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Ethics and Drug Development

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1. Social and scientific value
2. Scientific validity
3. Fair subject selection
4. Favourable risk–benefit ratio
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6. Informed consent
7. Respect for potential and enrolled subjects

Emanuel E.J., Wendler D. & Grady C. *JAMA*. 2000; **283**(20): 2701–2711

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2 RECs: organisation and tasks

There are different names and committees in medical practice

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2 RECs: organisation and tasks

Clinical Ethics Committee

- Ethics in clinical treatment
- Example: advice on ethical questions for patients receiving end-of-life care

Research Ethics Committee, Institutional Review Board

- Research on humans
- Independent expert committees found in medical institutions or university hospitals

2 RECs: organisation and tasks

Different medical disciplines: pharmacology, paediatrics, oncology, surgery, epidemiology, nursery *etc.*

Further non-medical experts from ethics, law or theology

EU clinical trials regulation (Regulation EU No. 536/2014) foresees also the participation of patient representatives

Working according to national legislation rules, the Declaration of Helsinki (World Medical Association) and ICH Guidelines

ICH Guidelines outline the principles of Good Clinical Practice and also research design in special patient groups

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2 Tasks and criteria of RECs: ethical, legal and scientific review

Ethics | Law | Science

- Is the research beneficial and acceptable for the research participants?
- What kind of risks are attached to the study?
- Is the patient information adequate and understandable?
- How are interests and rights of vulnerable groups secured?

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2 Tasks and criteria of RECs: ethical, legal and scientific review

Ethics | **Law** | Science

- By which national law is the submitted study regulated?
- What kind of legal criteria have to be fulfilled (certifications, insurance, qualifications)?
- Are the contracts between physicians / researchers and the industrial sponsor adequate?
- Are the measurements for data protection adequate?

2 Tasks and criteria of RECs: ethical, legal and scientific review

Ethics | **Law** | Science

- By which national law is the submitted study regulated?
  - Different areas of research must be distinguished, *e.g.*, drug research should be regulated by drug laws
  - Some countries combine all their regulations into one law that regulates all human research

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2 Tasks and criteria of RECs: ethical, legal and scientific review

- Is the study design adequate and according to the state of the art methods, tests, questionnaires?
- What are the research questions and aims?
- Can the defined study aims be achieved by the chosen study design (number of cases, statistic methods, *etc.*)?

2 Tasks and criteria of RECs: ethical, legal and scientific review

- Close contention of ethical and methodological issues
- A study can be ethical at the same time as having fulfilled scientific and methodological elements
- If a study does not meet the current standards of research, it would not be reasonable to recruit patients for the study

3 Ethics and research design: randomisation, blinding, placebo control

- Measurements of study design which can contradict the preferences and / or interests of patients
- Randomisation in the case of emergency patients, or the randomisation in a study with ill children
- In a double-blind study, neither the treating physician, nor the patient knows what medication the patient gets
- Even the regulatory agencies (EMA, FDA) and the REC do not know the outcomes of different study arms while a study is carried out

EMA: European Medicines Agency | FDA: Food and Drug Administration

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3 Ethics and research design: randomisation, blinding, placebo control

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- Randomisation in the case of emergency patients, or the randomisation in a study with ill children
- In a double-blind study, neither the treating physician, nor the patient knows what medication the patient gets
- Even the regulatory agencies (EMA, FDA) and the REC do not know the outcomes of different study arms while a study is carried out
- There is some risk with this element of blinding, so safety measures and monitoring of side effects are very important
- Placebo control: patients sometimes do not know whether they receive an active treatment
- Special safety measures are necessary for the protection of the participants

3 Preconditions for placebo control

- Exclusion of severe and persisting harm to the study participants
- Tight measurements of monitoring and control regarding the participant's state of health
- Possibility of disease progression under placebo — acceptability of placebo control in lighter diseases in contrast to graver diseases
- Example: for a patient with progressed cancer, it may be damaging to use a placebo in place of a real treatment

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Lenk C., Duttge G. & Fangerau H. *Placebo. Handbuch Ethik und Recht der Forschung am Menschen (Textbook on Ethics and Law in Research on Humans)*. Springer: Berlin & Heidelberg. 2014; 223–228

3 Preconditions for placebo control

- Normally no placebo control is used where a standard therapy exists
- Exception: the standard therapy induces severe side effects and / or is refused by numerous patients
- Discussion in the context of the Declaration of Helsinki (Article 34, in which cases are placebo controls acceptable for use in patients?)
- Interesting cases in psychological and neurological research

Depression

Multiple sclerosis

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4 Vulnerable patient groups

- **'Vulnerability'**: the special need for protection of different patient groups
- Populations with a **diminished capacity** for decision-making

Patients with dementia

Emergency patients

Vulnerability of COVID-19 patients

Cognitively impaired patients or study participants

Research with children and adolescents

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5 Challenges in the COVID-19 pandemic

Medical

- Generation of new knowledge
- The testing of new interventions
- Direct development of new drugs
- Prevention of adverse outcomes for patients
- Otherwise: triage and emergency measures

Ethical and legal

- Access to patient and treatment data
- Risk assessment for new therapies
- Rapid review of ethical and legal issues
- Protection of vulnerable groups and participants
- Human rights in the case of emergency measures

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5 Patient safety in ongoing studies

- Necessity to carry on other clinical trials, for example in neurology, oncology, internal medicine, *etc.*
- Normally achieved by exclusion of visitors and guests in hospitals and on research wards
- Safety measures like telemedicine, phone calls in conjunction with centre visits, takeover of examinations by general physicians
- Special safety measures for at risk populations in cardiology, oncology and pneumology
- EMA Guidance on the Management of Clinical Trials During the COVID-19 Pandemic (2021)

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5 WHO: ethical standards for research during public health emergencies (2020)

- Research without impeding emergency response efforts
- Maintenance of independent, local ethics review
- All research must have scientific validity and social value
- No suspension of free & informed consent for potential participants
- No routine exclusion of vulnerable groups from research
- Ethical obligation of researchers to share the information

(As soon as it is quality-controlled)

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5 WHO: ethical standards for research during public health emergencies (2020)

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- No routine exclusion of vulnerable groups from research
- Ethical obligation of researchers to share the information
- Rapid access of local populations to safe & effective interventions

6 Conclusions for practice

- Ethical, legal and scientific preconditions for the acceptability of a specific research design
- Previous counselling of clinical trials by *Research Ethics Committees* (RECs) according to national law and international rules and guidelines
- Elements of study design can in some cases contradict the interest of participating patients
- Research with vulnerable groups needs special measures for protection and safety monitoring
- Existing ethical and legal regulations are not suspended in emergency situations like the COVID-19 pandemic

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Literature

Considerations for the Design of Vaccine Efficacy Trials During Public Health Emergencies

Dean N. *et al.*, *Sci Transl Med.* 2019; 11(499): eaat0360

Guidance on the Management of Clinical Trials During the COVID-19 Pandemic

EMA. 2019; For further information, see the external links tab

What Makes Clinical Research Ethical?

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Ethical Standards for Research During Public Health Emergencies

World Health Organisation. 2020; WHO Working Group on Ethics & COVID-19

Thank you!

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