Ethics in Clinical Research and Pharmacovigilance

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Foundation place of ESoP/ISoP in 1992
The opinions expressed are not necessarily those of the ethic institutions I belong to.

There is no conflict of interest to declare.
STRUCTURE

• Roots and principles of medical ethics
• Ethical issues in clinical research
  – Emerging nations
    - Distributive justice
• Ethical issues in pharmacovigilance and pharmacoepidemiology
• Conclusions
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)
– gratefulness to teachers and willingness to share knowledge and experience

→ attitude and action orientated
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.

Schüklenk U. Developing World Ethics 2005;1:1471
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
Medical Ethics

• Medical ethics is rooted in a variety of different, but partly overlapping and contradictory ethical concepts.

• It is applied to an individual and societal level.

• Recently, issues of distributive justice (considers what is socially just with respect to the allocation of goods in a society) and equality of opportunity in medicine have become important, too.
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 in 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.
• The health of my patient will be my first consideration (A4).
• 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.)
Ethical issue for the physician-investigator

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 Informed Consent 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 legal ‘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.

International research is biomedical research that is carried out on populations in middle- or low-income countries and sponsored by a foreign entity, typically from a high-income country.

Of the 50,000 trials currently taking place globally, over 40% are now being conducted in non-traditional research zones.

## Number of clinical trials applied for in the EU

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>5,028</td>
</tr>
<tr>
<td>2008</td>
<td>4,618</td>
</tr>
<tr>
<td>2009</td>
<td>4,491</td>
</tr>
<tr>
<td>2010</td>
<td>4,193</td>
</tr>
</tbody>
</table>

- about 64% of clinical trials are sponsored by the pharmaceutical industry.

EU CTD Public Consultation Paper 2010, Annex
Corruption Perceptions Index 2011 - Results -

Source: Transparency International
Positive Aspects of the shift of clinical research to emerging Nations

• access to potentially beneficial medicines
• chance that regionally dominating diseases get treated
• capacity building locally
• Immediate access to considerable ethnic diversity, e.g. in India
Reasons for the shift to emerging Nations

• almost unlimited access to treatment-naïve patients → faster recruitment → more time to exploit patents
• less expensive trial costs (~ 50-60%)
• less regulation and supervision

Critical Ethical Issues of Clinical Research in Emerging Nations

- competent regulatory and ethical legislation as well as oversight often missing
- informed consent in a partly illiterate population
- recruitment of often helpless (vulnerable) people who need medical care, e.g. Keno, Nigeria meningitis trial*
- placebo-misuse, as often considered as ‘local standard treatment’
- diseases are treated which are not relevant to the country
- comparatively little research on tropical and poverty-driven diseases

*Annas GJ: NEJM 2009;360;2050-2053
Ethics Committee review in developing Nations

- Only 56% of 670 researchers surveyed reported that their research had been reviewed by a local IRB or health ministry (1,2)
- 90% of published clinical trials conducted in China in 2004 did not report an ethical review of the protocol and only 18% adequately discussed informed consent. (1,3)

1. Glickmann SW et al. NEJM 2009;360:816-823
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 stand to benefit from the results of the research. (B 17.)
Treatments tested in developing Nations

Reality:

Glickman et al. found among the ongoing US-sponsored clinical trials in developing countries in 2007 none for tuberculosis, but a variety of trials for allergic rhinitis or overactive bladder. ¹

¹ Glickman SW et al. NEJM 2009;360:819
The protocol should describe arrangements for post study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits (B14.)
Declaration of Helsinki
(Seoul 2008)

Reality

• Only 3 of 312 trials (HIV, malaria, tuberculosis) between 10/2004-04/2007 mentioned post trial benefits ¹.

• None of 34 protocols seen by a Mexican IRB mentioned post trial benefits ².

April 28, 2008 the USA gave up the requirement to comply with the DoH

The final rule replaces the requirement that these (foreign) studies be conducted in accordance with ethical principles stated in the Declaration of Helsinki, with a requirement that the studies be conducted in accordance with GCP …

USA Federal Register: 28/04/2008
Informed Consent

- Ethically sound informed consent needs fully informed free people who have access to adequate health care outside of clinical research.
- Patients in developing countries often have to use clinical trials as a means of getting access to medication and medical treatment.
- In such a situation IC is not given voluntarily, but a socially deprived situation is exploited.
Exploitation

There is

• exploitation that harms the research subject by making him/her worse off than he/she would otherwise have been.
  → ethically not acceptable

• exploitation that treats the research subject unfairly, but actually leaves him/her better off than he/she would have been in the absence of exploitation.
  → mutually advantageous exploitation

In developing nations the foreign sponsor is typically in a much stronger bargaining position, thus the ‘benefit’ is not shared in a fair manner.

At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits. (B 33.)
Clinical Trials

• Clinical trials should provide generalisable knowledge. This task should not be burdened with the ‘requirement’ to provide access to adequate healthcare in resource poor settings.

• Single sponsors or trials usually cannot fulfill this expectation.

• Access to adequate health care is the responsibility of the competent government.
‘Benefit’ of internationalising clinical research

e.g. India boasts that clinical trials in their country are about 50-60% less expensive than in the USA or Europe.
How to do research fairly in an unjust world: a Global Research Tax

<table>
<thead>
<tr>
<th>Original total trial costs - Uganda</th>
<th>Global research tax (% of trial costs)</th>
<th>Funds for research population in Uganda (millions)</th>
<th>New total trial costs - Uganda (millions)</th>
<th>Total trial costs in the U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$8.2 million</td>
<td>10%</td>
<td>0.82</td>
<td>9.02</td>
<td>$22.6 million</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>2.46</td>
<td>10.66</td>
<td></td>
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<tr>
<td></td>
<td>50%</td>
<td>4.10</td>
<td>12.30</td>
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<td></td>
<td>90%</td>
<td>7.38</td>
<td>15.58</td>
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Even with a global research tax the trials in emerging nations would still be significantly cheaper.

Benefit of the Global Research Tax

The revenue from the Global Research Tax should be used to provide adequate access to health care in the emerging Nations (where the clinical trials have been done).
Pharmacovigilance and -epidemiology

• As the safety of a drug is rarely ever fully known it is *ethically imperative* to carefully monitor its potential risks.
• All stakeholders have to be informed fully and without undue delay.
• Only then the competent drug authority, the prescribing physician and the patient can perform a sound benefit/harm evaluation to inform their rational decision-making.
Clinical Trials: Individual Ethical Issues

Pharmacovigilance/Pharmacoepidemiology: Individual Ethical Issues?

Data privacy & confidentiality issues prevail
Three ‘Ethical’ issues in PV/PE

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

Is PV/PE Research at all?

‘Research is the systematic investigation into and study of materials, sources, etc., in order to establish facts and new conclusions.’

The Oxford Encyclopedic English Dictionary 1991
Thus the Tax Declaration is research and needs to be reviewed by an EC?

Pharmacovigilance and epidemiology is very often public health case finding and surveillance, e.g. spontaneous reporting systems and drug utilization.

It may be difficult to decide whether a PV-Study (e.g. PASS) is a quality assurance activity or research.

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.“
In PV/PE 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 (expensive)
- 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 impediment.
Ethical Review of PV/PE-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

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

<table>
<thead>
<tr>
<th>PRO</th>
<th>CONTRA</th>
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<tbody>
<tr>
<td>- Respect for women’s informational autonomy</td>
<td>- Might cause unjustified concern and worry</td>
</tr>
<tr>
<td></td>
<td>- Rejections</td>
</tr>
<tr>
<td></td>
<td>- selection bias</td>
</tr>
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<td></td>
<td>- reduced power</td>
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<tr>
<td></td>
<td>- valid results may not be obtainable</td>
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<tr>
<td></td>
<td>- exposed may never learn about adverse effects/reactions</td>
</tr>
<tr>
<td></td>
<td>- medical knowledge</td>
</tr>
<tr>
<td></td>
<td>- How to get IC of the dead?</td>
</tr>
<tr>
<td></td>
<td>- Right to not know</td>
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</tbody>
</table>
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 pharmacovigilance are limited, Utilitarian Ethics asks that those areas where - per Euro or Dollar spent - the maximum of added drug safety 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.
CONCLUSIONS

• From an ethical point of view the situation of clinical research seems to be considerably worse in emerging nations.
• To improve that situation responsible governments and international cooperation are needed.
• Issues of distributive justice and equal access to health care cannot be solved by individual researchers or sponsors. A ‘global research tax’ may be good idea.
CONCLUSIONS

• Ethical issues in PV/PE 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 PV/PE should be considered.