the exposed and the interest to advance medical knowledge too, and not only the concept of informational self-determination.



Source [1]: M Hansson. BMJ 2010, volume 340: 1172

FINAL COMMENT

Given that the financial means for epidemiology are limited Utilitarian Ethics asks that those areas where - per Euro or Dollar spent - the maximum of added benefit can be achieved, are identified and focussed on.

CONCLUSIONS

- Due to the different roots there is no uniform ethics.
- Ethics has succeeded in providing accepted procedures for solving the ethical aporia and other relevant ethical issues.
- Even in the EU and USA there is considerable room for improvement. The common statement that the research was in agreement with the DoH is most often wrong and misleading.

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CONCLUSIONS

- Ethical issues in Epidemiology concern data privacy and confidentiality mainly.
- Thus the concept of balancing individual benefits and harm does not work.
- In addition to the right of informational self determination the ‘right to know’, freedom of research, and the interest to advance medical knowledge have to be taken into account too.

CONCLUSIONS

- Thus a revision of current ethical guidelines for Epidemiology should be considered.

How to develop a Research Question?

- Clinical Medicine
- Public Health and Epidemiology

Clinical Case History

A 59 yrs old woman complains about fatigue, lack of appetite and proneness to infections. At the physical examination an enlarged spleen is found. The hemogram looks like a chronic myeloid leukemia. Cytogenetic testing proves this diagnosis:

Chronic Myeloid Leukemia.

The woman is informed about the diagnosis. She asks:
„How long will I live?“

You do a literature search for prognosis and outcome. You find a text like this:

The 5-yrs survival rate ranges between 30% and 80%, depending to the course of disease.

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Treatment Options

Chemotherapy:

Well tolerated and fast action. Median survival time ~ 5 yrs; no cure.

Interferon-alfa:

Effective, but considerably less well tolerated. Improved median survival time. Cytogenetic remission: ~ 30%. Cure ? Primary nonresponse ~ 25%.

Bone marrow transplantation:

Potential for cure but considerable early transplant related mortality and GVHD.

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Clinical decision making

- There are four options to treat a patient with CML
  - „classical chemotherapy“ , e.g. HU
  - IFN-α-based treatments
  - BMT
  - palliation only

How to find the optimal treatment for a patient and how to answer the question of the patient ?

Research questions: PH and Epidemiology - Criteria

- Burden of disease
- Public Health impact
- Systematic literature search and review
- Probability of success
- Feasibility
- Funding