Ethical Background of Clinical Trials

F. Gerstenbrand, W. Struhal

4th World Congress for Neuro-Rehabilitation
Hong Kong, February 12-16, 2006

WS-02 "Clinical Research and Clinical Trials on Neurorehabilitation"

Occidental Ethics
Western ethical thinking, "Christian Ethics"

- Founders:
  - Socrates, Plato, Aristoteles
    Greek philosophy: moral virtue
    values are natural rather than conventional
    ethics as science
  - Saint Augustinus, Thomas Aquinas
    Incorporation of Greek ethics
    Attainment of happiness
    God-given natural order
  - Immanuel Kant
    Categorical imperative: the individual shall act in a way, that his action can be regarded as general law
  - Modern ethics
    Different schools:
    Value ethics, existentialistic ethics, American bioethics, Marxit ethics, theological ethics

Oriental Ethics
Non Western Ethics
partly religious fixed

- Ethical rules in Buddhism
  end of being rebirth, Nirvana
- Ethical rules in Konfucianism
  appreciation of well being of the community above the well being of the individual
- Ethical rules in Mosaic religion
- Ethical rules in Islamic religion
- Ethical rules of natural religions
  Massai religion, African religious communities, Schamanism

Definition of ethics

- **Ethics:** Part of philosophy dealing with morality
- **Moral** is search for an inner standard
- **Kant‘ s Categorical Imperativ**:
  The individual shall act in a way that this action can be regarded as general law

Ethics

- Altruism
- Sense of Honour
- Justness
- Respect for others
- Solidarity
- Ability to forgive

Bioethical principles

Medical conduct, physicians obligations

(Belmont Criteria, 1979)

- Autonomy of the patient
- Beneficience
- Nonmalefficiency
- Justice
- Trust

Patient-Doctor Relationship

- Expectation of personal attention
- Trust
- Individualized treatment
- Best available and best care
- Best benefit to risk/ratio

Hippocratic oath

Obligation to heal
Not do anything to harm the patient
No continuation of therapy in untreatable disease
No therapy in advanced physical and mental destruction
No continuation of life prolongation for hours or days
No prolongation of suffering during dying
Not to tell anyone the details of patients
No admitting of letal poison, even as advice

Will to respect the teacher like own parents, sharing one life support of successors of the teacher, treated as own brothers
Medical teaching to own sons and the sons of the teacher or to pupils bound on physicians rules and oath

World Medical Association, Helsinki Declaration, 1964
Medical Research Involving Human Subjects
Ethical Principles

- Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects
- In medical research on human subject, considerations related to the well-being of the human subject should take precedence over the interest of science and society
- International Code of Medical Ethics : A physician shall act only in patient interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient
- Ethical Principles to provide guidance for physicians and other participants in medical research involving human subjects
  Including identifiable material or identifiable data

UNESCO Bioethics Declaration on Human Rights

Paris, 2005

Person's identity includes

- biological
- psychological
- social
- cultural and
- spiritual dimensions

Human research and subject protection
(NIH, FDA)

basic rules

- Informed consent to the patient
- Education and training of investigator
- Appropriate training for investigator in bioethics and other issues related to research involving human subject
- Improved monitoring
- Conflicts of interests
- Civil monetary penalty for violation of research (investigator, research institute)

Rights and responsibilities

Physician and patient

- The treating physician has the individual responsibility for his patient. Highest level of his education and training is essential and necessary.
- The treating physician is guided by ethical principles, medical guidelines, declaration, domestic and international law and human rights law.
- "New ethics in medical treatment" are created.
- The personal responsibility of the physician to his patient can't be replaced.
- Patient's right is to accept or to refuse the recommendation of a treatment program.
- Patient's right is to interrupt a running treatment program
- The physician's obligation is to inform the patient about the danger for his health to refuse or to interrupt a treatment program.

Clinical Trials in Medicine
Basic Principles

- Patient changes to an examination object
- Physician changes to investigator

- Protocol of the trial, prepared in an exact form
- Protocol submission to the Independent Ethics Committee (IEC)
- Sponsor: industry, academic
- Investigator with exact training

- Procedure according to the principles of ICH – GCP
- Exact monitoring during the trial
- Audits and inspections procedure
- Strict anonymity of the trial results
- Careful archive of the results

Principles of ICH-GCP for Clinical Trials

- In accordance with ethical principles
- Only if benefits justify the risks
- Rights, safety and well-being of trial subjects are most important
- Supported by adequate non-clinical and clinical information
- Scientifically sound with clear detailed protocol
- Compliance with protocol and after approval by ethics committee
- Physician responsible for medical care of subjects and medical decisions

Good clinical practice (GCP) for trials on medical products

International Conference of Harmonization (ICH-GCP)

- Protection of trial subject
  - Ethics Committee
  - Informed consent (voluntary, detailed information)
  - Insurance
- Responsibility of the
  - Sponsor
  - Investigator
  - Monitor
- Data handling
  - Investigator
  - Sponsor/monitor
    Safety reporting of serious adverse events (SAE)
  - Archive of data
- Statistics (experimental design, randominisation, statistical analyse)
- Quality assurance

Bad Clinical Practice (1)

- Malevolence
  Sabotage of research, theft of data
- Fraud
  „Improvement" of data/results
  „Arbitrary" correction to meet inclusion criteria
  Totally or partially fabricated cases
- Violation of ethical principles
  Inadequate consequence
  Selection of subjects (inadequate exclusion of „high risk group")
  Dangerous or disturbing invasive procedures
  Distress by contact of study
  Dangerous treatment (inadequate safety information, withdrawal of the proved substance)
  Insufficient confidentiality
  Low insurance coverage

Bad Clinical Practice (2)

- Protocol violations
  - Insufficient knowledge/understanding
  - Omissions (tests left out)
  - Errors involving
    - patient selection
    - evaluation
    - dates
    - treatment (dose, concomitant medication, allocation)
    - blindness
- Erroneous Values
  - Work overload
  - negligence
  - incompetence

Best available medical care & quality of scientific evidence - 1

- Three factors will determine the quality of medical care:
- individual clinical expertise and experience
- scientific evidence

Best available medical care & quality of scientific evidence - 2

Providing the best possible medical care of an individual patient depends on the doctor´s

- ability and willingness to
- integrate individual clinical expertise
- and the best external evidence
- (true evidence-based medicine)

Best available medical care & quality of scientific evidence – 3

Sound scientific evidence is the basis for modern medicine

- **prevention**
- **diagnosis**
- **treatment**
- **rehabilitation**
- **but also for <u>regulatory approval</u>**

Best available medical care & quality of scientific evidence – 4

Conclusion:

the practice of contemporary medicine depends

crucially
on the quality of scientific evidence

Best available medical care & quality of scientific evidence – 5

Scientific evidence

- is never static
- is subject to constant change and adjustment (new facts)
- can be flawed in many different ways
- can never be perfect

Best available medical care & quality of scientific evidence - 6

But are we or/and the public still able to trust the scientific evidence ?

several high-profile cases have recently shaken the trust in the foundations of scientific evidence:

- Hormone replacement therapy/postmenopausal women
- Rofecoxib - VIOXX®
- Paroxetine - PAXIL®

Hormone replacement therapy for postmenopausal women-1

- **1997: Hemminki &McPherson** - BMJ 1997; 315: 149-53:

  HRT: increased cardiovascular risk

- **2000: Hemminki &McPherson** - Lancet 2000; 355:566-9

  include data from licensing trials

  access to unpublished licensing data by order of the High Court of Finland

Hormone replacement therapy for postmenopausal women-2

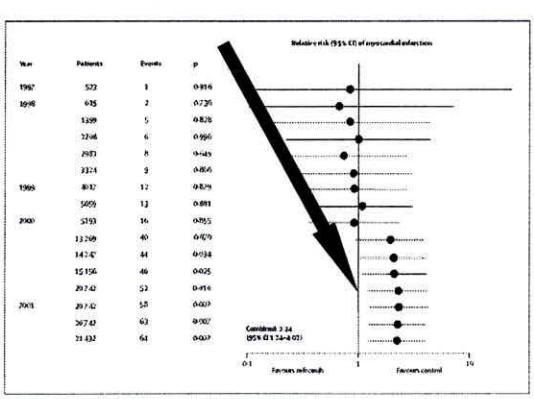
2004: Mc Pherson & Hemminki - BMJ 2004; 328: 518-20

Lessons from hormone replacement therapy

- risk of HRT could have been recognised before 1997
- licensing studies should be in registers of clinical trials

ROFECOXIB - VIOXX®

(Risk of cardiovascular events and rofecoxib - Lancet 2004; 364: 2021–2029)



...the reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified...

Best available medical care & quality of scientific evidence

Paroxetine - Paxil®

- **increased suicidal thoughts in some patients ?**

  (especially juvenils)
- **was this information withheld from the medical community/licensing authorities ?**

Future outlook for clinical trials

- ICH-GCP provides widely accepted and scientific standard for clinical trials

  ICH-GCP guidelines facilitates acceptance of foreign data
- Sponsors will increase their research activities outside of high-industrialized countries (USA, EU, etc.)
- Compliance with GCP, protocol and regulatory requirements

  Assurance that the results are credible and accurate

  Rights and integrity of trial subjects are protected

  More efficient clinical development

  Reduced number of necessary trials

  Facilitates use of global dossier for regulatory submissions in EU, USA, Japan, etc.