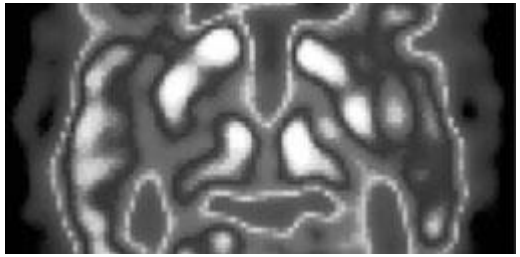
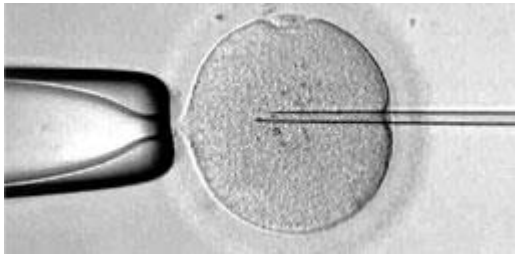
ETHICAL ASPECTS OF MEDICAL RESEARCH INVOLVING HUMAN BEINGS

ds Eric Koster MA

Barcelona, June 2016

MEDICAL RESEARCH INVOLVING HUMAN BEINGS: AN ATTEMPT AT A DEFINITION





- 'The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments)…'

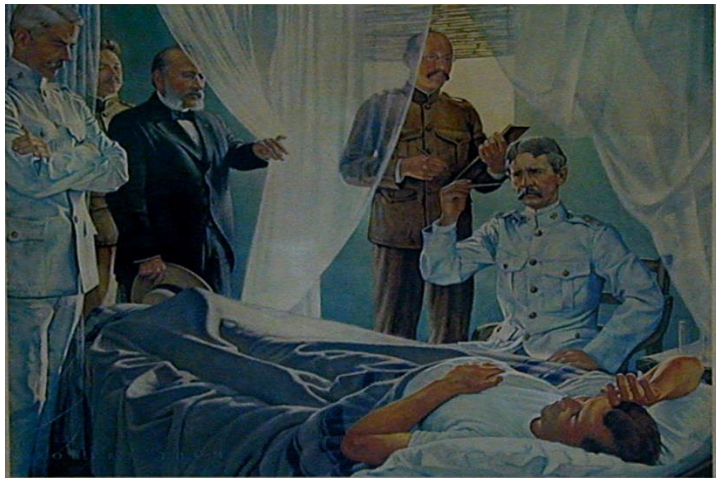
  (Declaration of Helsinki, General Principles art. 6)

- This type of research always subjects human beings to specific treatments or dictates rules of conduct to them

  (Dutch Law on Medical Research Involving Human Beings')

The need for assessment of medical research involving human beings

- **1900: Walter Reed and the transmission of yellow fever:**
  - taking risks which nowadays would be considered unacceptable

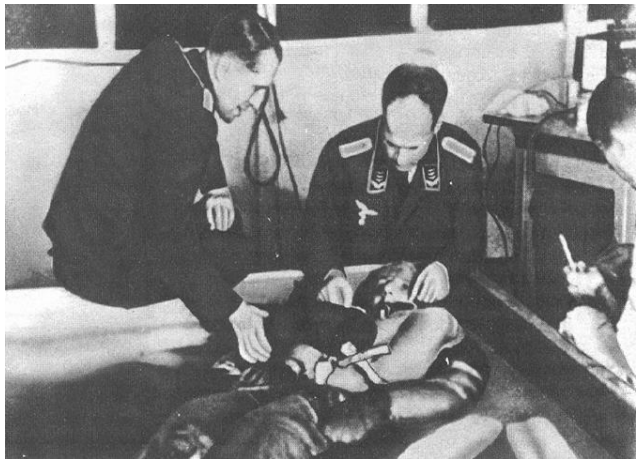


- **1932 – 1972: The Tuskegee experiment:**
  - no informed consent
  - withholding of available treatment
  - taking advantage of a vulnerable population
  - causing severe damage and even death

THE NEED FOR ASSESSMENT OF MEDICAL RESEARCH INVOLVING HUMAN BEINGS

WW II: Nazi Experiments on Concentration Camp inmates and prisoners of war:

In 1942 SS-physicians start medical experiments on POW's in Dachau to find the best way to rewarm pilots who have ditched in ice-cold seawater.
Of the 300 POW's involved about 90 die



Cold water immersion experiment on a POW wearing an experimental Luftwaffe garment

In the concentration-camp Auschwitz SS-physician Joseph Mengele carries out genetic experiments on 1500 twins he personally selects on the 'Rampe'
Only 200 children survive

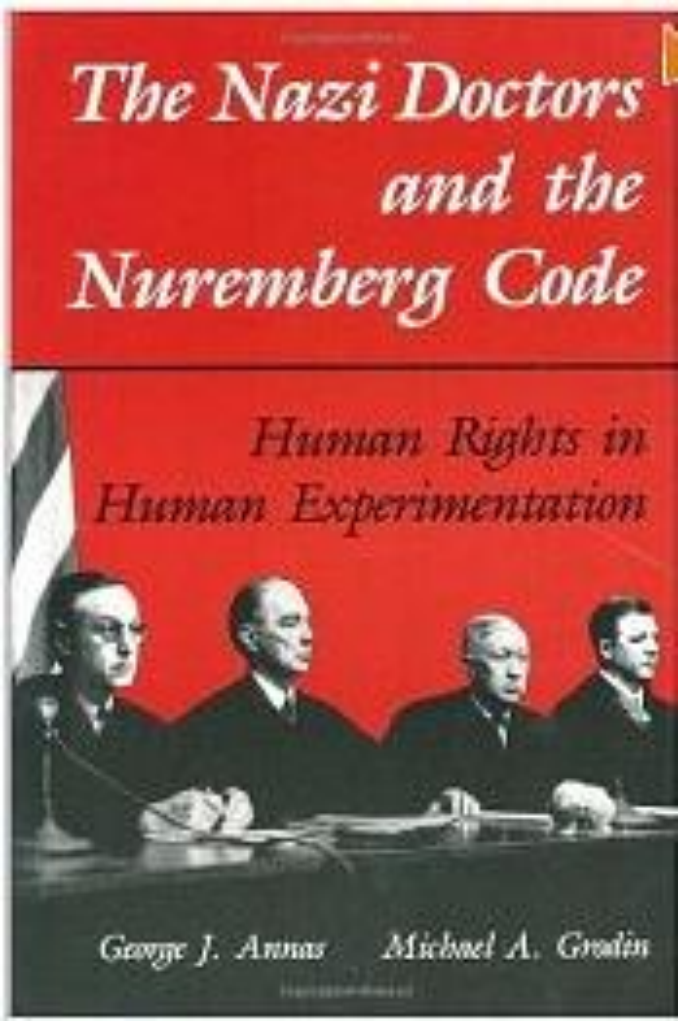
Surviving twins on the day of their liberation by the Red Army

EURORDIS
Rare Diseases Europe

The Nuremberg Code (1946)

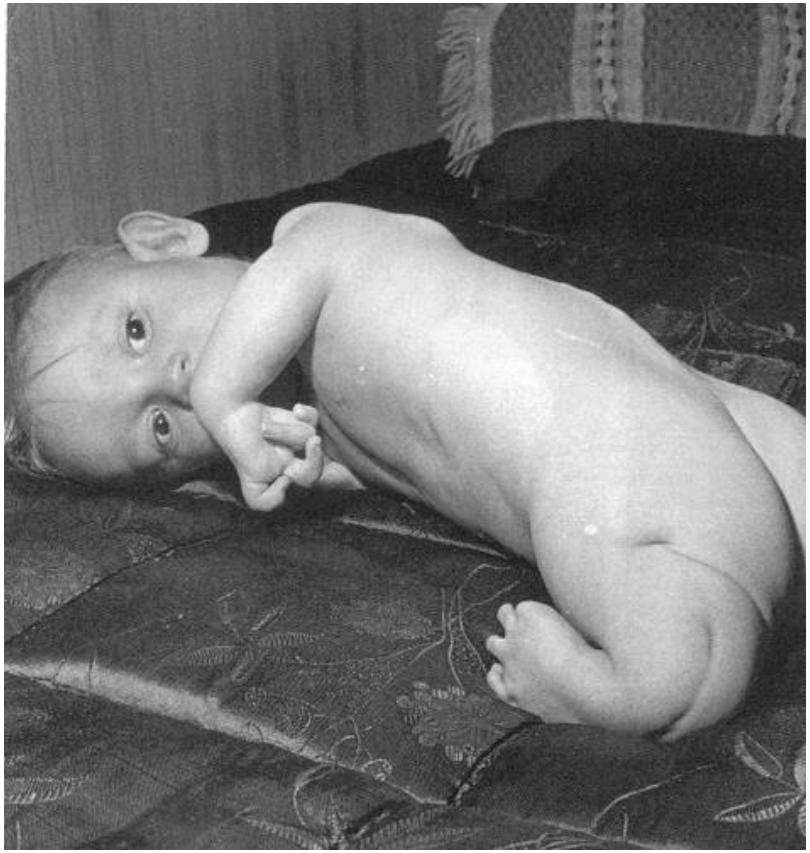
Art. 1:

‘**The voluntary consent of the human subject is absolutely essential**. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.’



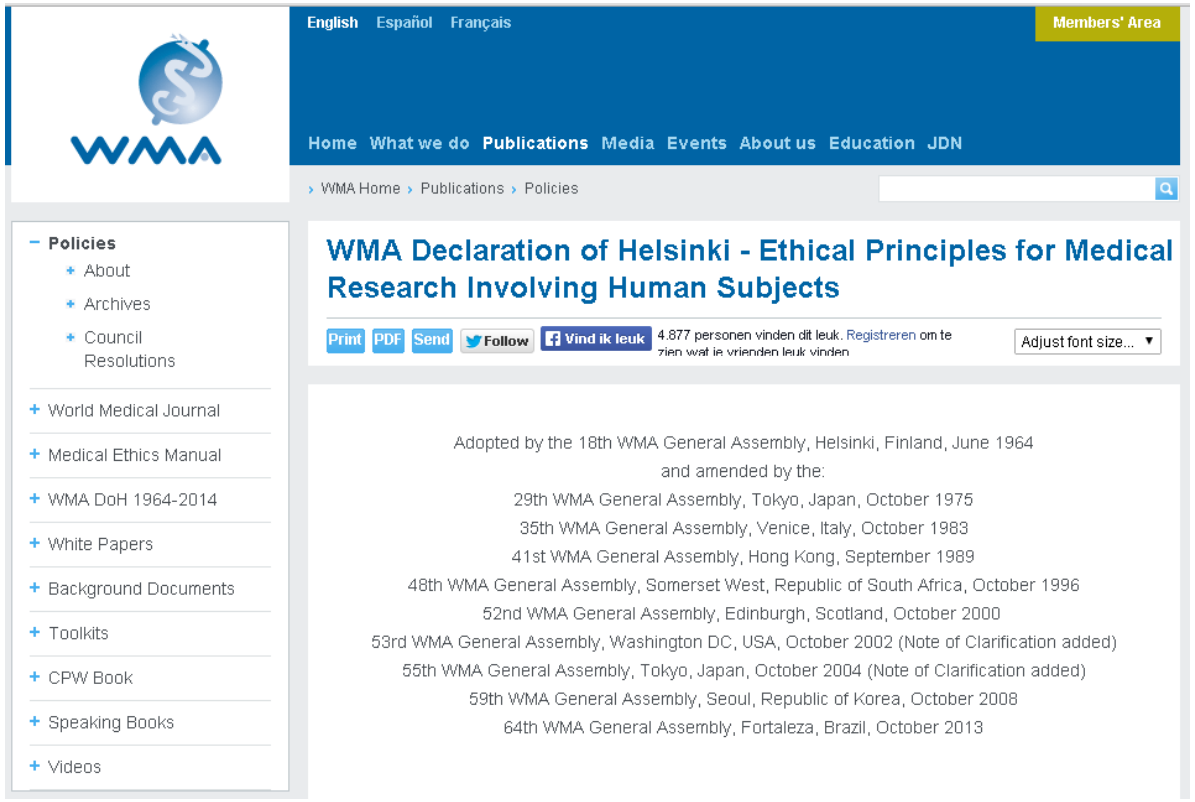
THE 'SOFTENON-SCANDAL'

- In 1961 public opinion around the world is shocked by the Thalidomide-scandal. 2000 children die, 10.000 are seriously disfigured.
- Authorities are demanded to take action and make regulatory arrangements to oversee the testing of medicines



THE HELSINKI DECLARATION (1964)

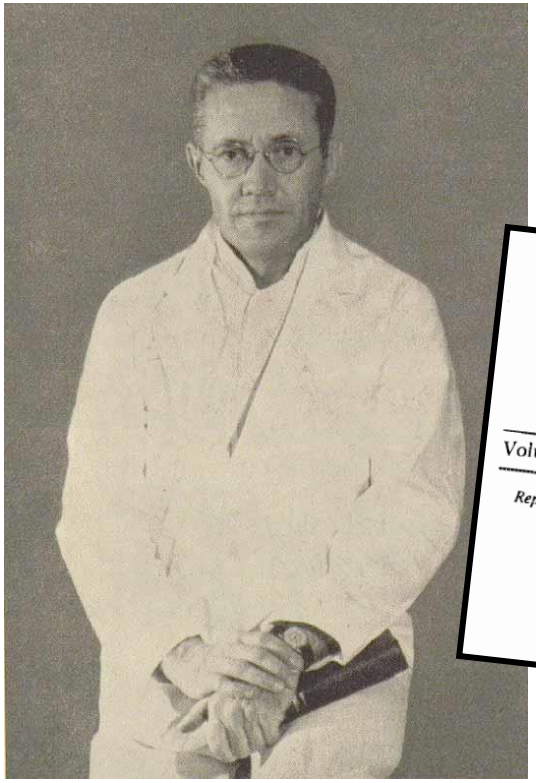
- A set of 'Ethical principles for Medical Research Involving Human Subjects' adopted by the World Medical Association
- Widely regarded as the cornerstone document of human research ethics
- Constantly updated



EURORDIS Rare Diseases Europe

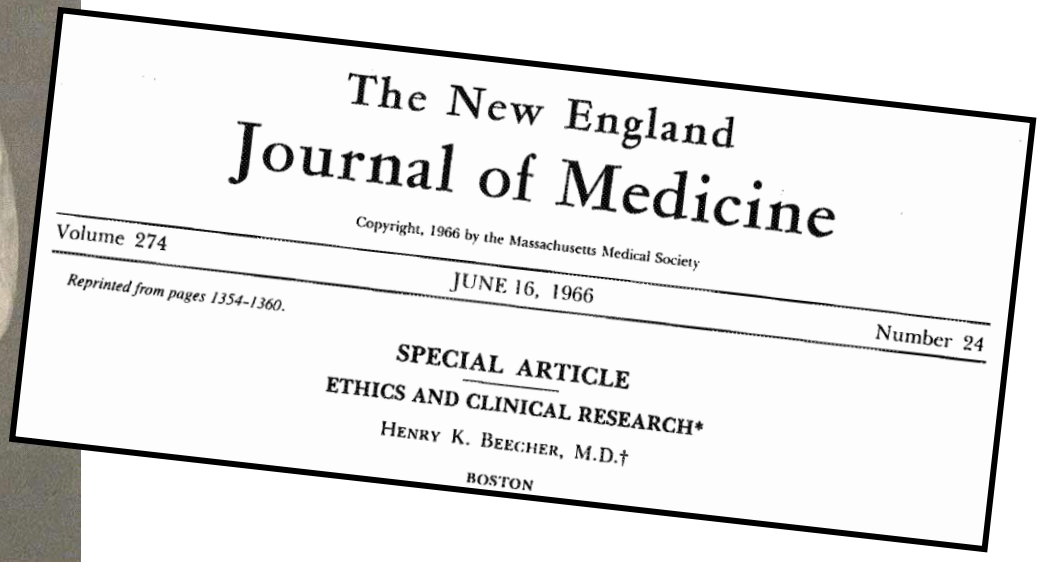
SELFREGULATION FAILS

- The Nuremberg Code and the Declaration of Helsinki lead to the development of standards, protocols and the instrument of the Randomised Controlled Trial (RCT)
- Self-regulation is not always succesful



Henry Beecher: 'Ethics and Clinical Research'

New England Journal of Medicine, 1966



The New England
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SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

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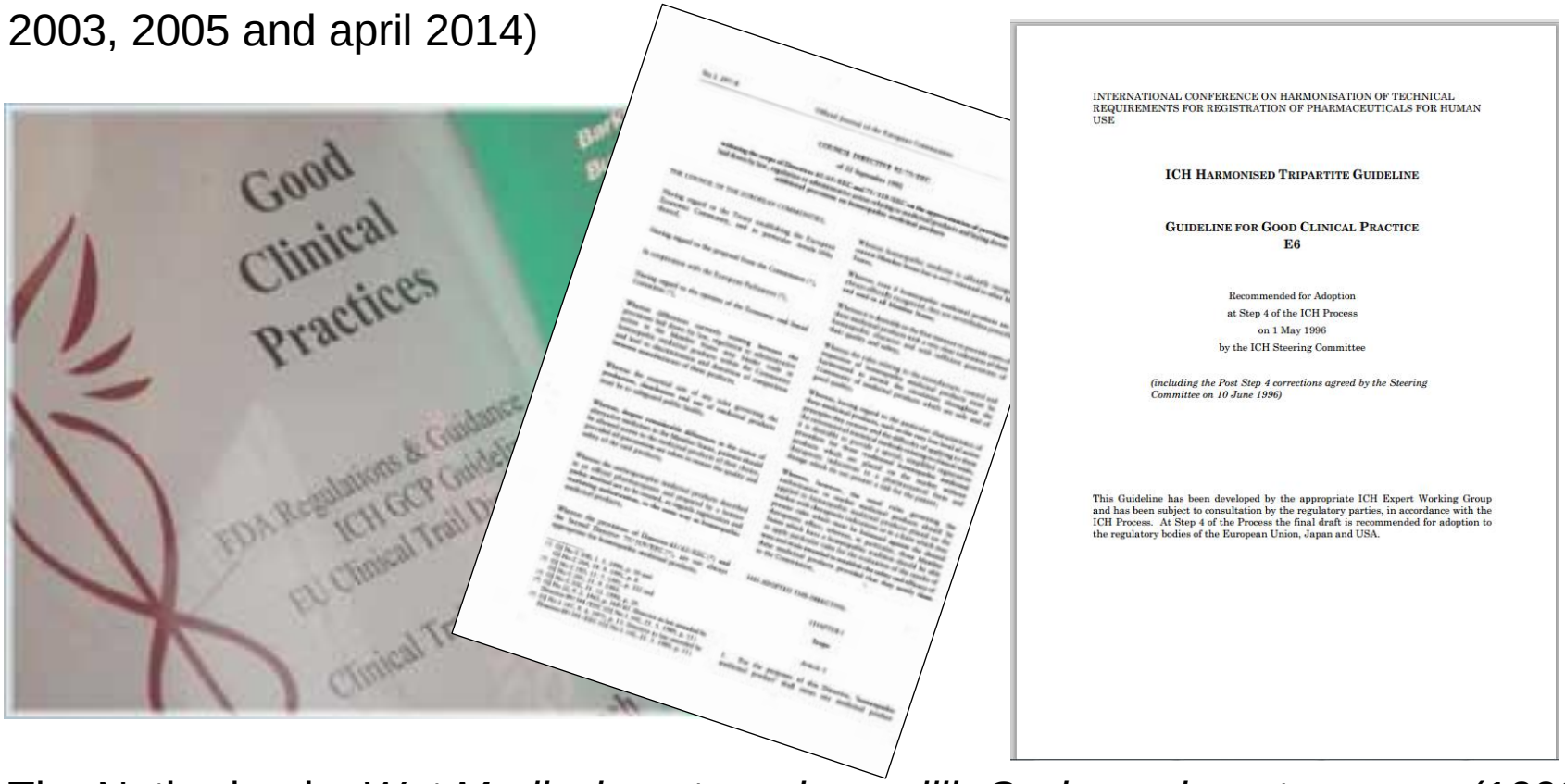
EURORDIS
Rare Diseases Europe

LAWS AND REGULATIONS

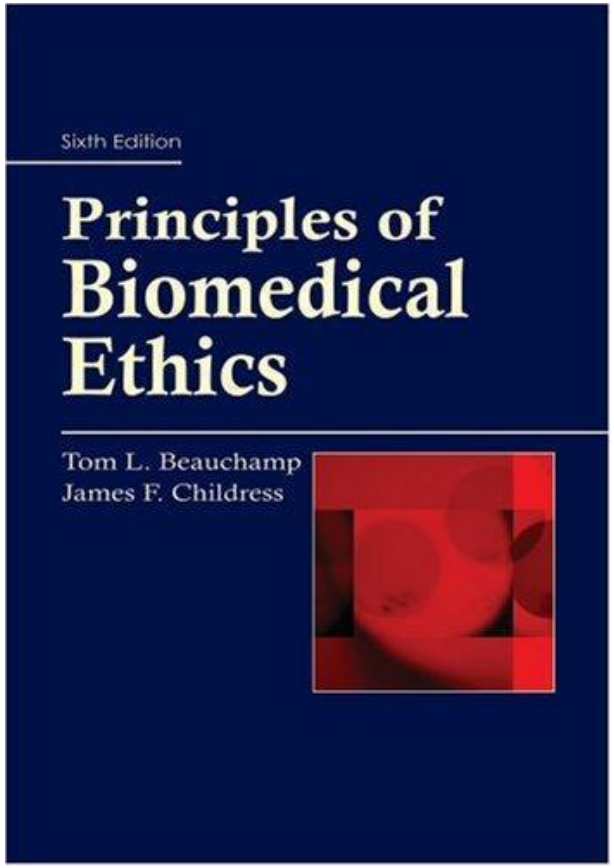
The Directive ‘Good Clinical Practice’ (1996) and the European Directives Clinical Trials on Medicinal Products for Human Use (2001, 2003, 2005 and april 2014)



The Netherlands: *Wet Medisch-wetenschappelijk Onderzoek met mensen* (1998)

The four guiding principles in western medical ethics ('Georgetown Mantra')

- **Autonomy:**
  - to respect the autonomy of the participant or of the participant's representative
- **Beneficence:**
  - to act always in the best interest of the participant
- **Non-maleficence:**
  - to do as little harm as possible to the participant
- **Justice:**
  - to act fairly by all men

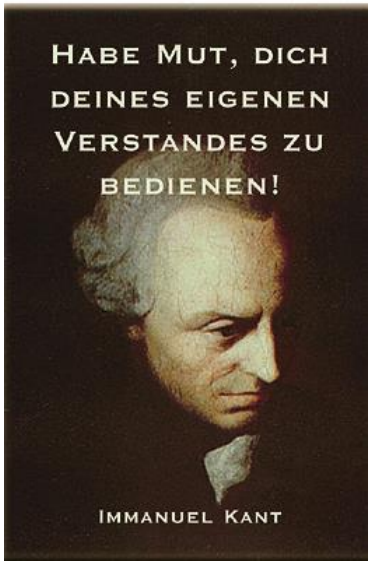


The four guiding priciples in western medical ethics
Origin

- **The principles of Beneficence and Non Maleficence have their roots in the Hippocratic tradition. They lead to questions like:**
  - who benefits from the experiment?
  - what is the risk/benefit ratio?

'In dubio abstine!
Primum non nocere!'

- **Respect for the autonomy of the participants has its roots in the tradition of the Enlightenment. It involves:**
  - the absence of force or coercion and
  - the obtaining of informed consent



'Have the courage to make up your own mind!'

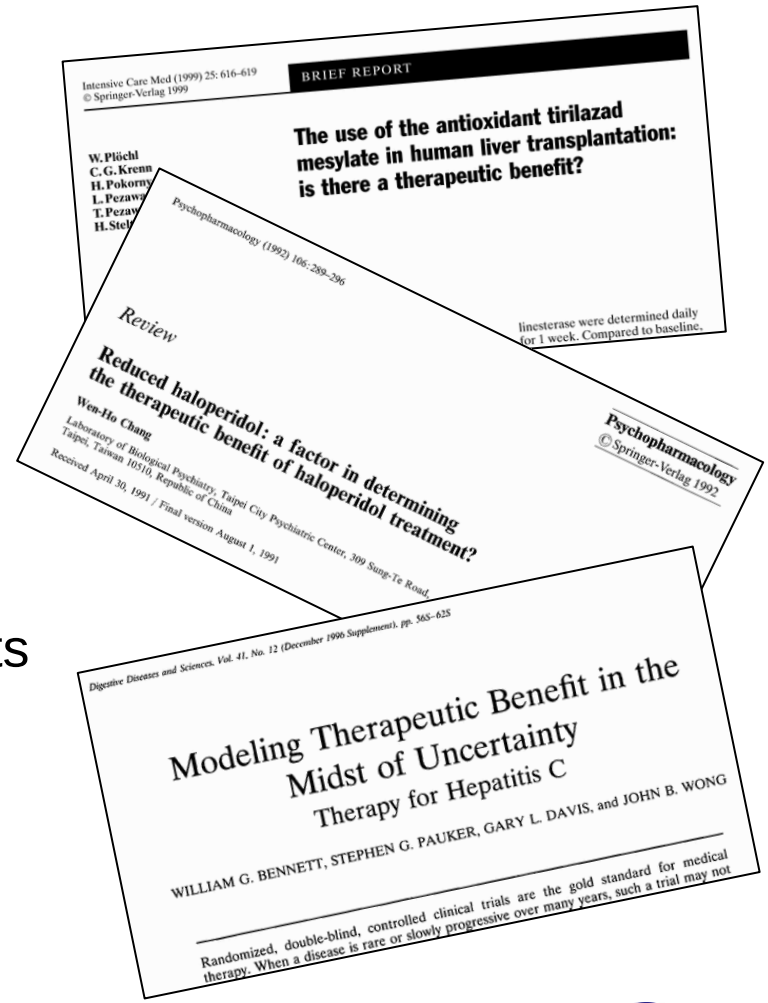
A CLOSER LOOK: BENEFICENCE THERAPEUTIC EFFECT?

- **Non-Therapeutic experiment:**
  - No therapeutic effect on participants is intended

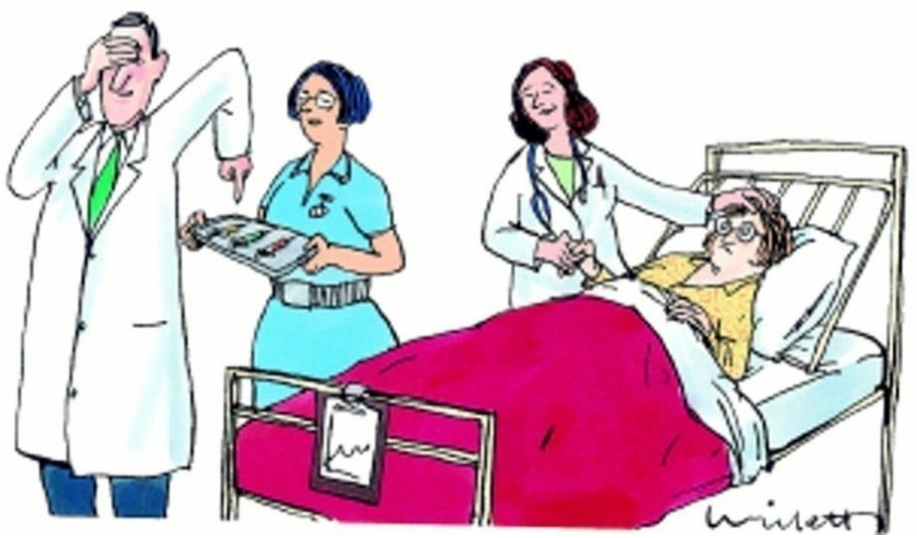
    (f.e. Phase I trials)

- **Therapeutic experiment:**
  - Aims at therapeutic effect on participants

    (f.e. Phase III trials - but what about the controlgroup in a placebo-controlled Phase III trial?)



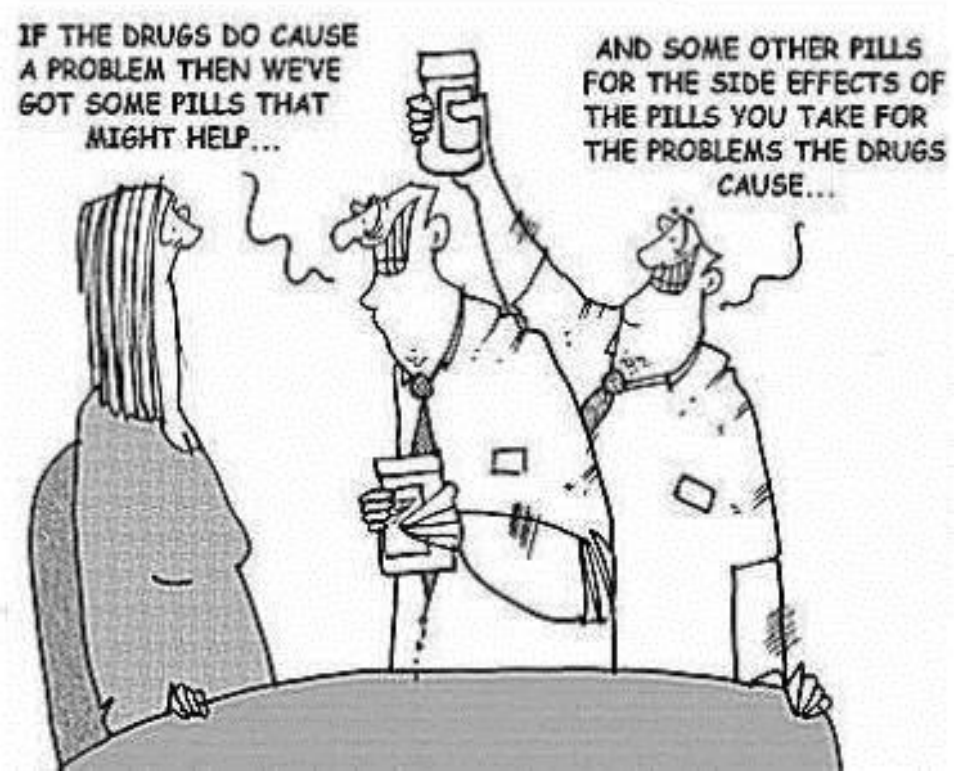
A closer look: Maleficence
Unsound research



- Methodically unsound: design unfit to test the hypothesis
- Dangerous: causes damage to the participants
- No qualified personnel available
- Logistics and equipment of the studycentre insufficient
- Preliminary investigations insufficient (laboratory research, research on animals, study of literature)

A CLOSER LOOK: MALEFICENCE RISKS

- **Physical:**
  - side-effects
  - interference with other treatments
- **Psychological:**
  - depression
  - suicide
- **Social:**
  - genetic information
  - stigmatisation
- **Economic:**
  - hospitalisation
  - insurance problems



A closer look: Maleficence Burdens and Inconveniences

- **Investment of time:**
  - how many hours must a participant invest in the trial?
  - what is the length of the inclusion period?
- **Hospital visits:**
  - how many?
  - out-clinic or hospitalisation?
- **Rules of conduct:**
  - influence on daily rhythm and/or diet
  - medication
  - keeping diaries etcetera
- **Choices:**
  - do paticipants see themselves confronted with difficult choices?

A closer look: Autonomy
Informed consent on the basis of full information

- The aim of the experiment
- The reason why the participant is asked to participate
- The importance of the experiment
- The obligations of the participant
- The burden that is laid on the participant (and the inconveniences)
- The risks involved for the participant
- Any measures that are taken to contain those risks
- Compensation in money (if there is any)
- Insurance
- The confidentiality of collected data

A closer look: Autonomy
Informed consent on the basis of full information

- The right to refuse to be included without repercussions on subject treatment
- The right to withdraw at any time (without giving an explanation) without repercussions on participant treatment
- Identity of the investigator and information on how to reach her/him
- Opportunity to ask questions and consult an independent physician
- The opportunity to consult family, acquaintances or one's own General Practitioner

A closer look: Autonomy
Extra demands in case participants are under age or unable to express their wishes

- All participants (or the group of patients they belong to as a whole) must benefit directly from the experiment
- Burden and risks must be minimised
- Prior to inclusion a procedure must be agreed upon to determine expressions of refusal from the side of the participants
- Subject must be represented by a next of kin who gives written consent

A closer look: Justice

- Fair selection of participants (male/female; age-groups)
- No exploitation of vulnerable populations (cf. Tuskegee, underdeveloped countries)

- Research Ethics Committees only have the right to make comments on the soundness and reasonability of a study-protocol. REC's are not allowed to make comments on the desirability of any specific trial

To Conclude

- The instrument of the Randomised Clinical Trials and the assessment of trial protocols by Research Ethics Committees guarantee *up to a certain extent* that medical research involving human beings is conducted in a sound, careful and responsible way
- *up to a certain extent*:
  - Assessment will always remain necessary. As long as it makes sense to ask the question ‘This is our practice, but is it a good practice?’ there will be reason for ethical debate...
- As the following example makes clear:

THE CONSTANT NEED FOR ASSESSMENT OF MEDICAL RESEARCH INVOLVING HUMAN BEINGS

2008: The Pro Patria Probiotics trial in Utrecht, The Netherlands
Devastating judgment by the Health Care Inspectorate:

ALMOST EVERYTHING WENT WRONG!

inadequate study-design; investigators not experienced enough; trial not conducted conform GCP; inadequate monitoring; inadequate information; in some cases no informed consent; Data Safety Monitoring Committee not satisfactorily informed: consequently a late discovery of significant higher mortality in the studygroup as compared to the controlgroup; etcetera