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Fundació Doctor Robert
UAB

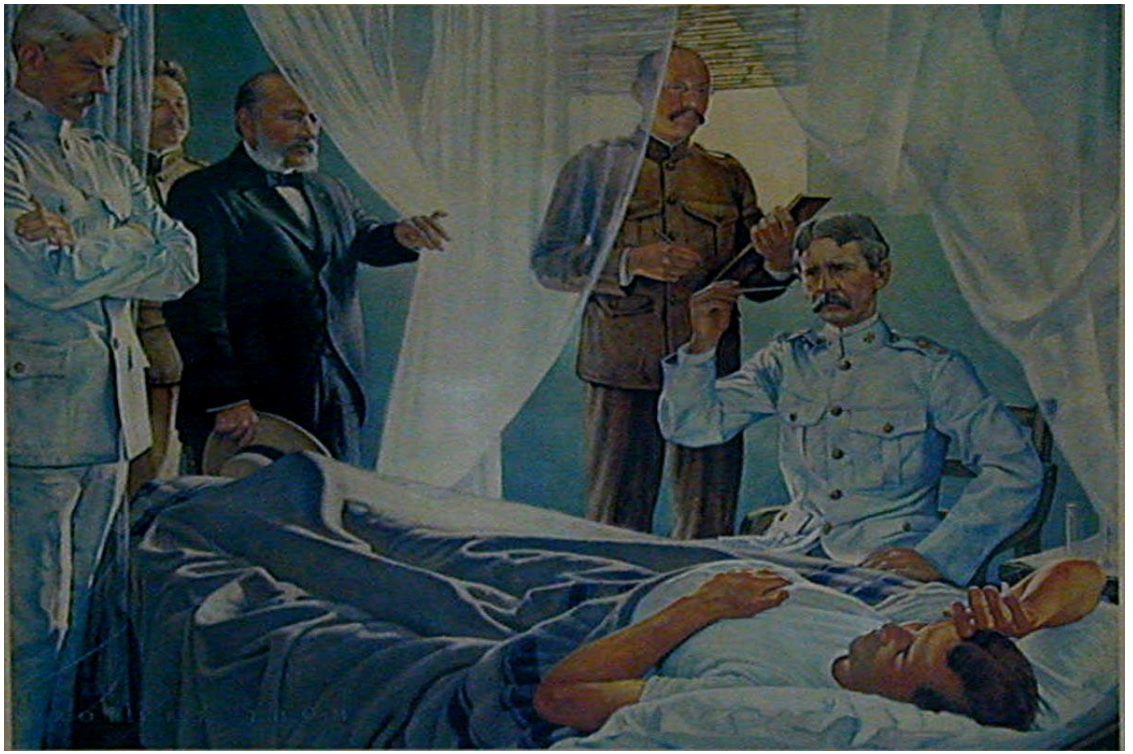
# ETHICAL ASPECTS OF MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

**ds Eric Koster MA**

# The need for assessment of medical research involving human subjects (1)

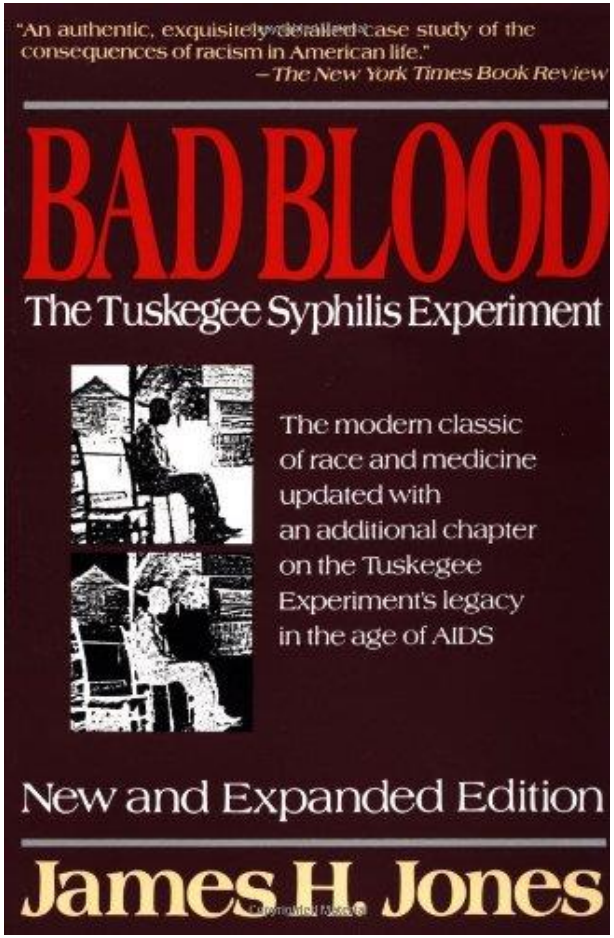
## 1900: Walter Reed and the transmission of yellow fever:

taking risks which nowadays would be considered unacceptable



# The need for assessment of medical research involving human subjects (2)

## 1932 – 1972: The Tuskegee experiment:




no informed consent;

withholding of available treatment;

taking advantage of a vulnerable population

damage: 28 patients dead of syphilis

100 patients dead of complications

40 wives infected

17 children born with congenital syphilis

# The need for assessment of medical research involving human subjects (3)

**2008: The Pro Patria Probiotics trial in Utrecht, The Netherlands:**

**Devastating judgment by the Health Care Inspectorate:**

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 control group; etcetera

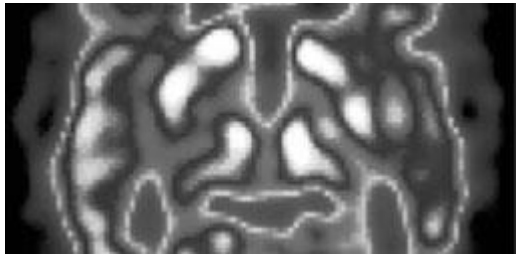
# The need for assessment of medical research involving human subjects (4)

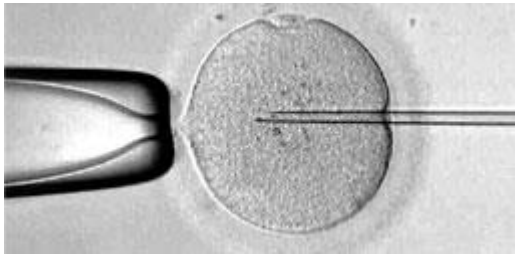
**2015: Randomised Clinical Trials using placebo in underdeveloped countries:**

withholding standard treatment, which would be unacceptable in the western world (and thus taking advantage of a vulnerable population?)

study medication not available after closing of study


# CLINICAL RESEARCH: 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). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.'(Declaration of Helsinki, 6)

- This type of research **always subjects human beings to specific treatments or dictates rules of conduct to them** (WMO definition: Dutch 'Law on Medical research involving human subjects')



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# Four periods in the history of research (1): The 'Philosophical ' Era

Doctrine dictates the development of medicine

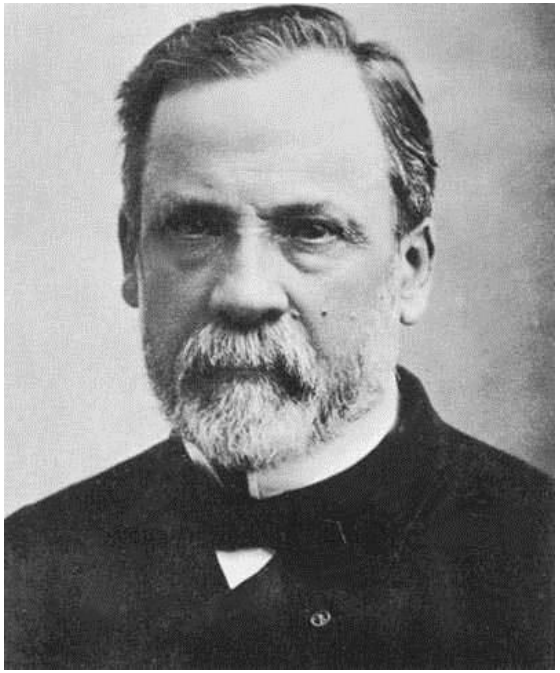
Clinical practice is of less importance


**Galen:**
**'Hmm, bright red...**
**dark red...how come?'**

# Four periods in the history of research (2): The 'Romantic' Era

Great achievements and discoveries by geniuses who dare to undertake experiments

**Louis Pasteur**



**Ignaz Semmelweis**

**Maria Skłodowska-Curie**

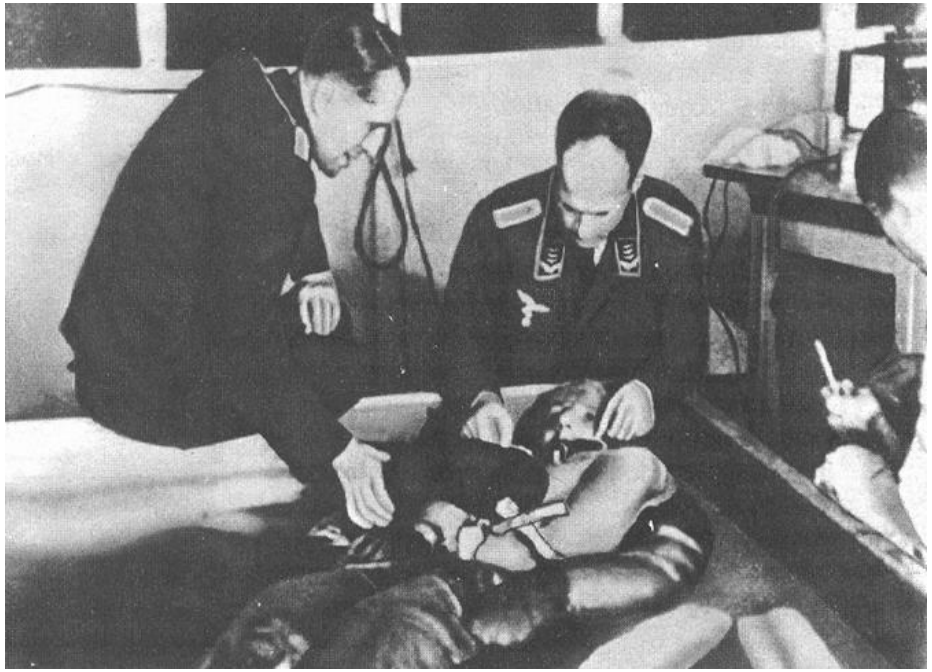
# Four periods in the history of research (3): The Era of 'Natural Science'

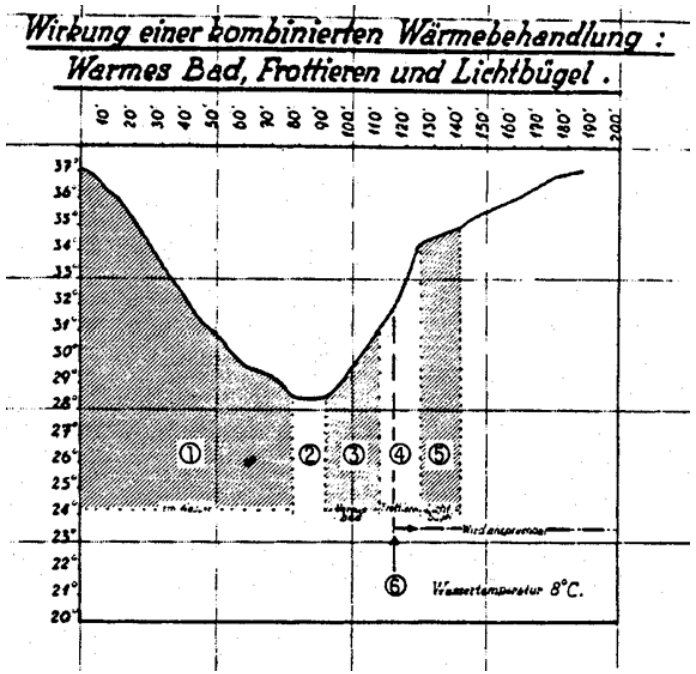
Experiments and observations lead to generalisations and steps forward in medical science

These experiments unfortunately are sometimes conducted in a most irresponsible and unethical way (Mengele, Tuskegee)

Eva Kor pointing out herself, holding hands with her twin-sister Miriam, on the day the Red Army liberated Auschwitz

# Four periods in the history of research (3): The Era of 'Natural Science'






In 1942 SS-physicians started medical experiments on inmates of the concentration-camp Dachau to find out the best way to rewarm pilots who had baled out and fallen into ice-cold seawater. Russian prisoners of war were put into a basin that was filled with icewater. After a while they were taken out again and different types of rewarming were tested. Of the 300 POW's involved about 90 died. The results of te tests are still being used...



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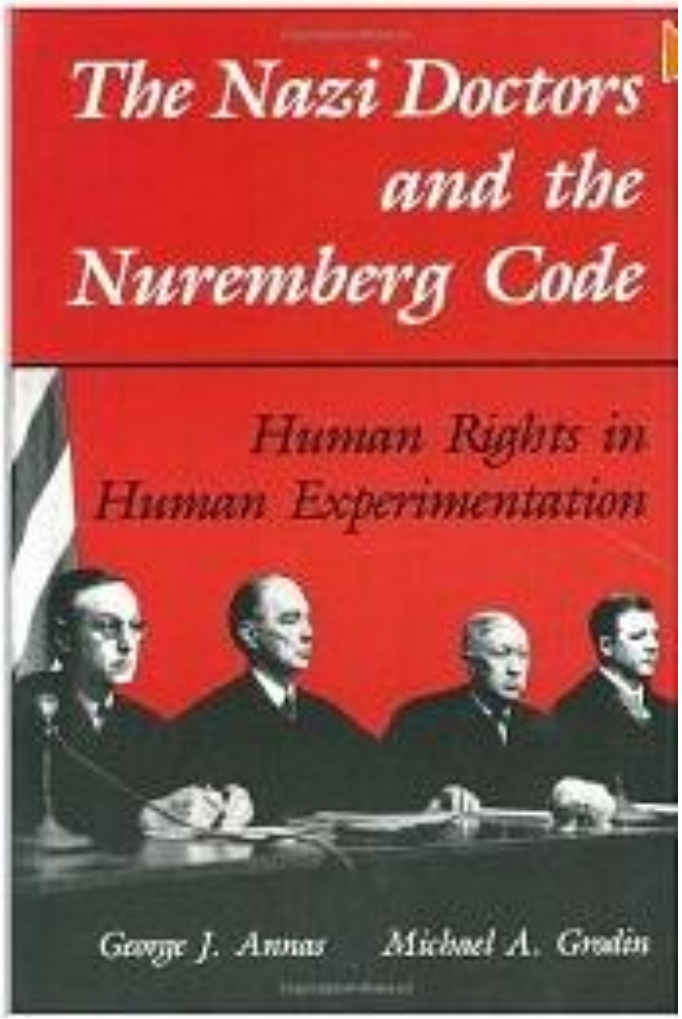
# RESEARCH - ETHICS

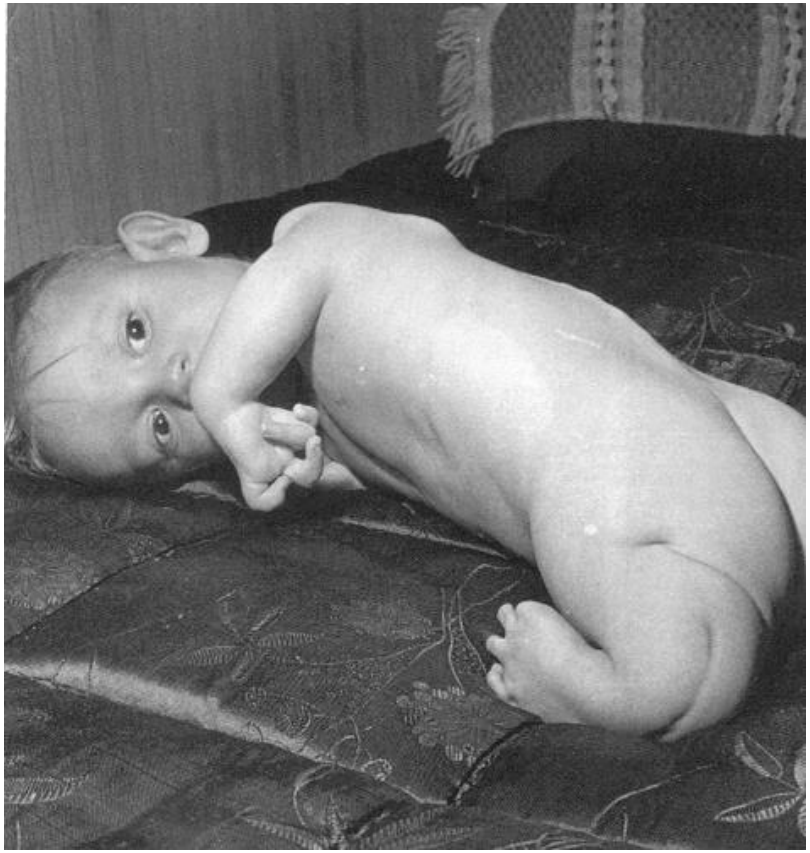
- **THE NUREMBERG CODE (1946), ART. 1:**

‘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.’



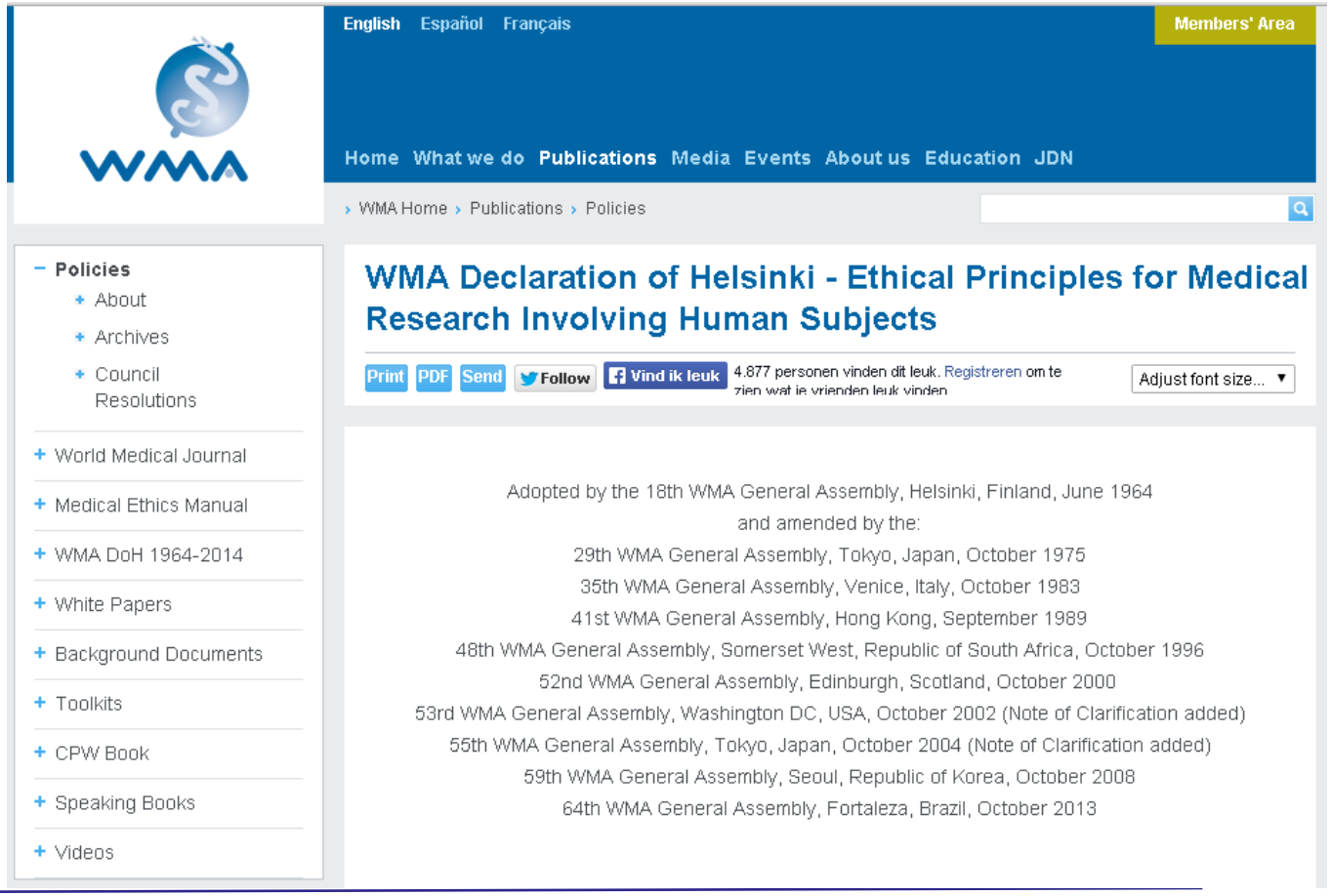
# THE 'SOFTENON-SCANDAL'

- In 1961 public opinion araound 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 drugs

# THE HELSINKI DECLARATION (1964)

**The Declaration of Helsinki** is a set of ethical principles regarding human experimentation developed for the medical community. It is widely regarded as the cornerstone document of human research ethics. Last update: 2013.



# THE HELSINKI DECLARATION (1964): MAIN TOPICS

- ***8 While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects***

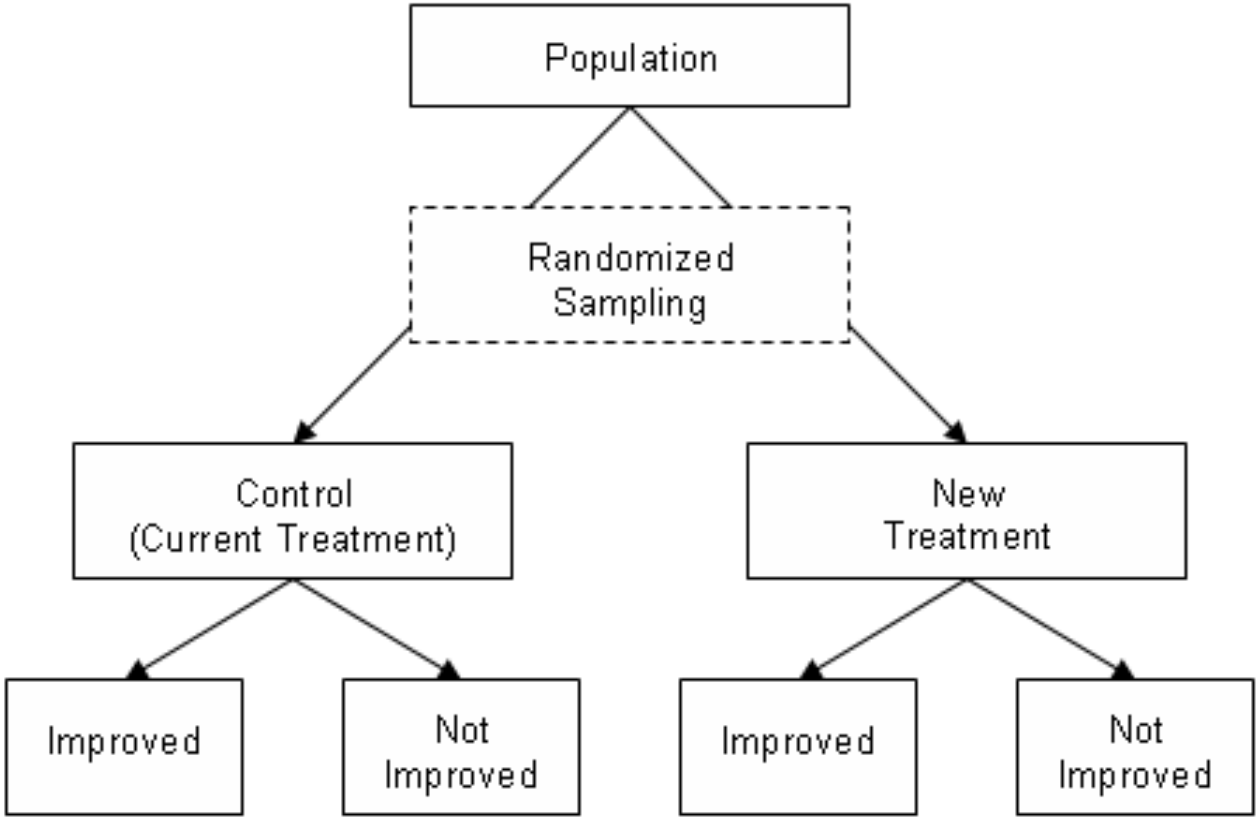
- 21 Medical research involving human subjects **must conform to generally accepted scientific principles**...
- 22 The design and performance of each research study involving human subjects must be clearly **described and justified in a research protocol**
- 23 The research protocol **must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee** before the study begins

- 9 It is the duty of physicians... to **protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information** of research subjects
- 31 The physician **must fully inform the patient** which aspects of their care are related to the research...

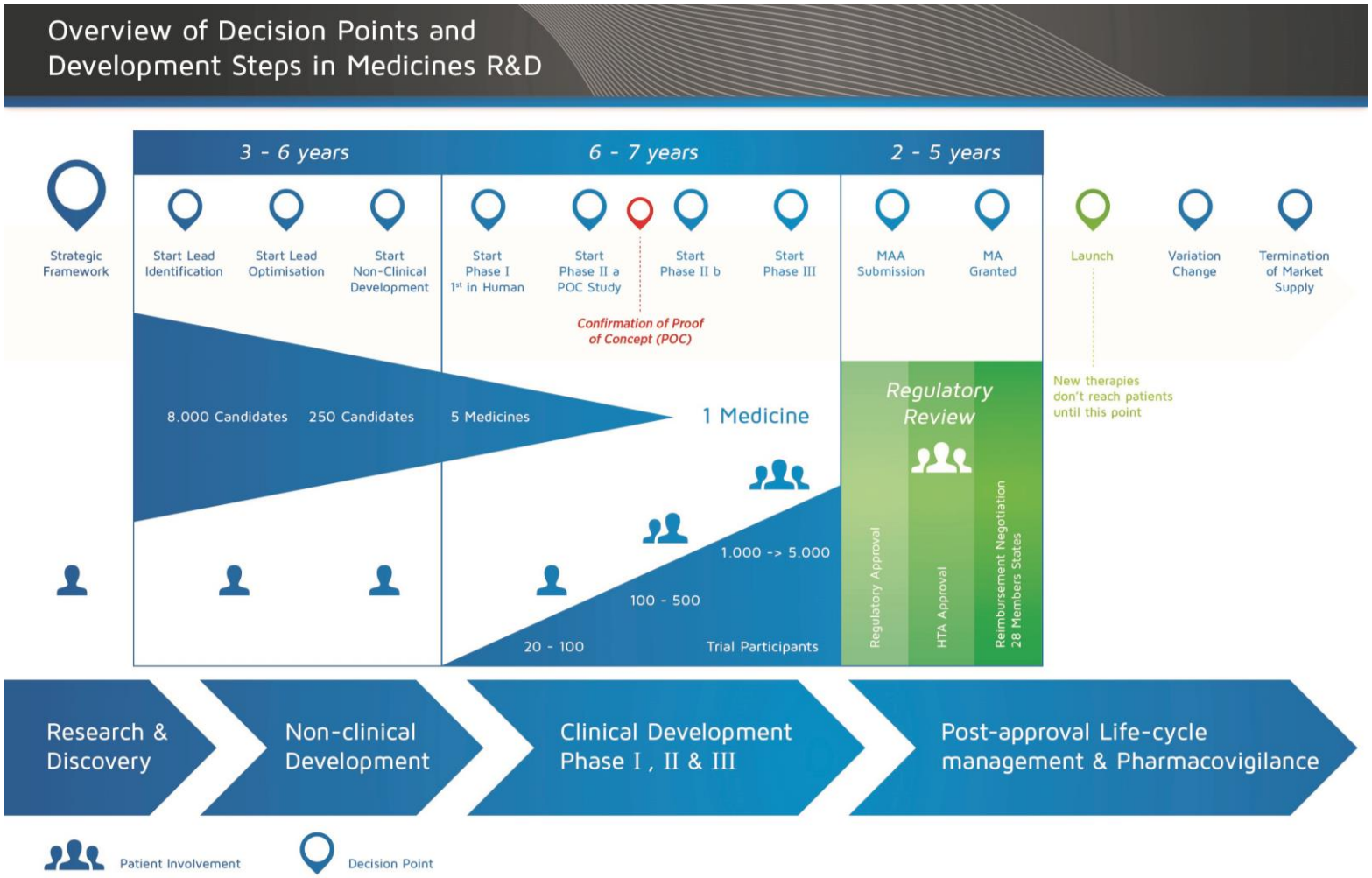
- 36 ...**Negative and inconclusive as well as positive results must be published** or otherwise made publicly available...

# Four Periods in the History of Research (4): The Era of 'Evidence Based Medicine'

Development of standards and protocols. Randomised Controlled Trial (RCT) becomes the standard. This development is founded on the Nuremberg Code (1946) and the Declaration of Helsinki (1966)



# An example of standardisation: Stages of medicine development



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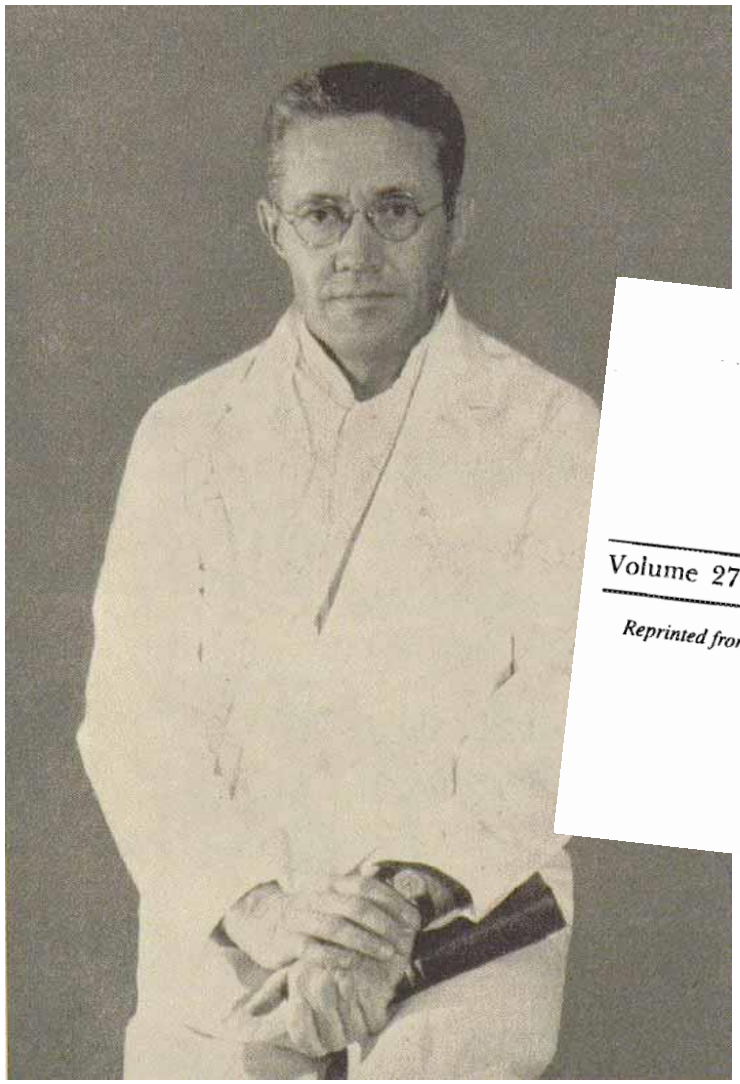
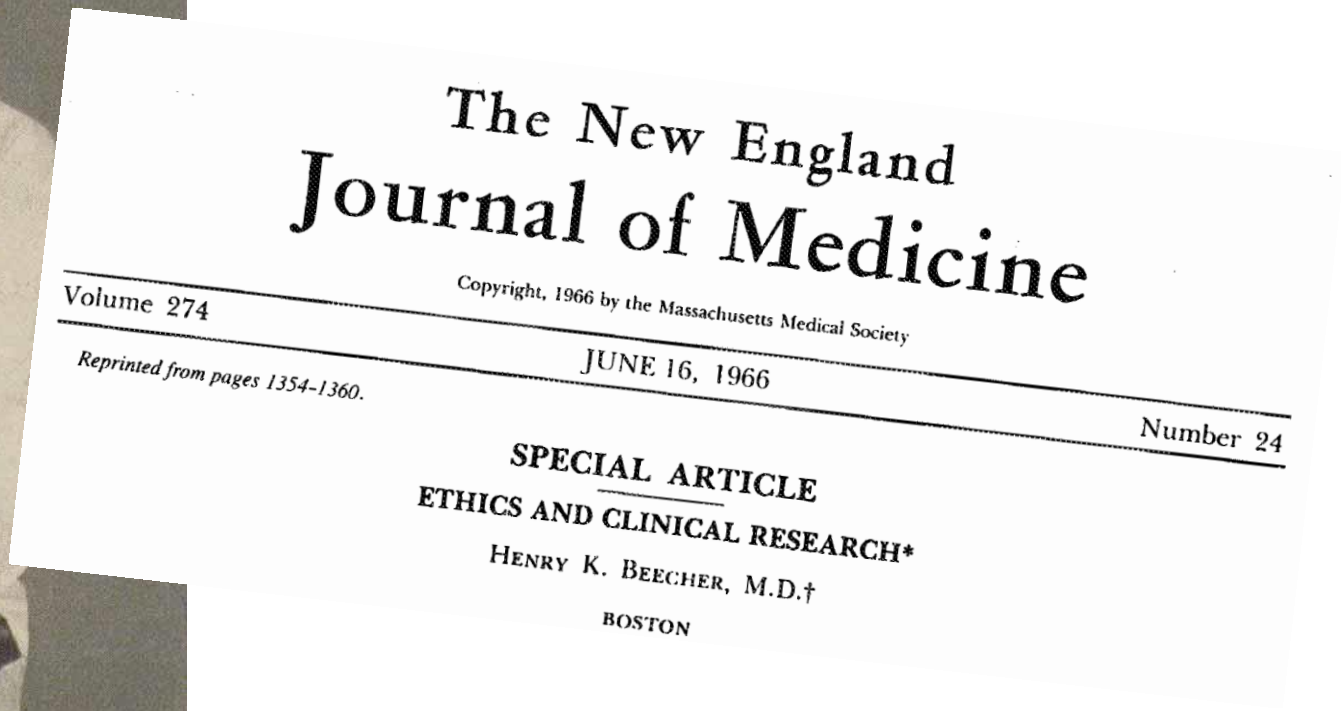
# Four Periods in the History of Research (4): The Era of 'Evidence Based Medicine'



Henry Beecher: 'Ethics and Clinical Research'

New England Journal of Medicine, 1966



The New England
Journal of Medicine



Volume 274 JUNE 16, 1966 Number 24

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SPECIAL ARTICLE

ETHICS AND CLINICAL RESEARCH*

HENRY K. BEECHER, M.D.†

BOSTON



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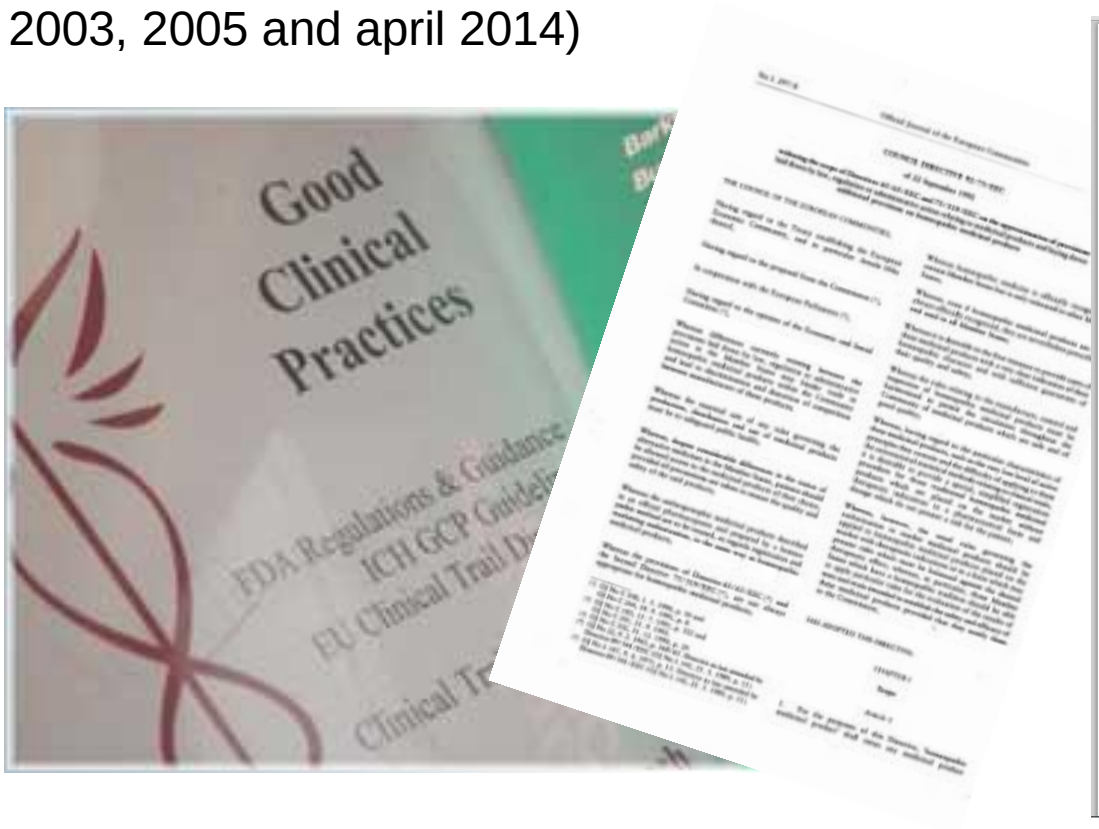
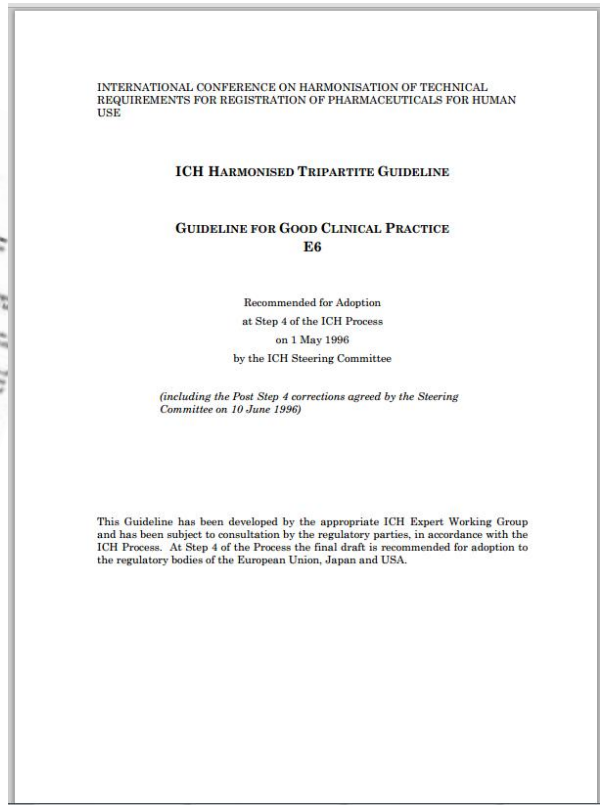
# Four Periods in the History of Research (4): The Era of 'EBM': Laws and Regulations

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



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH Harmonised Tripartite Guideline

Guideline for Good Clinical Practice
E6

Recommended for Adoption
at Step 4 of the ICH Process
on 1 May 1996
by the ICH Steering Committee

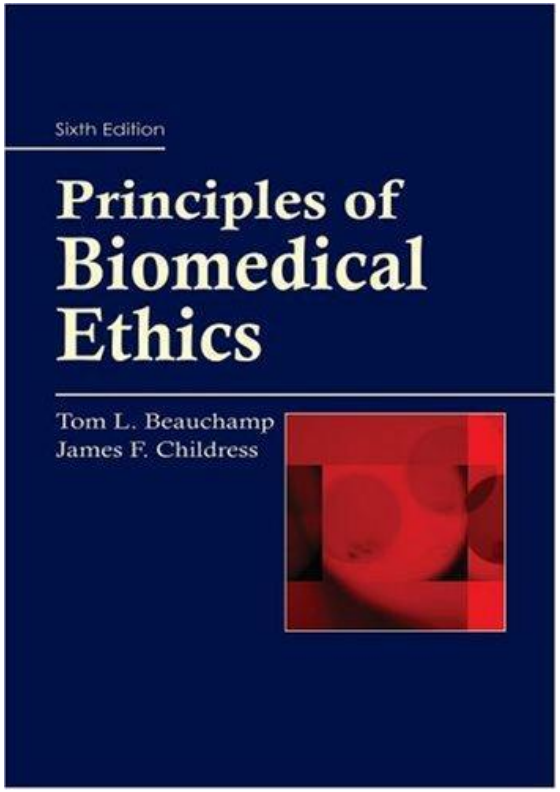
*(including the Post Step 4 corrections agreed by the Steering Committee on 10 June 1996)*

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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

# The four guiding priciples in western medical ethics ('Georgetown Mantra'):

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

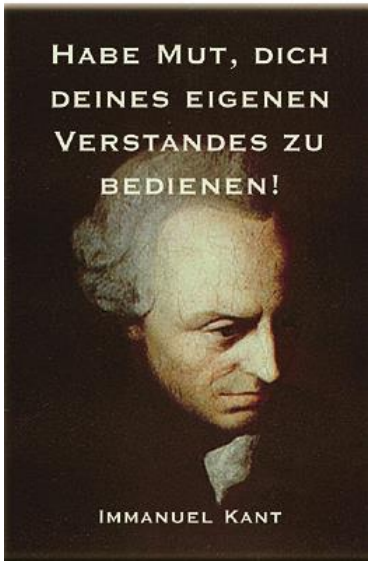


# THE FOUR GUIDING PRICIPLES IN WESTERN MEDICAL ETHICS ('GEORGETOWN MANTRA'):

- **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 subject 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!'**

# BENEFICENCE:

# The slippery slope of therapeutic and non-therapeutical experiments (1):

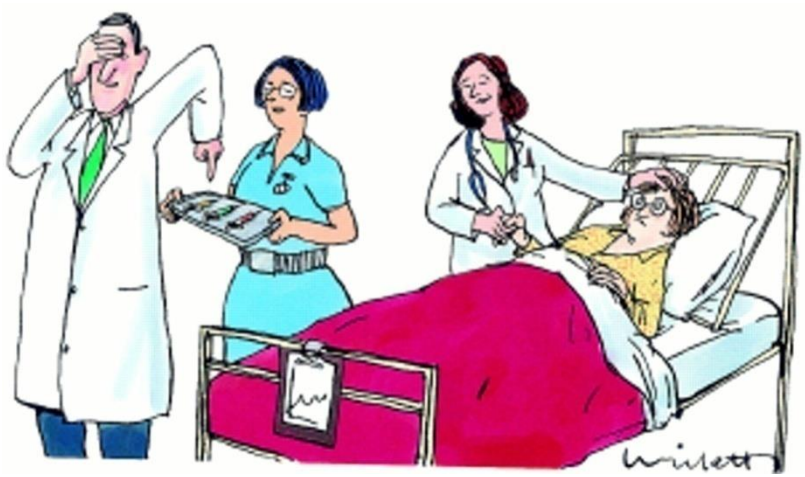
- **Experimental treatment:**
  - Aims at therapeutic effect on the individual patient (no experimental conditions, no protocol, strictly spoken no experiment)
- **Therapeutic experiment:**
  - Aims at therapeutic effect on the included human subjects (what about placebo-controlled trials?)

# The slippery slope of therapeutic and non-therapeutical experiments (2):

- **Group-indicated experiment:**
  - No direct therapeutic effect on the included subjects is intended; but possibly there is a contribution to such an effect in the long run for the group of patients as a whole


- **Non-Therapeutic experiment:**
  - No therapeutic effect on the included human subjects is intended

# MALEFICENCE (1): UNSOUND RESEARCH:



- Dangerous in such a way as to damage the included human subjects
- Methodically unsound: the design of the experiment makes it impossible to find the answer to the main hypothesis of the trial
- No qualified personnel is available
- Logistics and equipment of the studycentre are insufficient
- Preliminary investigations are insufficient (laboratory research, research on animals, study of literature)

# MALEFICENCE(2): RISKS:

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


*Come now. You don't expect us to warn you of every teeny-tiny little side-effect of Klonopin, do you?*

# MALEFICENCE (3): BURDENS AND INCONVENIENCES:

- **Investment of time:**
  - How many hours must a subject 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 etc..

- **Choices:**
  - Do subjects see themselves confronted with difficult choices?

# AUTONOMY (1): INFORMED CONSENT ON THE BASIS OF FULL INFORMATION (1):

- The aim of the experiment
- The reason why the subject is asked to participate
- The importance of the experiment
- The obligations of the subject

# AUTONOMY (1): INFORMED CONSENT ON THE BASIS OF FULL INFORMATION (21):

- The burden that is laid on the subject (and the inconveniences)
- The risks involved for the subject
- Any measures that are taken to contain those risks
- Compensation in money (if there is any)
- Insurance
- The confidentiality of collected data

# AUTONOMY (1): INFORMED CONSENT ON THE BASIS OF FULL INFORMATION (3):

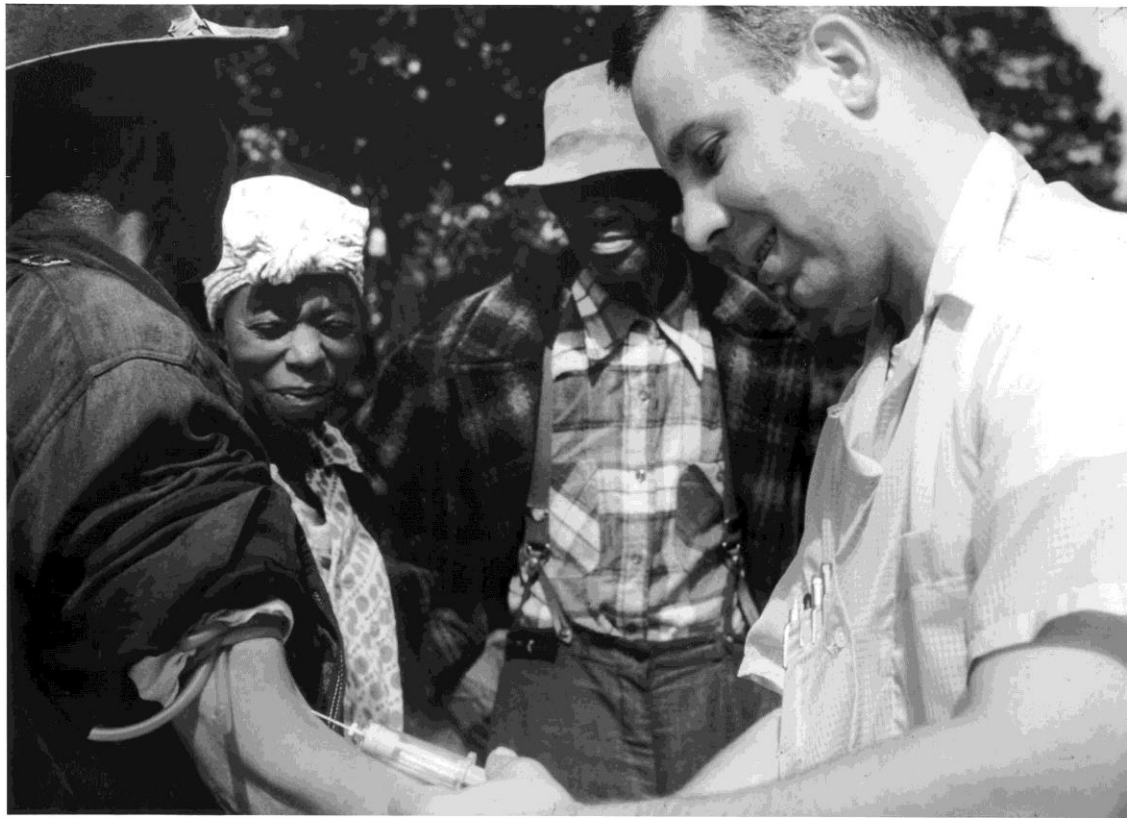
- The right to refuse to be included without repercussions on subject treatment
- The right to withdraw at any time (without giving an explanation) without repercussions on subject treatment
- Identity of the investigator and information on how to reach her/him
- Opportunity to ask questions and consult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

# Autonomy (2): Extra demands in case subjects are under age or unable to express their wishes:

- All subjects (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

# JUSTICE (1)

- Fair selection of subjects (male/female; age-groups)
- No exploitation of vulnerable populations (Tuskegee, Underdeveloped countries)



# JUSTICE (2)

Nieuws Cultuur & Leven **deVolkskrant**

Wetenschap

De kosten van kankergeneesmiddelen zijn de afgelopen 10 jaar bijna verdrievoudigd, van 270 naar 733 miljoen euro. © ANP

## KWF Kankerbestrijding: rem op te dure kankermedicijnen

Er moet een prijsplafond komen voor nieuwe, dure kankermedicijnen. Een speciale commissie moet binnen een half jaar een voorstel doen aan minister Schippers van Volksgezondheid over het maximale bedrag dat mag worden uitgegeven aan een kankerbehandeling. Dat schrijft een werkgroep van vooraanstaande kankerspecialisten in een rapport van KWF Kankerbestrijding, dat vandaag verschijnt.

Door: Ellen de Visser 20 juni 2014, 02:00 0

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

**But who then decides which direction medical research should take?**



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# In brief:

- The development of Randomised Clinical Trials and the assessment of these trials by Institutional Review Boards guarantees up to a certain extent that medical research involving human subjects is conducted in a sound, careful and responsible way

- Up to a certain extent:
  - Assessment will always remain necessary. For we will always be able to say: 'This is our practice. But is our practice good?' And as long as we can ask that question there will be reason for an ethical debate
  - The role of regulatory authorities, pharmaceutical industries and patient-associations in the ongoing debate about ethical assessment should constantly be evaluated
  - The burden that is laid on the populations of developing countries asks for consideration

# Extra Learning Slides

# THE HELSINKI DECLARATION (1964) (1):

- In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.


- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

# THE HELSINKI DECLARATION (1964) (2):

- The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence.
- Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
- Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject.

# THE HELSINKI DECLARATION (1964) (3):

- Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others.
- Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
- The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

# THE HELSINKI DECLARATION (1964) (4):

- In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal.
- Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.