MEDICAL ETHICAL ASPECTS

Eric van Roon – September 30 2017 – EAHP Academy Seminar

mcl
medisch centrum leeuwarden

university of groningen

CONFLICT OF INTEREST

THERE ARE NO CONFLICTS OF INTEREST TO DECLARE

QUESTIONS

- Yes or no: respect for autonomy, non-maleficence, beneficence and justice are the four principles for bioethics?

- Yes or no: the framework of biomedical ethics is defined sharply

- Yes or no: methodological issues may be grounds for non-accceptance of a study protocol for a research ethics committee

ETHICAL DILEMMA

- For a birthday you give a friend a ticket for the national lottery

- You bought a ticket for yourself also

- The next day you see that your friend forgot to take the ticket home

- You won't see your friend for the next two weeks

- Before you can hand over the given ticket, the ticket of your friend receives a price of 150,000 EURO in the lottery; your ticket does not receive a price

- Your friend doesn't know the lottery results nor the number of the ticket you gave

- What do you do?

ETHICS

Ethics: the discipline dealing with what is good and bad and with moral duty and obligation [1]

1. https://www.merriam-webster.com/dictionary/ethic (Visited July 3 2017

BIOETHICS

- Application of ethics to the field of medicine, healthcare, biotechnology and ecology

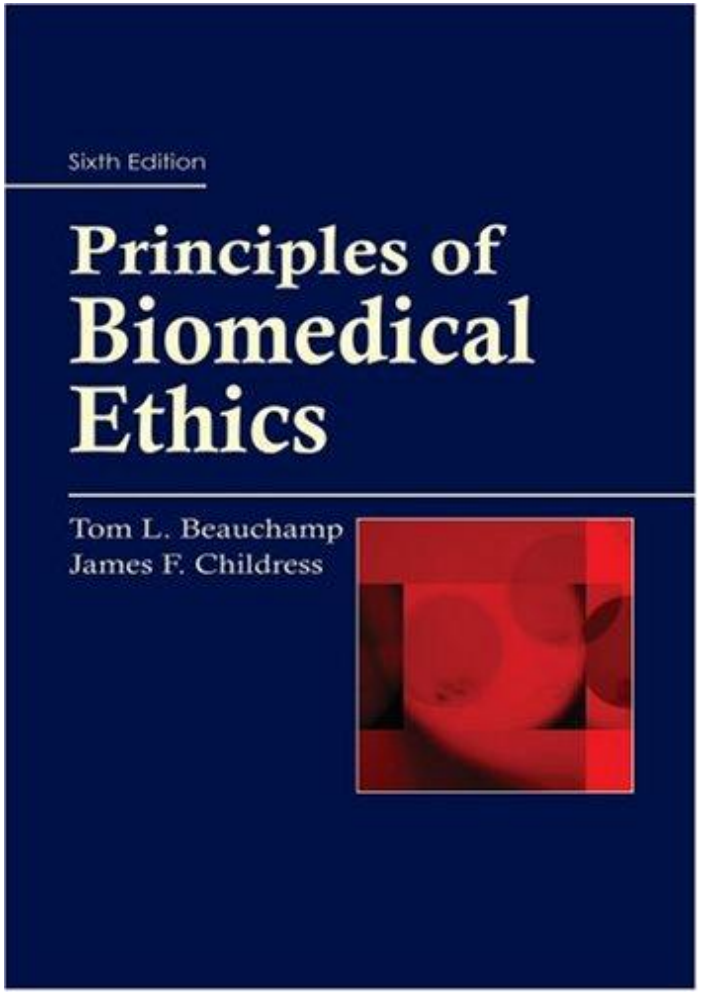
- No absolute standards

- Standards are developed in time

BIOETHICAL PRINCIPLES

A.k.a. Georgetown mantra

- Respect for autonomy
- Non-maleficence
- Beneficence
- Justice



http://medanth.wikispaces.com/Bioethics (visited July 3 2017)

RESPECT FOR AUTONOMY

- Right tot self-rule

- Free from both
  - controlling interference by others and
  - from limitations, such as inadequate understanding, that prevent meaningful choice.

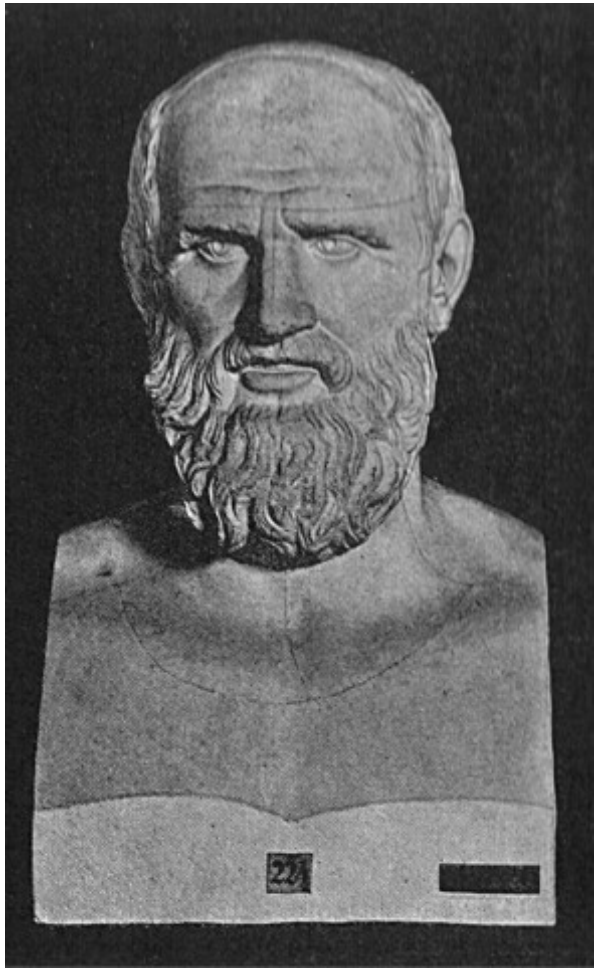
- Respect for autonomy supports other specific actions
  - such as telling the truth,
  - respecting the privacy of others,
  - protection of confidential information,
  - obtaining informed consent, and
  - helping others making important decisions.

NON-MALEFICENCE

- Duty to refrain from causing harm

- Non-maleficence underlies the medical maxim found in the Hippocratic Oath, “above all (or first) do no harm.”

- The principle of Non-maleficence includes
  - do not kill, cause pain or suffering, incapacitate, cause offense, and deprive others of the goods of life.



Hippocrate (400 B.C.)

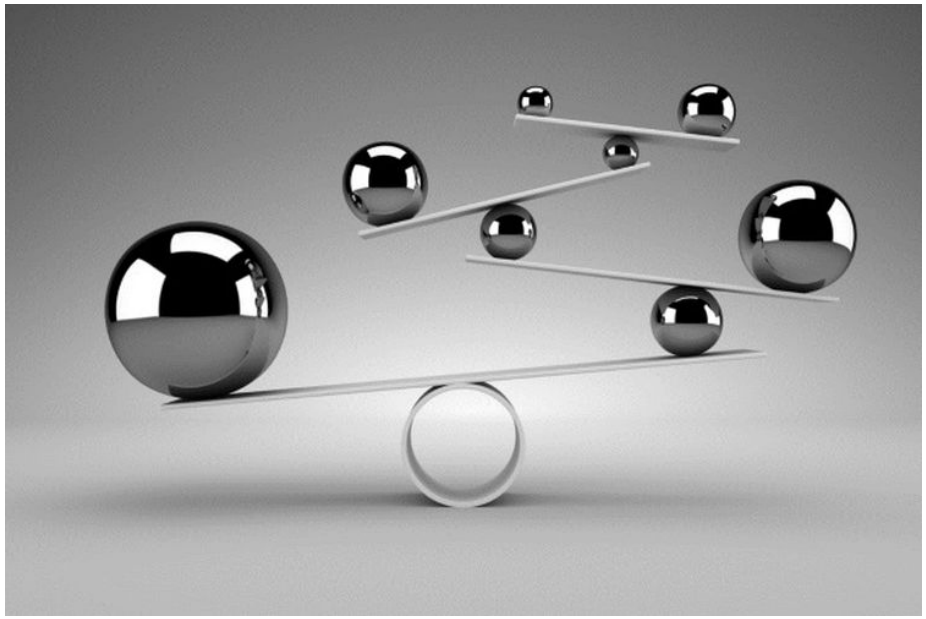
BENEFICENCE

- Beneficence is to bring or create benefit.

- Under beneficence, one ought to prevent evil or harm, remove evil or harm, and do or promote good.

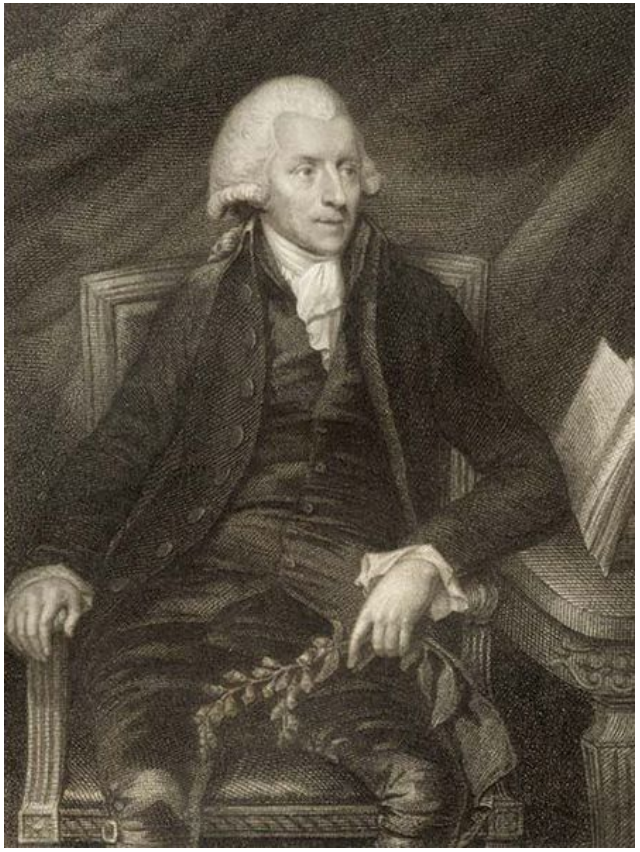
- The principle of beneficence also includes protecting and defending the rights of others, preventing harm from occurring to others, and removing conditions that will cause harm to others

JUSTICE



- Justice
  - how social benefits and burdens should be distributed.

BIOETHICS: THE BEGINNING



William Withering (1741-1799)
English botanist & geologist

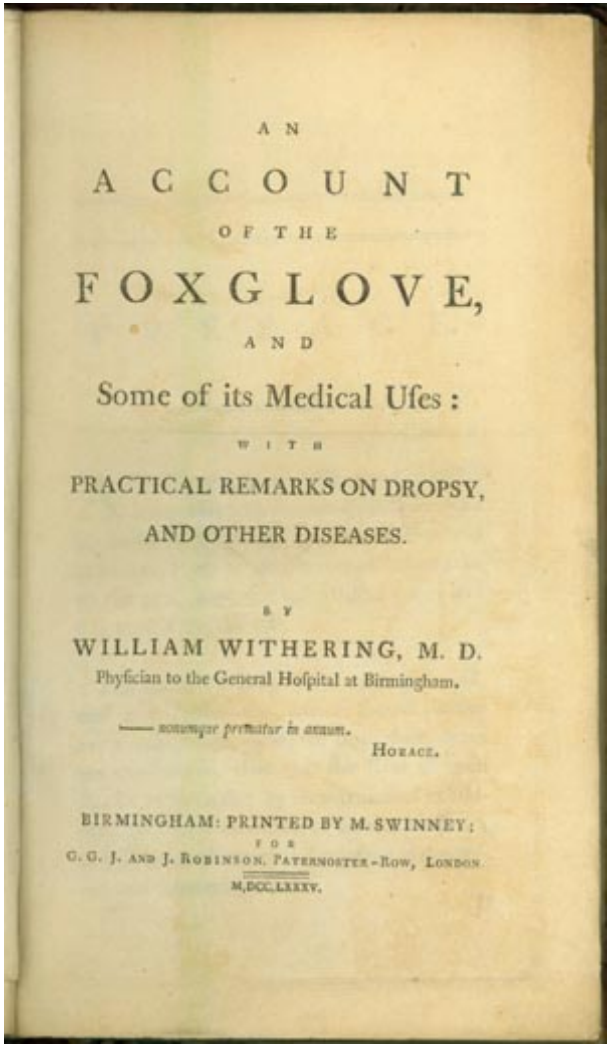
BIOETHICS: THE BEGINNING

- Anecdotal evidence (from 'old mother Hutton') for efficacy of a herbal mixture in 'dropsy' (edema due to congestive heart failure)

- Identified foxglove as principal therapeutic component in the mixture

- Treated 158 patients with dropsy

- Described the efficacy and safety in every case



AN

ACCOUNT

OF THE

FOXGLOVE,

AND

Some of its Medical Uſes:

WITH

PRACTICAL REMARKS ON DROPSY,

AND OTHER DISEASES.

BY

WILLIAM WITHERING, M. D.

Phyſician to the General Hoſpital at Birmingham.

—— nonumque prematur in annum.

HORACE.

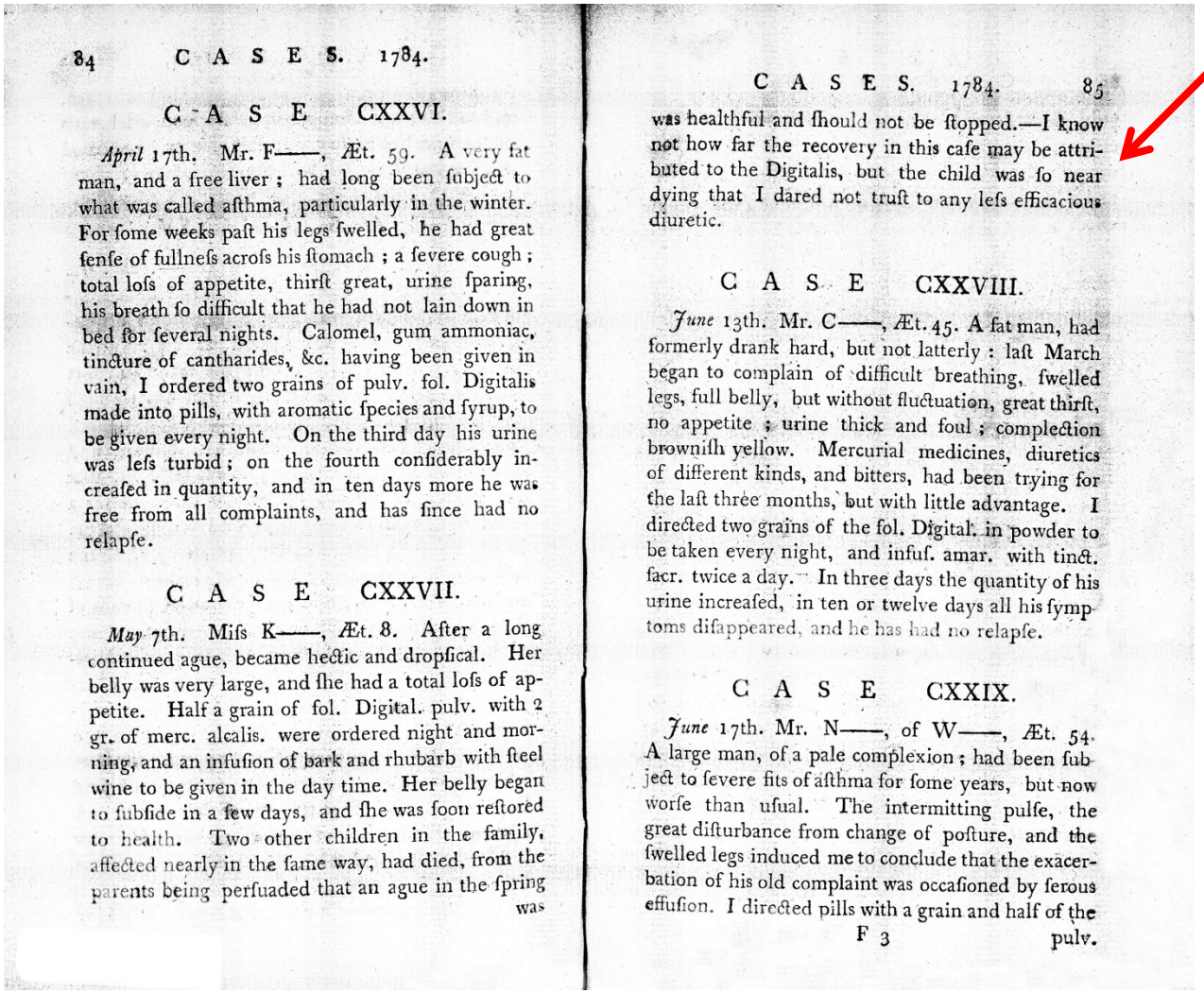
BIRMINGHAM: PRINTED BY M. SWINNEY:

FOR

G. G. J. AND J. ROBINSON, PATERNOSTER-ROW, LONDON.

M,DCC,LXXXV.

BIOETHICS: THE BEGINNING



CASE CXXVI.

April 17th. Mr. F——, Æt. 59. A very fat man, and a free liver; had long been ſubject to what was called aſthma, particularly in the winter. For ſome weeks paſt his legs ſwelled, he had great ſenſe of fullneſs acroſs his ſtomach; a ſevere cough; total loſs of appetite, thirſt great, urine ſparing, his breath ſo difficult that he had not lain down in bed for ſeveral nights. Calomel, gum ammoniac, tincture of cantharides, &c. having been given in vain, I ordered two grains of pulv. fol. Digitalis made into pills, with aromatic ſpecies and ſyrup, to be given every night. On the third day his urine was leſs turbid; on the fourth conſiderably increaſed in quantity, and in ten days more he was free from all complaints, and has ſince had no relapſe.

CASE CXXVII.

May 7th. Miſs K——, Æt. 8. After a long continued ague, became hectic and dropſical. Her belly was very large, and ſhe had a total loſs of appetite. Half a grain of fol. Digital. pulv. with 2 gr. of merc. alcalis. were ordered night and morning, and an infuſion of bark and rhubarb with ſteel wine to be given in the day time. Her belly began to ſubſide in a few days, and ſhe was ſoon reſtored to health. Two other children in the family, affected nearly in the ſame way, had died, from the parents being perſuaded that an ague in the ſpring was

was healthful and ſhould not be ſtopped.—I know not how far the recovery in this caſe may be attributed to the Digitalis, but the child was ſo near dying that I dared not truſt to any leſs efficacious diuretic.

CASE CXXVIII.

June 13th. Mr. C——, Æt. 45. A fat man, had formerly drank hard, but not latterly: laſt March began to complain of difficult breathing, ſwelled legs, full belly, but without fluctuation, great thirſt, no appetite; urine thick and foul; complection browniſh yellow. Mercurial medicines, diuretics of different kinds, and bitters, had been trying for the laſt three months, but with little advantage. I directed two grains of the fol. Digital. in powder to be taken every night, and infuſ. amar. with tinct. facr. twice a day. In three days the quantity of his urine increaſed, in ten or twelve days all his ſymptoms diſappeared, and he has had no relapſe.

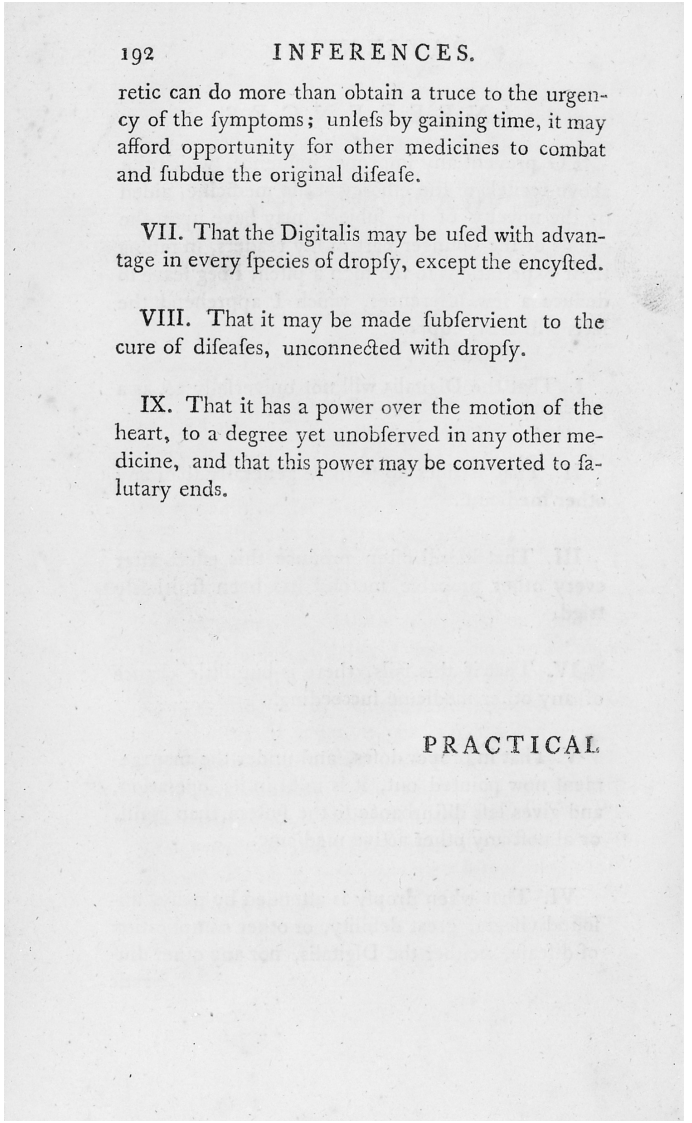
CASE CXXIX.

June 17th. Mr. N——, of W——, Æt. 54. A large man, of a pale complexion; had been ſubject to ſevere fits of aſthma for ſome years, but now worſe than uſual. The intermitting pulſe, the great diſturbance from change of poſture, and the ſwelled legs induced me to conclude that the exacerbation of his old complaint was occaſioned by ſerous effuſion. I directed pills with a grain and half of the

BIOETHICS: THE BEGINNING

Remarkable perspectives

- Structural assessment of therapeutic value
- Case reports
- Formulated general conclusions
- Admitted to have overdosed patients



192 INFERENCES.

retic can do more than obtain a truce to the urgency of the ſymptoms; unleſs by gaining time, it may afford opportunity for other medicines to combat and ſubdue the original diſeaſe.

VII. That the Digitalis may be uſed with advantage in every ſpecies of dropſy, except the encyſted.

VIII. That it may be made ſubſervient to the cure of diſeaſes, unconnected with dropſy.

IX. That it has a power over the motion of the heart, to a degree yet unobſerved in any other medicine, and that this power may be converted to ſalutary ends.

PRACTICAL

ALBERT LUDWIG NEISSER (1855-1916)

- Discovered Neisseria gonorrhoea
  - Pathogen causing gonorroe

- Injected cell-free serum of syphilis patients in healthy volunteers, mostly prostitutes, as vaccination

- Conclusions:
  - vaccination is ineffective
  - syphilis infection is result of the work, not of the serum injection

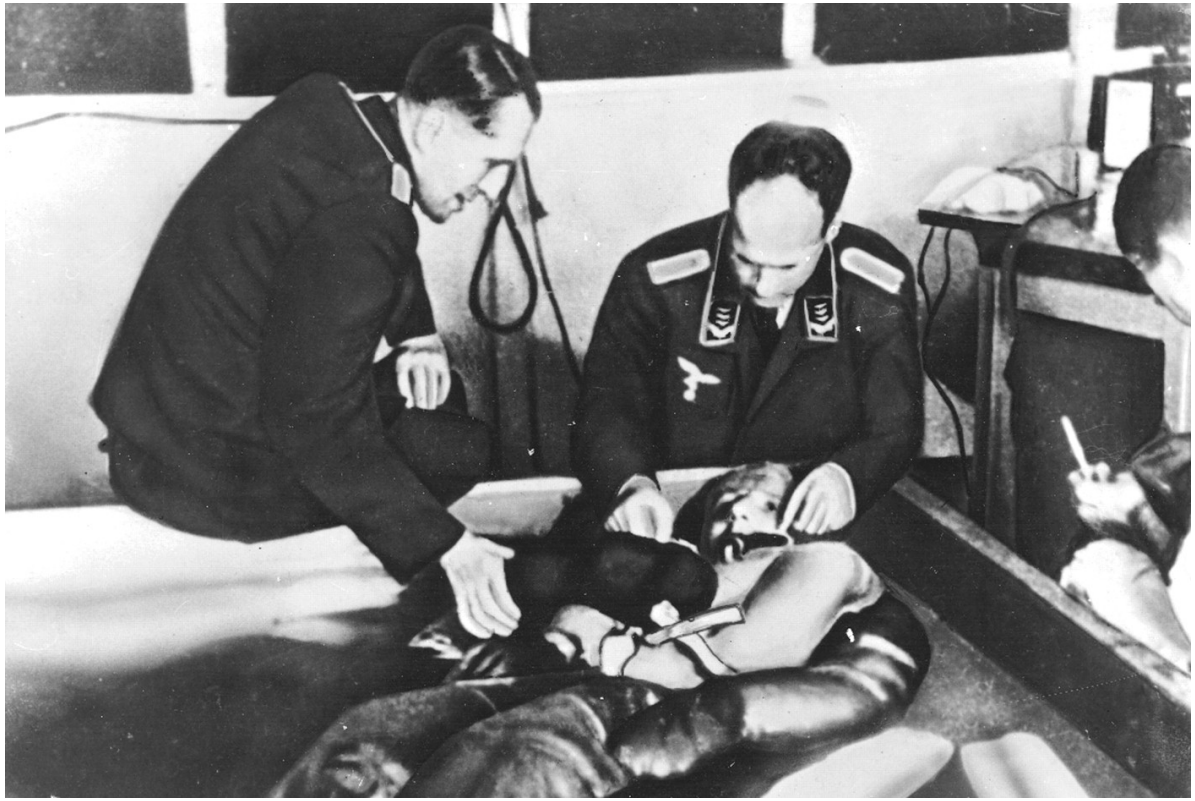
- Participants were not informed on the trial, nor signed informed consent
  - In 1898 Neisser was fined by the Royal Disciplinary Court for not asking IC

THE AFTERMATH

- 1898: Neisser was fined
  - Not asking informed consent
- 1899: Report of the 'Scientific Council
  - Experiments have to be useful
  - Participant is autonomous an makes the decision whether or not to engage in the trial
- 1900: Prussian Guideline
  - No medical experiments in minors
  - Informed consent obligatory after informing the participant
  - Guidelines on documentation of the experiment
- 1931: ReicksZirkular
  - Guidelines and precautions for 'therapeutical' versus 'non-therapeutical' experiments

Vollmann, et al. BMJ 1996;313:1445-9.

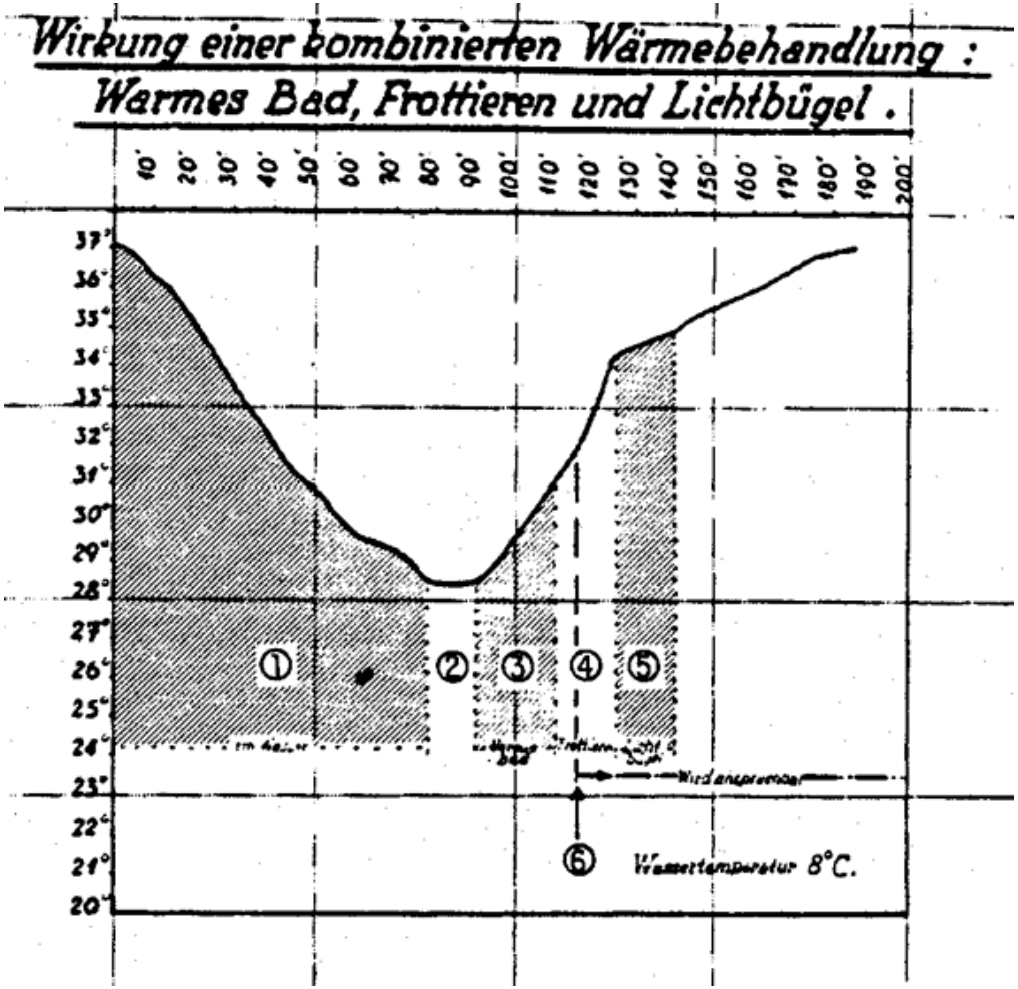
AND THEN …



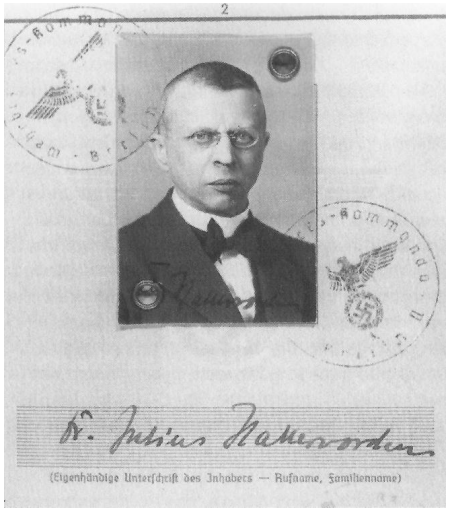
Rascher & Holzlöhner, 2nd WW, SS physicians

- Experiments on hypothermia in cold water
  - Resembling pilots landing in sea

DO WE USE THESE RESULTS?



DO WE USE THE RESULTS?



Prof. Dr. Julius Hallervorden ('German physician, neuroscientist; 1882-1965) said in the Nuremberg Trials:

"Look boys, if you feel you have to kill these people please remove the brains so that we can use the material."

"...those brains offered wonderful material, of mentally poor, deformities and early children's diseases. Of course I accepted the brains. It really wasn't my concern where they came from and how they were brought to me."

THE NUREMBERG CODE 1947: 10 POINTS

1. Required is the voluntary, well-informed, understanding consent of the human subject in a full legal capacity.

2. The experiment should aim at positive results for society that cannot be procured in some other way.

3. It should be based on previous knowledge (e.g. an expectation derived from animal experiments) that justifies the experiment.

4. The experiment should be set up in a way that avoids unnecessary physical and mental suffering and injuries.

5. It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.

THE NUREMBERG CODE 1947: 10 POINTS

6. The risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits.

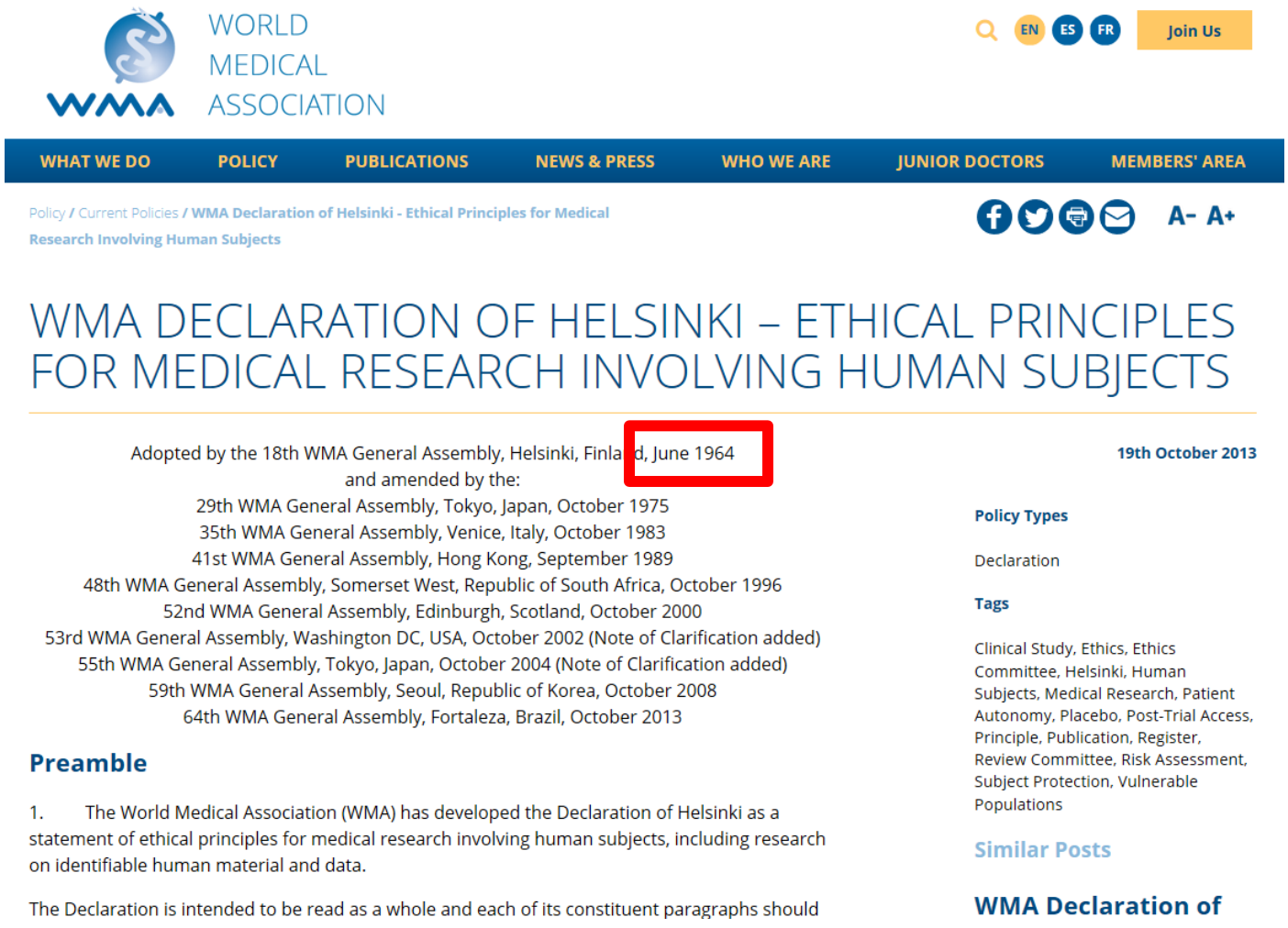
7. Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.

8. The staff who conduct or take part in the experiment must be fully trained and scientifically qualified.

9. The human subjects must be free to immediately quit the experiment at any point when they feel physically or mentally unable to go on.

10. Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous.

DECLARATION OF HELSINKI



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Policy / Current Policies / WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

A- A+

WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

19th October 2013

Policy Types

Declaration

Tags

Clinical Study, Ethics, Ethics Committee, Helsinki, Human Subjects, Medical Research, Patient Autonomy, Placebo, Post-Trial Access, Principle, Publication, Register, Review Committee, Risk Assessment, Subject Protection, Vulnerable Populations

Similar Posts

WMA Declaration of

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (visited July 3 2017)

DECLARATION OF HELSINKI

- 37 statements on (among others):
  - Risks, burdens and benefits
  - Vulnerable Groups and Inidividuals
  - Scientific Requirements and Research Protocols
  - Research Ethic Committees
  - Privacy and Confidentiality
  - Informed Consent
  - Use of Placebo

A SELECTION OF ASPECTS IN THE DOH THAT ARE IMPORTANT FOR THIS WORKSHOP

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DOH: SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

Scientific Requirements and Research Protocols

21. 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 adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

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DOH: RESEARCH ETHIC COMMITTEES

Research Ethics Committees

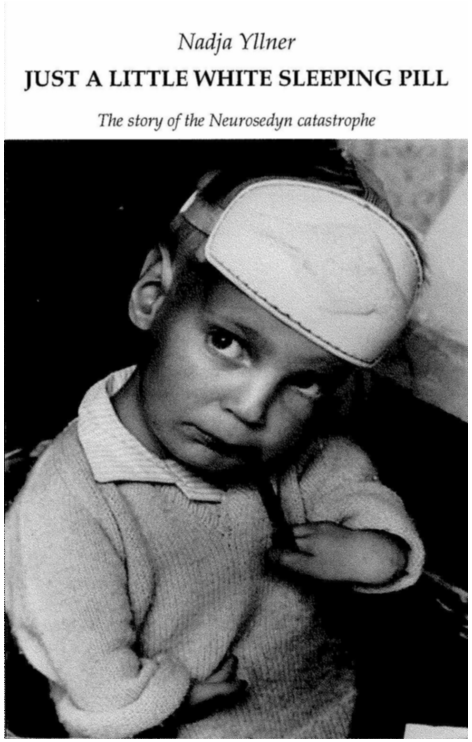
23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

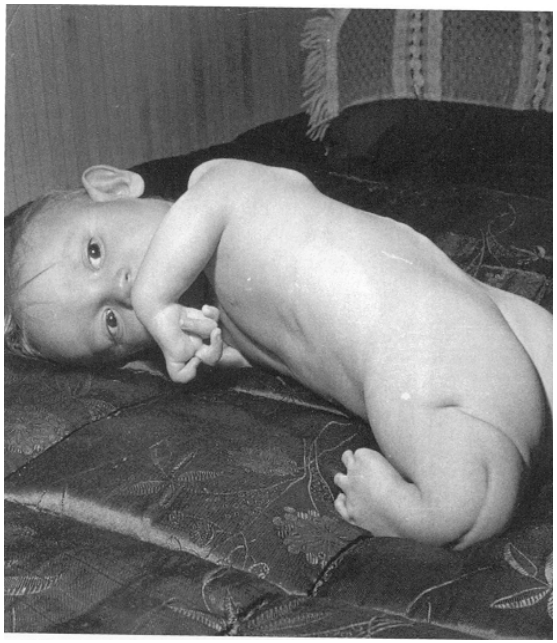
The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

DID ALL GO WELL? THALIDOMIDE

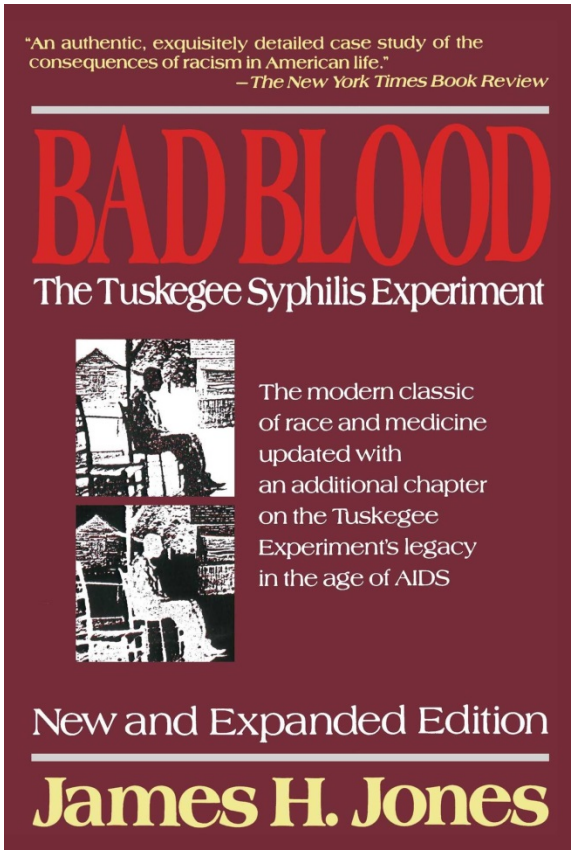
Consequences of the thalidomide (Softenon®) disaster

1. More attention for safety of drugs in clinical trials
2. More attention on ADR for future generations





TUSKEGEE SYPHILIS STUDY



- 1932 – 1972 (!)

- 399 black men, with syphilis (3rd stage)

- Goals:
  - to discover how syphilis affected blacks as opposed to whites
  - learning syphilis from autopsies

- Methodology: no treatment
  - '..they were thus deliberately left to degenerate under the ravages of tertiary syphilis..'

- Misleading information participants:
  - treatment for 'bad blood' = aspirin
  - 'last chance for free treatment' = spinal tap
  - 'free hospital care' = post mortem

https://www.infoplease.com/us/race-population/tuskegee-syphilis-experiment

TUSKEGEE SYPHILIS STUDY

- Study end:
  - 28 deaths through syphilis
  - 100 deaths due to related complications
  - 40 wives infected
  - 19 children suffered congenital syphilis

The United States government did something that was wrong—deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens. . . . clearly racist.

—President Clinton's apology for the Tuskegee Syphilis Experiment to the eight remaining survivors, May 16, 1997

A New Colonialism? — Conducting Clinical Trials in India

Samiran Nundy, M.Chir., and Chandra M. Gulhati, M.D., D.T.M.&H.

N Engl J Med 2005:352;1633-6.

A Private, "One-Man" Clinic in New Delhi Where Letrozole Was Tested.

Letrozole trials in India

Drugs:	letrozole
Treatment:	Inducing ovulation
Sponsors:	Sun Pharmaceuticals
Period:	2003
Location:	India

Unethical aspects:

Letrozole, which belongs to the group of aromatase inhibitors, was tested by Sun Pharmaceuticals to induce ovulation. The drug has been approved globally for the treatment of breast cancer in post-menopausal women, but it is not approved for any other use in any country. More than 400 women who had been trying in vain to conceive were enrolled in 2003 without their knowledge or consent to take part in clinical trials conducted at nine or more centres across India.

[1] https://www.wemos.nl/wp-content/uploads/2016/07/Testimonies_Wemos.pdf (Visited July 3 2017)

"My antecubital vein was my financial pipeline."

"I was lucky to get into a study, so I could survive financially."

"I do not really understand what a clinical trial means, but we are poor farmers and the most important thing for us is saving money."

The Globalization of Clinical Trials: Testimonies from Human Subjects. December 2010 [1]

Tages-Anzeiger WIRTSCHAFT

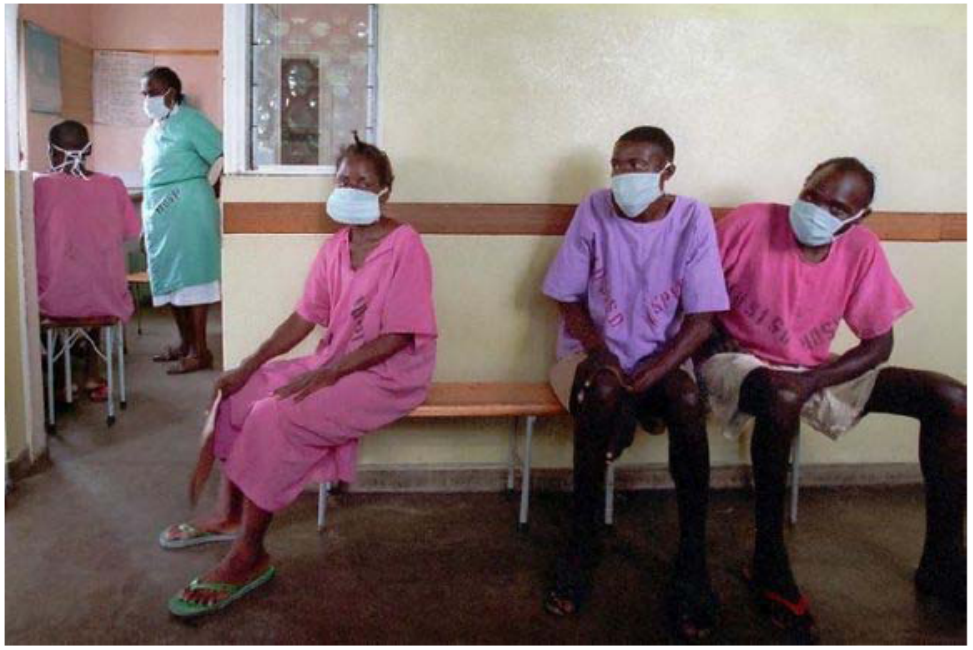
ZÜRICH SCHWEIZ AUSLAND WIRTSCHAFT BÖRSE SPORT KULTUR PANORAMA

Unternehmen **Konjunktur** Geld Karriere Vorbörse Weiterbildung Never Mind The Markets Beruf &

Die Versuchskaninchen der Pharmaindustrie

Von Andreas Möckli. Aktualisiert am 16.06.2011 10 Kommentare | Empfehlen 1

Klinische Studien werden immer öfter in Entwicklungs- und Schwellenländern durchgeführt. NGO werfen den Pharmafirmen vor, sich nicht an die ethischen Regeln zu halten.



Aidskranke Tuberkulosepatienten warten in einem Spital in Zimbabwe auf ihre Medikamente. Nur jeder hundertste Kranke im Land hat Zugang zu einer Therapie.

GOOD CLINICAL PRACTICE (GCP)

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

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE
E6(R1)

Current *Step 4* version
dated 10 June 1996

(including the Post Step 4 corrections)

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
And www.ichgcp.net (Visited July 5 2017)

GOOD CLINICAL PRACTICE (GCP)

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

This GCP-principle states

- minimal quality demands on biomedical (drug) studies involving humans

AND THEN ALL WENT WELL….

- Tegenero-disaster in London 2006

- TGN1412 = 'superagonistic' anti-human CD28 mAb
- Activating immunosuppressive regulatory T-cells
- Focus of development: haematological malignancies & inflammatory diseases (e.g. RA)

- First-in-human study
- N = 6 volunteers
- Within 1 hour of administration: severe systemic inflammatory response ('cytokine storm')

AND THEN ALL WENT WELL….

- Lessons learned (among others)
  - Slower infusion rate in ‘high risk’ biological studies (to terminate administration)
  - Sequential inclusion instead of all first infusion to all volunteers at one time
  - Recommendation: FIH ‘high risk’ biological conducted at sites with immediate access to acute/intensive care settings

AND THEN ALL WENT WELL….

AND THEN ALL WENT WELL….

- BIAL-disaster in Rennes 2016

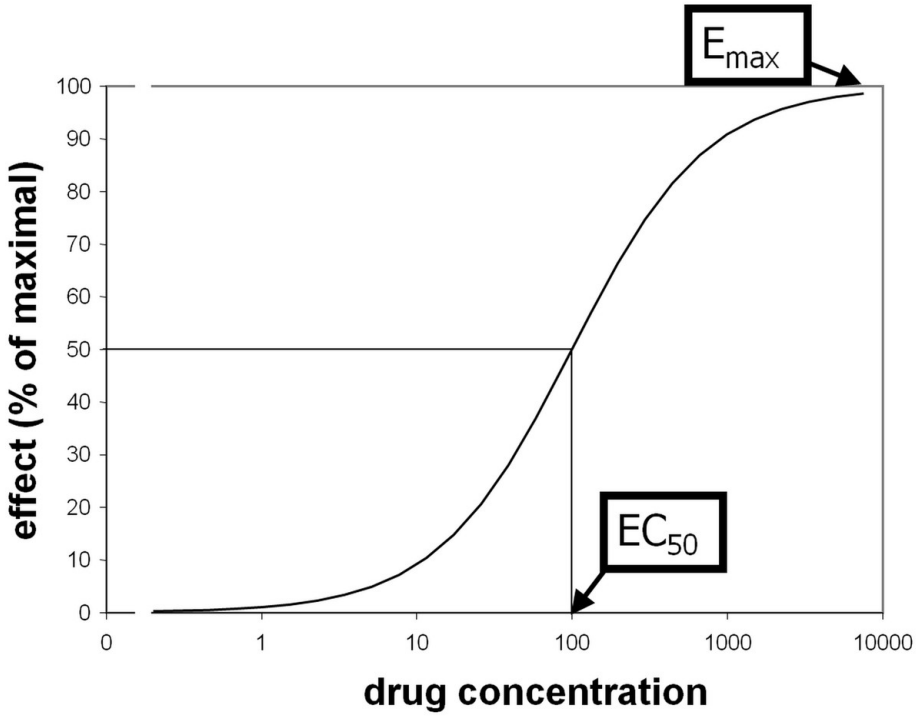
- BIA 10-2474 = inhibitor of fatty acid amide hydrolase (FAAH)
- Earlier FAAH-inhibitors tested in phase I & II; no phase III due to lack of efficacy

- Earlier study with repeated oral doses
- Daily doses: 2,5 - 5 - 10- 20 mg for 10 days each → no toxicity seen
- This study: 50 mg daily, repeated dosing, n = 6
- At day 5: serious neurological symptoms
- 1Volunteer died, 3 volunteers were admitted to hospital and recovered

AND THEN ALL WENT WELL….

In retrospect (!!)

- Why this high dose?
  - Complete inhibition of FAAH at 2 mg dose



- Non-linear pharmacokinetics → drug cumulation?
  - No serum levels are known in the public domain up to today

- Multiple volunteers at same dosing level at the same time

WHY THESE EXAMPLES?

- Unexpected effects in early development lead to serious safety issues, despite the presence of detailed guidelines and medical-ethical evaluation

- Adaptation/evolution of guidelines is essential for optimizing safety

- Continuous scrutiny in study development is of major importance

FOCUSING ON YOUR FUTURE PROTOCOL

- Protocol has to live up to the criteria as mentioned

- My experience in > 10 years of study evaluations in research ethic committees
  - Patricia will complete what I forget

- A selection of major problems

- Goal: to avoid these problems in your future research

A SELECTION - I

- Irrelevant study questions
  - Question already answered in existing medical literature
  - Who wants to know the answwer on the study question?

- Study method not suitable for the study question
  - Statistics, methodology, follow-up, collected data

- Power calculation not present

- Study title does not correspond with primary end point does not correspond with study question does not correspond with Figure 1/Table 2

A SELECTION - II

- Principal investigator not sufficiently qualified
- In sponsored trials: exaggerated financial compensation
- Vulnerable patients included in non-therapeutic study
- Patient burden insufficiently weighted
  - Questionnaires: time consumption, kind of questions, repetitions
  - Venapunction for collection blood samples: number, volume per sample
  - Visits to hospital
  - Keep in mind: only the extra burden in relation to the protocol is relevant for ethical considerations
- Patient information
  - Too difficult
  - Too positive, not/insufficiently mentioning negative aspects (e.g. ADR)
  - Claiming an advantage
  - Too long/ too detailed

When the study protocol offers insufficient guarantees that the study question is relevant and will be answered, the ethical research committee will have objections with any burden posed on the participants; independent of how low this burden may be.

RECOMMENDED READING

- Declaration of Helsinki
  - 30 minutes reading time
- Good Clinical Practice guideline
  - www.ichgcp.net
- Nadja Yllner. Just a little white sleeping pill. Recito 2008 (ISBN 9186035320).
- Stebbings R, et al. Safety of biologics, lessons learnt from TGN1412. Curr Opin Biotechn 2009;20:673-7.
- Kerbrat A, et al. Acute neurologic disorder from an inhibitor of fatty acid amide hydrolase. NEJM 2016;375:1717-25.

THANKS FOR YOUR ATTENTION
QUESTIONS?

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QUESTIONS & ANSWERS

- Yes or no: respect for autonomy, non-maleficence, beneficence and justice are the four principles for bioethics?
  - Yes, these are the four basic principles, a.k.a. the Georgetown mantra.

- Yes or no: the framework of biomedical ethics is defined sharply
  - No, bioethical considerations within the framework of guidelines are subject to interpretation depending on the individual study protocol, research question and methodology.

- - Yes or no: methodological issues may be grounds for non-accceptance of a study protocol for ethical committee
  - Yes, as methodological issues may interfere with the chance of getting the answer to the study question these issues may therefore be a ground for non-acceptance.