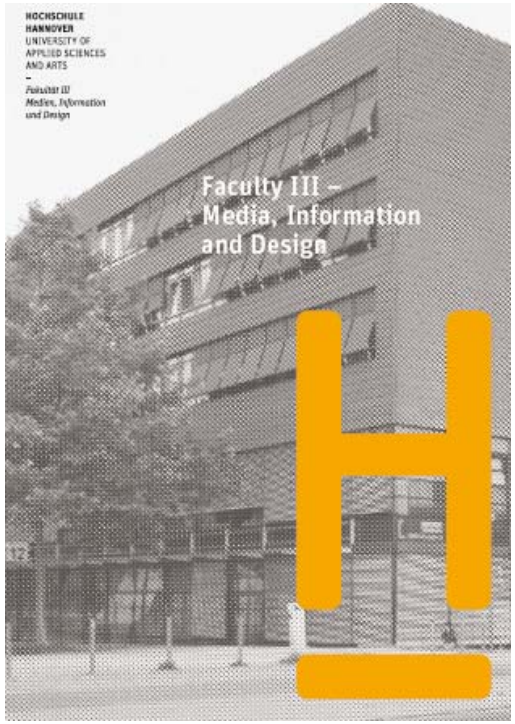
Erasmus Staff Exchange Program



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Agenda item

Good science as basis
for good clinical practice

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Let´s start with some definitions

- Good clinical practice
- Good science – why talking about science when talking about medical care?
- Knowledge pyramide – how do we build our knowledge?

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Knowledge building

- To be considered:

1) Source of knowledge

2) Information flow

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Knowledge building

Look at this – how would you classify them?

- Case study
- Systematic review
- Clinical guideline
- Controlled research trial
- Randomized controlled research trial etc.

EbM

Approach: information flow

- EbM (Evidence based Medicine)
  - ”Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”. *

- [*Sackett et al:Evidence based medicine: what it is and what it isn't, BMJ 312 : 71 (Published 13 January 1996]

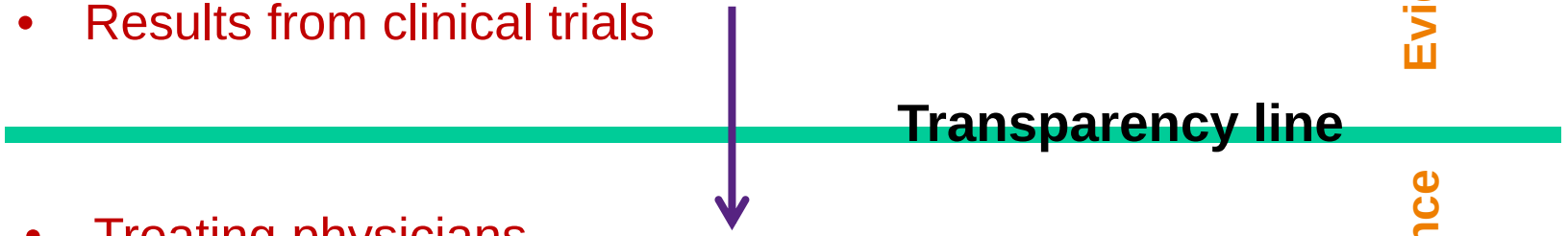
EbM

Transfer of information

- From research to practice

Any information related to medical questions, e.g.

- Results from clinical trials



- Treating physicians
- Hospitals and medical institutions
- Agencies / health authorities
- Patients

Evidence production

Use of evidence

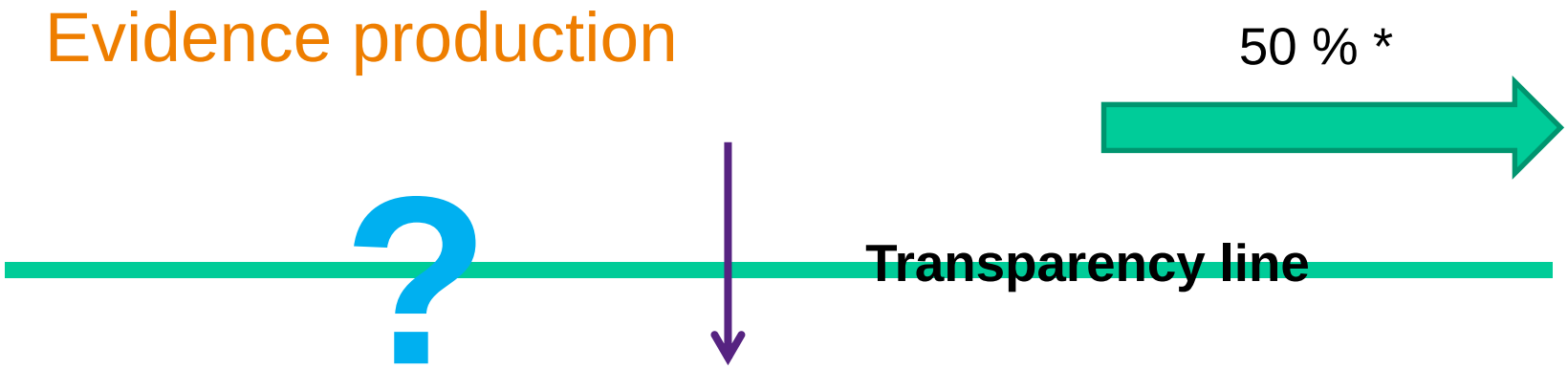
EbM

Consequence:
2 main roadblocks

- Loss of information – information does not go through to recipient/user
  - Not published
  - Miss-interpreted, not understood?
- Information received by recipient/user does not reflect reality (transparency issue!)

EbM

Loss of information



[*Antes, G.: Guest lecture at University of Applied Sciences and Arts, Hannover, 6th June, 2011]

Obsolescence of medical knowledge (half-live period 4 years)

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Why are clinical trials conducted?

- Trials are performed
  - On new medicinal products
  - On medical devices
  - On new products with biological origins (biotechnology)
  - On new surgical, medical or physiotherapeutic techniques
- To thoroughly investigate them before they are released for general use !

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Example:

Before *clinical trials (for drugs)* in humans are performed

- Extensive testing in animals is indicated
  - toxicity
- Extrapolation of results in animal experiments to predict what will happen in man

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Determination of efficacy and safety

- Through clinical trials undertaken in human subjects

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Clinical trials are complex with regard

- To their design
- To regulations

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Therefore standards are needed which

- Clearly define the way in which clinical studies have to be undertaken

- Is there a link between Good Science and GCP?

… any idea? … some example areas follow

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Good Science

Risks and benefits

For each trial in humans there are risks and benefits for the

- Company / sponsor
- Investigator
- Patient/subject

- Topics of concern:
  e. g. medical care, responsibility of medical person

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Good Science

Number of sites?

Single centre	Multicentre
- one observer	- many observers
- minimises variability	- increase variability

Topics of concern:
e.g. study protocol, informed consent, documentation, adverse event reporting etc.

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Good Science

Randomization, stratification and blinding (drug trials)

All of these design strategies are used in order to avoid or minimise bias (systematic errors)!

Topics of concern (mainly for drug trials, but …): handling of trial medication, keeping the blind, being prepared for a medical emergency case in which the given product must be known!

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Good Science

Statistical considerations

Exploratory trials

- Are not intended to examine clinical effects – needed for decision making/to design the (clinical) development strategy

Confirmatory trials

- An adequately controlled trial
- Where hypotheses are stated in advance and
- So called pivotal trials – confirmatory trials!

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There is a long history to the development of the legislation and guidelines governing clinical research

- Summary of major events

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History

1947 – Nuremberg trials

- E.g. experimentation on prisoners of war in Nazi Concentration Camps
- As a result a document called «Nuremberg Code» was drawn up
  - Responsibility of a physician for the welfare of human research subjects
  - Need for informed consent from anyone used as human research subject

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History

Two more incidents which highlighted the need for much stricter controls

- E.g. Syphillis trial (US) used black men to study the progress of the disease
  - No treatment for their condition, even though effective treatments became available during the trial period
  - Went on from 1932 up until 1972 (surprisingly recent)
- Thalidomide tragedy of the 1960s
  - Experimental drug used a sleeping aid
  - When given to pregnant women it resulted in birth defects in the babies

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DoH

DoH – Declaration of Helsinki

- In 1964 produced by the World Medical Assembly
  - Is based on Nuremberg Code
  - Ethical standard for research on human standards
  - Most clinical trial protocol contain a statement that the trial will be conducted in accordance with the Declaration of Helsinki
  - Various updates , subject of some controversy, last version from 2008

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«European» GCP

- It wasn´t until the 1980s that GCP guidelines were produced in some countries of Europe
- Most of them did not carry force of law
- Majority of these have been superseded by the EU Directives in 2001 and 2005

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ICH

ICH – International Conference on Harmonization

- In the 1990s founded by regulatory and industry representatives from the EU, the US and Japan
  - Aims: to develop a standard set of requirements for development and registration of medicines worldwide
  - To reduce subject exposure to experimental drugs
  - To reduce development time and costs
- Several series of guidelines covering many aspects of drug development

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Summary

In summary you should be aware of all the following documents which may apply when conducting research using human subjects:

- Declaration of Helsinki
- CFR 21
- ICH GCP
- your local legislation

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Agenda item

Informed Consent
How to prepare?
How to conduct?

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We will look at...

- Regulations / medical law
- Process of obtaining informed consent and documentation
- Problem areas

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Regulations

- ICH GCP 4.8.10
- CFR Part 50, Subpart B
- [EU Directive Art. 3 - 5 &
  Guidance note ENTR/CT2; 6.1.2.5]
- Declaration of Helsinki
- Local medical law(s)

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Obtaining IC
What is it and why do we need it?

- Main legal purpose is to protect physicians against criminal charges of assault and battery!
- The primary reason is to protect rights & well-being of subjects!
  - Subjects accept or refuse participation in an ethically approved experiment that potentially carries both unknown benefits and risks
  - Subject is informed of all relevant aspects of trial
  - IC is documented by signed + personally dated IC consent form

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When is IC obtained?

- Before any trial-related activity
- Continuing throughout trial!!!

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Elements of IC documentation

- *ICH GCP 4.8.10*

1. Trial involves research
2. Purpose of trial
3. Treatments; probability for random assignment
4. Trial procedures
5. Subject's responsibilities
6. Experimental aspects

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Elements of IC documentation [cont]

7. Reasonable foreseeable risks and inconveniences
8. Reasonable expected benefits; if none, say so
9. Alternative procedures / treatments
10. Compensation
11. Anticipated prorated payment
12. Anticipated expenses
13. Subject participation is voluntary throughout

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Elements of IC documentation [cont]

14. Monitor, auditors, inspectors: access to notes
15. Confidentiality (anonymized data, direct access)
16. Pledge to inform subject of new information
17. Contacts: information, trial-related injury
18. Foreseeable circumstances of termination
19. Duration of subject's participation
20. Approximate no. of subjects

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The 21st element(s)

- Permission to contact GP/family doctor (ICH GCP 4.3.3)
- Data protection / privacy issues
  - ✓EU: Data Protection Directive 95/46/EC
  - ✓US: HIPAA *

[* HIPAA = **Health Insurance Portability and Accountability Act, 1996]**

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Verbal & written information

- Adequate information needs to be provided to each subject .....
  - Verbal discussion
  - Written patient information sheet
  - Language as non-technical as practical
  - Clear and well written – saves delays

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Consent Form

- Consent form should be signed and “personally dated“ by the subject and by the person who conducted the informed consent discussion
- Investigator (original) and subject (copy)
- Witness only needed if subject cannot read
- Subject to local laws

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Who obtains consent?

- Declaration of Helsinki required a physician to obtain consent (no longer – since 2008)
- ICH GCP allows investigator to delegate this process, e.g. to study coordinator / study nurse
- Compromise:

  Doctor gives information, nurse obtains signature?

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Consent problem areas

- Can consent be complete or full?
- Ethical view: it can only be sincere
  - True, comprehensible information
  - To understand purpose and implications of participation

The simpler and clearer it is, the more complete the informed consent will be!

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When is consent legally valid?

- Three pivotal elements
  - Does the person providing consent have legal capacity?
  - Was consent given voluntarily?
  - Was consent based on sufficient prior information?
- Let‘s look at capacity, voluntariness and information in more detail!

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Legal capacity

- Respect for individual autonomy
  - Any decision must be respected
    - A patient is entitled to make a decision based on their own value system
  - Having capacity is not the same as making a decision that others would perceive as reasonable, rational or sensible

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Legal capacity [cont.]

- Capacity is not an <u>all or none</u> faculty
  - The more a person must comprehend before making a decision the less likely they will have the necessary capacity to decide!
  - Different levels of capacity are required to make different decisions, depending on their complexity and gravity
  - Legally seen it‘s the doctors‘ responsibility to ensure that the information provided is intelligible and relevant to that subje

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Legal capacity [cont.]

- Capacity
  - Subject-centred barriers, e.g.
    - Age
    - Level of education
    - Affected temporarily by factors such as confusion, panic, fatigue, pain, illness and medication etc.
  - … diminish subject's capacity to understand, evaluate and decide, so undermining their ability to consent!

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Voluntariness

- Ultimate expression of autonomy is freedom to choose
  - Valid consent is vitiated if it is obtained through
    - Coercion
    - Threats
    - Fear
    - Force
    - Misrepresentation
    - Deception

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Voluntariness [cont.]

- Could be influenced ...
  - A patient may feel obliged to help his doctor
  - Through payments to patients
    - Generally undesirable
    - Legally only invalidate a volunteer's consent if obviously disproportionate
  - Dependant relationship with the researcher
    - Student – teacher; nurse – medical doctor; family members of researcher

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Voluntariness [cont.]

- Dependant relationship ...
  - Informed consent should be obtained by a
    - Well-informed physician
    - Who is not engaged in the investigation
    - Who is completely independent of this relationship

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Information

- Both intentions, to provide treatment and to perform research, have explicitly to be disclosed
- Any information provided is only to be judged by the scientific knowledge existing at the time of information
- Process-centred barriers, e.g.
  - Information provided is not clear
    - No ideal timing of discussion about clinical trial
    - Not enough time allocated for subjects to ask questions
    - Not ample time allocated to make final decision
    - Readability / content / quantity

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Consent problem areas

- Legal representatives – who are they?

  = country-specific; term „legally authorized representative“ is not applicable in all countries

- What is „ample time“ to decide?
- Vulnerable subjects (illiterate, mentally impaired, unconscious)

  ➢ Specify details of how “consent” will be obtained in protocol

Local laws must always be followed!

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Consent problem areas [cont.]

- Signature of minors
  - Declaration of Helsinki
    - Informed consent from legally authorised representative in accordance with national law
    - Assent must also be obtained if possible
    - (only included if necessary)

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Consent problem areas [cont.]

- Signature of minors
  - ICH GCP
    - Subject's legally acceptable representative
    - Inform subject to extent compatible with their understanding and, if capable, subject also signs and dates consent form

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Summary

- One-size-fits-all approach (if still current) must be reconsidered
- Subject's information needs must be addressed
- Subject must be supported through every stage of the informed consent process

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Summary [cont.]

"We must move beyond the culture of compliance (with regulatory requirements alone), to move to a culture of conscience and responsibility."

Greg Koski

[Office of Human Research Protections (OHRP)]