Ethical review of medical research in Germany and current ethical issues in a world of globalized clinical research

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STRUCTURE

- Structure of MECs in Germany
- Roots and principles of medical ethics
- Risk assessment
- Unsolved issues
- Ethical issues in clinical research in emerging nations and distributive justice
- Conclusions

Structure of the Ethical Assessment of Biomedical Research in Germany

Legal Basis

According to the German Constitution there is freedom of research to be protected by the state.

As the integrity and the autonomy of biomedical research participants is at risk there are special provisions by laws however for

- studies with medicinal products (i.e. medicines)
- studies with medical devices or radiation exposure
- all biomedical and epidemiological research has to be approved by a REC according to the DoH and German physicians' professional regulation.

Structure of the Ethical Assessment of Biomedical Research in Germany

Medical Ethics Committees

- 53 Medical Ethics Committees, organized by universities (33), medical associations of the federal states (17) and federal states (3).
- Act absolutely independently, but in compliance with German laws and regulations.
- MECs are multidisciplinary: physicians(majority), ethicists, lawyer/judges, statisticians, lay persons.

Structure of the Ethical Assessment of Biomedical Research in Germany

Medical Ethics Committees

The MECs founded the Association of MECs in Germany, which organizes continued education for MECs‘ members, harmonizes the procedures of MECs in Germany and represent the MECs in the public.

The Scope of Assessment of Clinical Trial Applications

Clinical trials with medicines are regulated by the EU-CTD and corresponding national laws; the Clinical Trial Directive 2001/20/EU asks MECs to review;

- the relevance of the clinical trial and the trial design;
- whether the evaluation of the anticipated benefits and risks is satisfactory and whether the conclusions are justified;

The Scope of Assessment of Clinical Trial Applications

- the protocol;
- the suitability of the investigator and supporting staff;
- the investigator's brochure;
- the quality of the research facilities;
- the adequacy and completeness of the written infor-mation to be given, and the procedure to be followed for the purpose of obtaining informed consent;

The Scope of Assessment of Clinical Trial Applications

- provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;
- any insurance or indemnity to cover the liability of the investigator and sponsor;
- the amounts and, where appropriate, the arrange-ments for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site;
- the arrangements for the recruitment of subjects.

Why are Ethics Committees essential ?

1st Key Ethical Conflict in Medical Care and Research:

- It is unethical to administer a therapy whose safety and efficacy has not been properly proven.
- It is, however, unethical too to evaluate the efficacy of a new therapy in humans as the risk of noxious effects cannot be excluded.

Why are Ethics Committees essential?

2nd Key Ethical Conflict in Medical Care and Research:

- A patient rightly expects that his/her physician acts in his/her best interests**. Thus in routine health care the physician acts as a therapist only.**
- In research however, the physician-investigator has to comply with the directions of the trial protocol, too.

➡ **Role conflict:**

therapist vs physician-investigator

Methods for the moderation of these ethical conflicts

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

Methods for the moderation 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

Conflict Resolution/Moderation

- Since 1975 the Declaration of Helsinki has been requesting that these ethical issues are mitigated and moderated by Independent Ethics Committees.
- Many international conventions like the ICH-GCP, the Additional Protocol of the Council of Europe and WHO/CIOMS have adopted this successful and by now very well-tried solution.

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**

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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**

Medical Ethics

- Medical ethics is rooted in a variety of different, but partly overlapping and ***partly contradictory*** ethical concepts.
- It is applied to an individual and at societal level.
- **MECs have to balance by multidisciplinary discussions these principles.**
- 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.

Research with Humans – General Provisions

- **The interests and welfare of the human being participating in research shall prevail over the sole interest of society and science.**
- **Research on human beings may only be undertaken if there is no alternative of comparable effectiveness.**
- **Research shall not involve risks and burdens to the human being disproportionate to its potential benefits.**
- **In case there is no potential for direct benefit (PDB) to the health of the research participant, such research may only be undertaken if it entails no more than acceptable risk and acceptable burden for the participant.**

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Council of Europe: Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research

The German Drug Law, Art. 40

„The foreseeable risks and disadvantages of the study are acceptable from a medical point of view in consideration of the potential benefit for the research subject, ***and*** the expected relevance of the test drug for medicine.“

Two separate risk/benefit analyses have to be done.

Criteria used for Risk Assessment

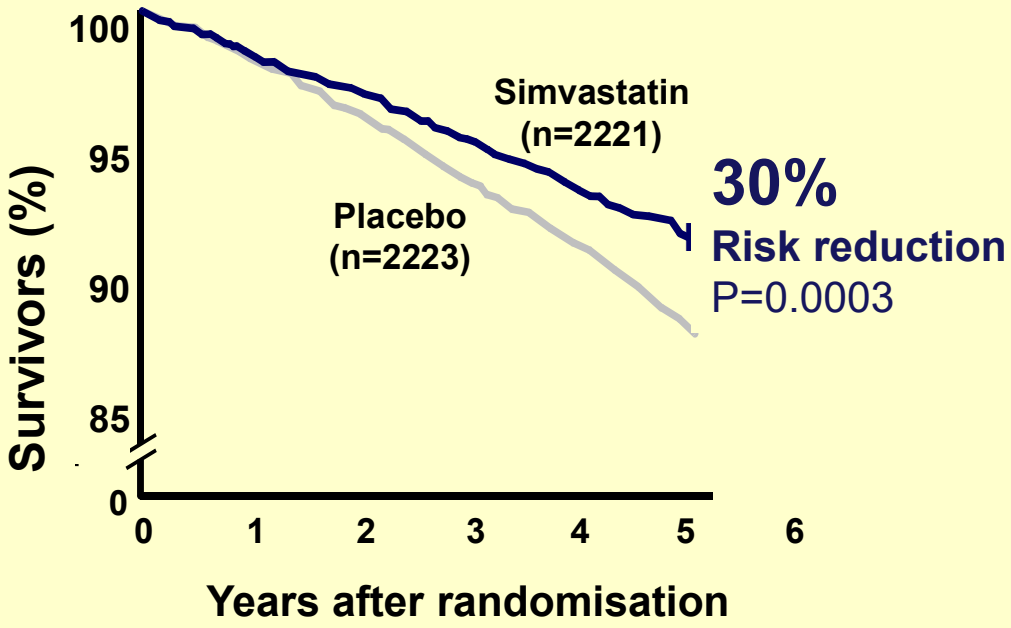
- results from preclinical and prior clinical testing (IB)
- knowledge about the risks of similar drugs
- dosage(s) and duration of exposure
- risks of the disease if untreated
- risks of therapeutic alternatives
- risks of study related procedures
- consideration of patient related risk dispositions
- trial design issues, e.g. placebo-control, clinical endpoints, safety monitoring (DSMB)

The role of MECs in Germany re drug trials

- there are about 1200 - 1600 drug trials in Germany per year
- about 3 % of all submissions get rejected
- about 3% of all submissions pass without any modification
- more than 90% of all submissions pass with modifications only, protecting patients‘ rights , well-being and safety.

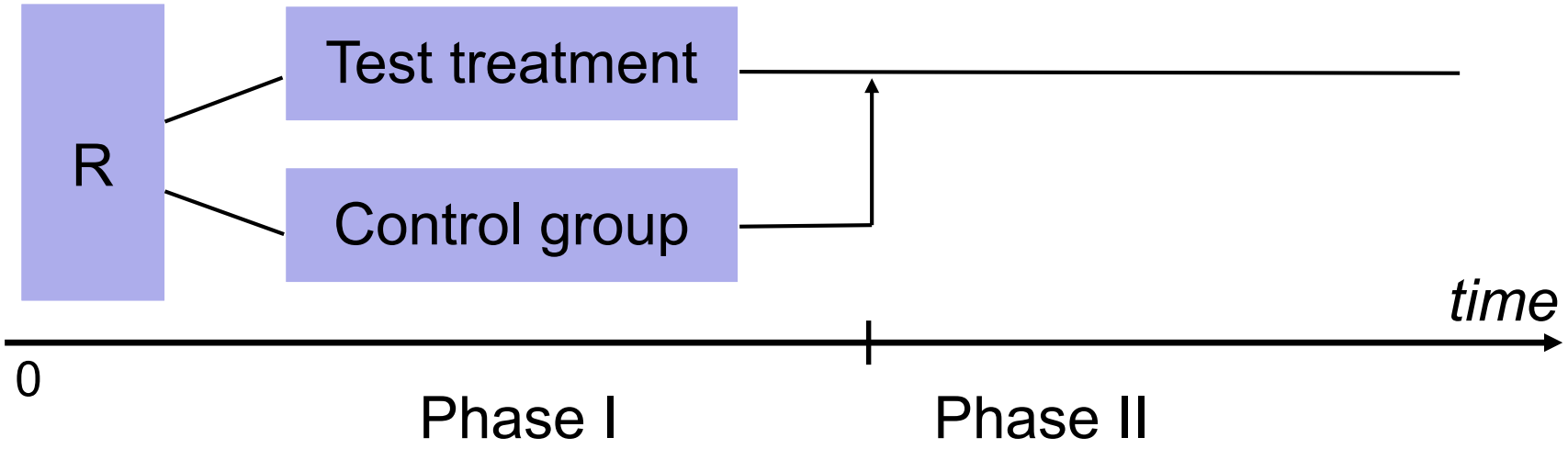
Ethical issue: When to inform about trends?
Overall survival with Simvastatin

Overall survival after therapy with Simvastatin



Graph generated by MSD using data of the Scandinavian Simvastatin Survival Study Group, Lancet 1994;344:1383-1389

Ethical Issue: Change of Design



Phase I randomised trial, precondition: lack of knowledge which treatment is superior

Phase II Observational study with test treatment, precondition: test treatment is superior

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 some EU member states.

Further Ethical Issues

- placebo-controlled trials, e.g. in MS,
- repetitive research, partly due to missing systematic reviews about the state of the art,
- lack of biostatistical expertise in RECs → inadequate sample sizes, inefficient study designs,
- too small p-values.

International Research

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.

AJ Ballantyne. Am J Bioethics 2010, 10: 26-35

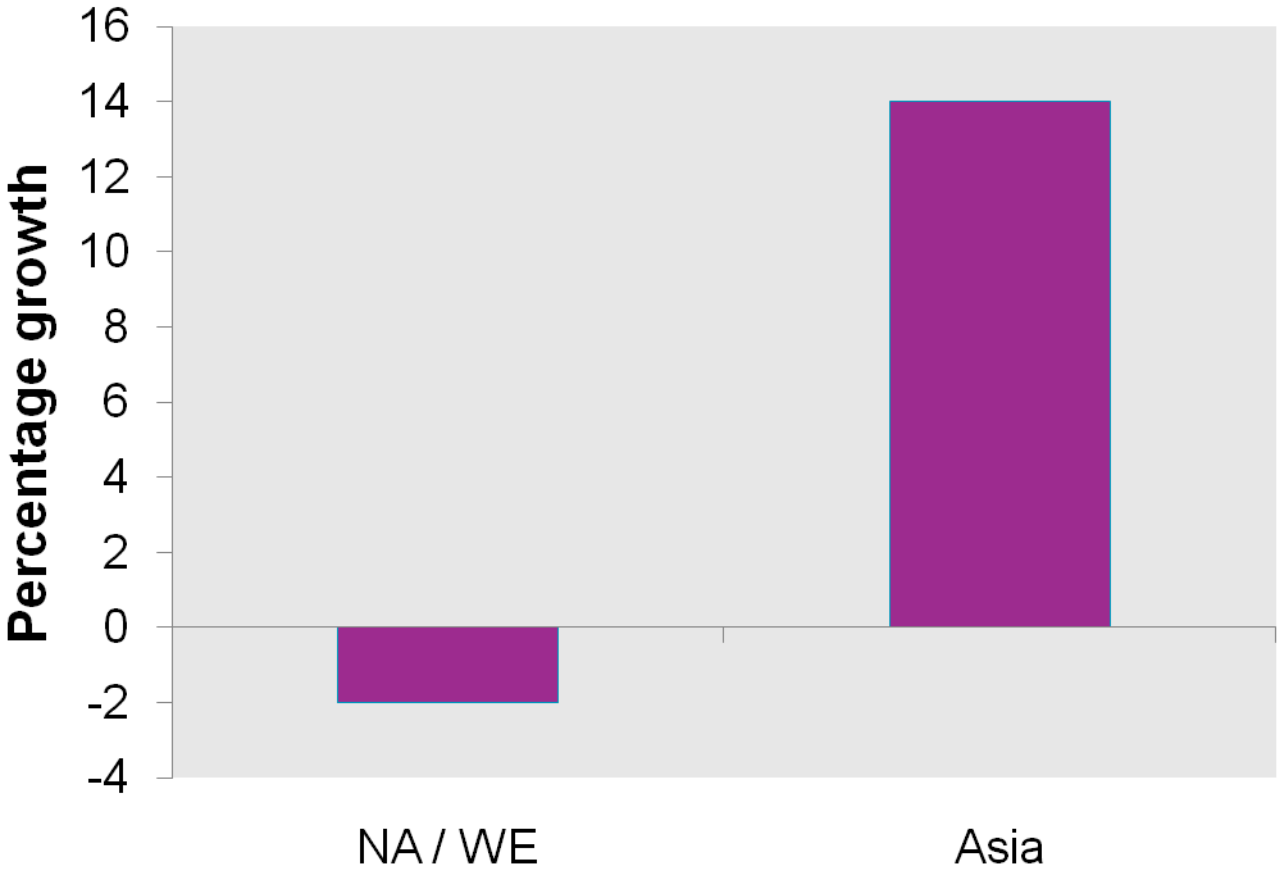
Number of Clinical Trials applied for in the EU

2007	2008	2009	2010	2019
5,028	4,618	4,491	4,193	ca. 4100

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

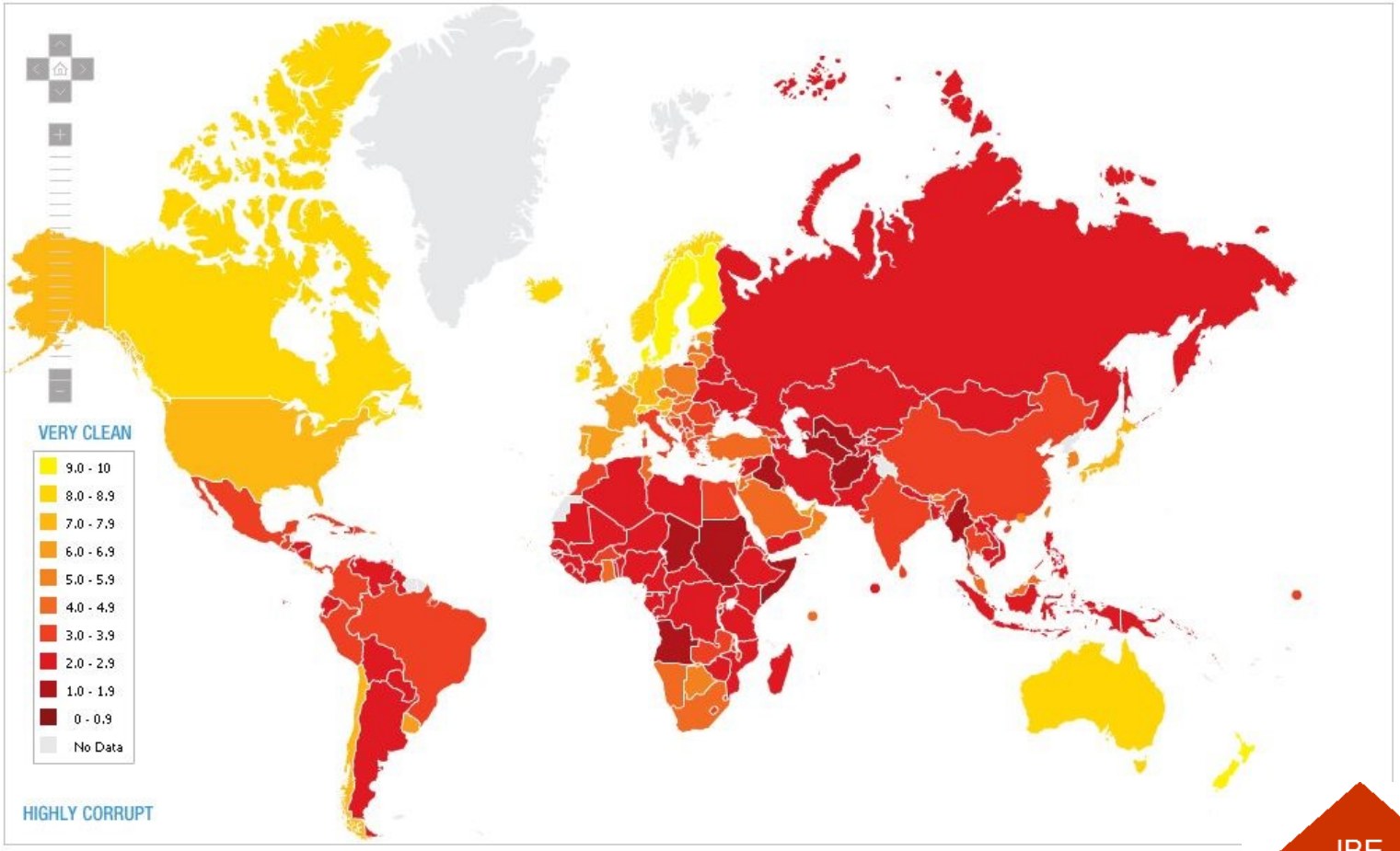
PCP 2010, Annex

Emerging Nations “Drift” 2006 / 2008 to 2008 / 2012



Johann Karlberg, Clinical Trial Magnifier, Feb 2011

Corruption Perceptions Index 2011
- Results -



Source: Transparency International

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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
- access to considerable ethnic diversity, e.g. in India

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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, corruption

Reasons for the Shift to Emerging Nations

- e.g. India boasts that clinical trials in their country are about 50-60% less expensive than in the USA or Europe.

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
- placebo-misuse, as often considered as ‘local standard treatment’
- diseases are treated which are not relevant to the country
- comparatively little research re tropical and poverty-driven diseases

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
2. Hyder AA et al. J Med Ethics 2004;30:68-72
3. Zhang D et al. Trials 2008;9:22

Declaration of Helsinki
(Seoul 2008)

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 (or Chagas disease), but a variety of trials for allergic rhinitis or overactive bladder. [1]

[1] Glickman SW et al. NEJM 2009;360:819

Declaration of Helsinki
(Seoul 2008)

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].**

[1] Cohen ERM et al. Dev.World Bioeth 2008;9:74-80
[2] Paer R, Garcia de Alba Dev.World Bioeth 2008;9:65-73

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 (IC)

- 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.

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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.

Declaration of Helsinki
(Seoul 2008)

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 generalizable knowledge. This task should not be burdened with the ‘requirement’ to provide access to adequate healthcare in resource poor settings.
- Single sponsors or trials cannot fulfill this expectation.
- Access to adequate health care is the responsibility of the competent government.

How to do research fairly in an unjust world: a global research tax

Original total trial costs- Uganda	*Global research tax (% of trial costs)*	*Funds for research population in Uganda (millions)*	*New total trial costs – Uganda (millions)*	*Total trial costs in the U.S.*
$ 8.2 million	10%	0.82	9.02	$22.6
	30%	2.46	10.66	million
	50 %	4.10	12.30	
	90%	7.38	15.58	

Even with a global research tax the trials in emerging nations would still be significantly cheaper.

A.J. Ballantyne. Am J Bioethics 2010

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Conclusions

- The system of MECs is well developed in Germany.
- There are still many unsolved problems however. More research is needed.
- It is only fair that more clinical research takes place in emerging countries.
- The governments of emerging countries should invest in the ethical oversight of clinical research and consider to introduce a ‚fair share tax' to raise financial means to improve the health care of their citizens.

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