Clinical Trial Registration:

Improving transparency, accountability and public trust

Introduction

Franz Gerstenbrand, Holger Baumgartner

Physicians all over the world will agree that it is their most important duty to provide the best available medical care for their patients.

Unfortunately we all know that in reality this translates on a global scale into medicine of a widely differing quality for different people.

WFN as a global actor is addressing these realities in the program of the 18th World Congress of Neurology taking place in Sydney 2005. The organizers are to be commended for including into the program as

Main topics:

- Problems and Solution of Practice in the Developing World
- Neurology Infections Main Theme (focusing on the Developing World)
- Burden of Stroke: WHO/ISS – The Global Strake Initiative

Furthermore

Five regional meetings (Pan-American; Pan-Arab; European, Pan-African- Asian, Oceanian Regional Symposia) are dealing with regional aspects.

However, regardless of the prevailing conditions, the medical doctor has the duty to provide the best **possible** medical care for his or her patients.

Three factors will determine the quality of medical care:

- individual clinical expertise and experience
- scientific evidence (internet...)
- availability of resources

All three are necessary for delivery of optimal medical care.

Utilizing the best scientific evidence for the best possible care for an individual patient depends on the doctor's ability and willingness to integrate individual clinical expertise and the best external evidence, which is the hallmark of true evidence based medicine.

The internet has made scientific evidence globally available. Unfortunately, availability of resources will frequently be the limiting factor for doctors in the developing countries.

However, sound scientific evidence is the basis for all of modern medicine. Prevention, diagnosis, treatment and rehabilitation – all depend on scientific evidence. Moreover, regulatory approval and marketing authorization are also based on scientific evidence.

Thus, the practice of medicine depends critically on the quality of scientific evidence. Obviously, scientific evidence is never static but subject to constant change and adjustment as new facts materialize. We also know that evidence can be flawed in many different ways. Thus we are fully aware that scientific evidence can never be perfect.

Recently however, several high-profile cases have shaken the trust in our system of medical care resting on the foundations of scientific evidence. The medical community, regulators and industry, all play their part in these events. We will focus on 3 examples.

The first example:
Hormone replacement therapy for postmenopausal women.

For years the medical community has fallen into the trap of surrogate thinking. Observational studies have shown an association between postmenopausal hormonal changes and the increase in cardiovascular disease in women. Replacing hormones was considered to be the logical countermeasure and widely practiced. Women were not only told that they would feel better but that hormone replacement therapy was also good for their health. Recently, several big randomized controlled trials (financed by public institutions) showed that postmenopausal hormone replacement does not protect from but rather increases cardiovascular risks.

However, based on available data Hemminki had already shown in 2001 that the regulatory approval was based on biased data; the cumulative evidence at the time showed an in-creased cardiovascular risk. Their conclusion: regulatory approval and post-marketing surveillance do not work properly; medical doctors trusting the approval process might be misled.

A point of particular importance: Hemminki got only access to the data available at the regulatory authorities after obtaining court approval to do this. The conclusion: Medical data on which regulatory decisions are based are kept out of the public domain, a highly unscientific and unethical situation.

The second example:
Rofecoxib or better known as VIOXX®.

Vioxx® and some other COX-2-Inhibitors have been shown to increase cardiovascular risk, particularly in patients prone to such risks. VIOXX® was voluntarily withdrawn by MSD in the fall of 2004.

However, a cumulative meta-analysis of the risk of cardiovascular events and VIOXX® published in December 2004 in the Lancet showed that the excess cardiovascular risk was already evident as early as in the year 2000.

The authors conclude: "The reasons why manufacturers and drug licensing authorities **did** not continuously monitor and summarize the accumulating evidence need to be clarified." This process of clarification is currently part of the on-going court proceedings in the US.

The third example:

Paroxetine (brand name: Paxil®) belonging to the class of SSRI (Serotonin re-uptake inhibitors), an antidepressant.

The drug was introduced in the early nineties. The drug company producing PAXIL is supposed to have known for many years that PAXIL might increase suicidal thoughts in some patients, particularly in juvenile suffering from depression without informing the medical community or the licensing authorities.

In an out of court settlement with the state of New York the company has agreed to make all its clinical trials publicly available. In the US, there are several more ongoing lawsuits in this matter.

Both, FDA and EMEA have recently updated their information on the use of Serotonin re-uptake inhibitors.

These 3 examples demonstrate that:

1) by far not all data from clinical trials are available to the scientific community;

2) neither **manufacturers nor drug licensing authorities** are currently fulfilling their obligation to **monitor and summarize accumulating evidence continuously;**

3) the medical community does not have the means to compensate for these deficiencies.

The scientific medical community has been calling for a public registry of all interventional clinical trials for many, many years.

Industry has claimed a need for confidentiality in order to protect economic interests and intellectual property rights.

However, at stake is the safety of patients and the credibility of medicine and the medical profession. In addition, respect for trial participants and their risk-taking have to be considered. In conclusion, when balancing these opposing interests "full access to all the data" is a clear ethical imperative and moral obligation.

Recently the editors of several leading medical journals have changed their publication policy demanding that clinical trials be registered in a publicly accessible registry before inclusion of the first patient.

The above three examples have also led to political action:

In the UK, the Health Commission of the House of Commons published a report of their findings from an inquiry taking place in the fall and winter of 2004-2005. In this report entitled "The influence of the pharmaceutical industry" they call for sweeping reforms including a publicly accessible registry. This report pinpoints also deficits of the medical community and of medical education both pre- and postgraduate.

In the US, as law has been proposed in order to grant free access to clinical. Called FACT - for Fair Access to Clinical Trial Data – this law intends to make registering clinical trials mandatory.

In conclusion, the idea for Clinical Trial Registration has definitely arrived. We can be sure that Clinical Trial Registration will be an important step for improving transparency, accountability and public trust. However, it will be up to the scientific community and politicians to find the proper way to achieve this goal in a globalized world. Obviously, WHO is a good candidate for taking care of such a global effort. The future will show, if the political will is there to entrust WHO with this important mission.

Today's presentations will bring us up-to-date with this important topic.

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Clinical Trial Registration

Introduction

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Ludwig Boltzmann Institute for Restorative Neurology, Vienna, Austria

World Congress of Neurology
Sydney, November 5-11, 2005
Neuroethics

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 lethal poison, even as advice

Will to respect the teacher like own parents, sharing one's 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

Declaration on Bioethics and Human Rights

Paris, 2005

Person's identity includes

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

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.

Ethics

Altruism

Sense of honour

Justness

Respect for others

Solidarity

Ability to forgive

Ethics in medicine I

... is necessary for each human being :

- any preventive, diagnostic and/or therapeutic medical intervention
- scientific research (basic research, clinical studies) according to
  - ICH-GCP (Good Clinical Practice)
  - GMP (Good manufacturing practice)
  - Clinical trials for new diagnostic and therapeutic methods

Ethics in medicine II

... based on:

- Declaration of Helsinki (with amendments)
- Declaration on Bioethics and Human Rights, Paris, 2005
- Domestic and international law in confirmity with human rights law

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

<u>Conclusion:</u>

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/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

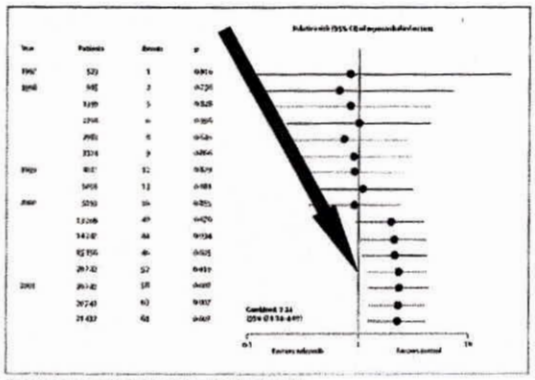
2004: Mc Pherson & Hemminki - BMJ 2004; 328: 518-20

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 <u>manufacturer and drug licensing authorities</u> did not continuously monitor and summarise the accumulating evidence <u>need to be clarified</u>...

Best available medical care & quality of scientific evidence

<u>Paroxetine - Paxil®</u>

- **increased suicidal thoughts in some patients ?**
  (especially juvenils)
- **was this information withheld from the medical community/licensing authorities ?**

Program – Monday 7 November 2005

Chairs: *Allan Ropper (USA); Stephan Mayer (USA)*

1115 – 1145 Malignant MCA syndrome – *Werner Hacke*

1145 – 1215 Treatment of intracerebral hemorrhage – *Daniel Hanley*

1215 – 1245 The neurology of sepsis – *Jeremy Farrar*

Muscle and Nerve

Tumbalong Auditorium

Chairs: *David Burke (Australia); Gerard Said (France)*

Advances in Neuromuscular Diseases: Immune-mediated Neuromuscular Disorders

0915 – 0935 Guillain-Barre Syndrome – *Nobuhiro Yuki*

0935 –0955 Chronic Immune-mediated Neuropathies – *John Pollard*

0955 – 1015 Vasculitic Neuropathy – *Gerard Said*

1015 – 1035 HIV related neuromuscular disease – *Bruce Brew*

1045 – 1115 Morning Tea

Chairs: *Frank Mastaglia (Australia); Marianne De Visser (Netherlands)*

Inherited Neuromuscular Disorders

1115 – 1135 Early and late onset Neuropathy in patients with CMT1B – *Michael Shy*

1135 – 1155 Amyloid Neuropathy – *Mary Reilly*

1155 –1215 Myotonic Disorders – *Charles Thornton*

1215 – 1235 Limb-girdle Muscular Dystrophies – *Corrado Angelini*

Ethics in Neurology

Tumbalong Room 1

Clinical Trial Registration: improving transparency, accountability and public trust

Chairs: *Franz Gerstenbrand (Austria); Holger Baumgartner (Austria)*

0915 – 0925 Introduction – *Franz Gerstenbrand, Holger Baumgartner*

0925 – 0945 Why clinical trial registration & open access publishing – *Martin van der Weyden*

0945 – 1005 Consequences for the clinical investigator – *Jim Toole*

1005 – 1020 Will transparency improve public trust? – *Johan Aarli*

1020 – 1040 2005 and beyond: The view from the industry – *Michael Berelowitz*

1040 – 1050 Discussion – *Franz Gerstenbrand*

1050 – 1115 Morning Tea

Brain death : Minimal standards – Round Table Discussion

1115 – 1245 Introduction – *Franz Gerstenbrand*

William Carroll

Jagjit Chopra

Daniel Hanley

Ashraf Al Kurdi

Holger Baumgartner

Résumé – *William Carroll*

Concluding remarks – *Franz Gerstenbrand*