



"CLINICAL TRIALS ON TRIAL"

HAI Europe Open Seminar 2008, 21 November 2008

Venue: Neues Stadthaus, Parochialstraße 3, 10179 Berlin

Programme:

10.00: Doors open for Registration and coffee

11.00: Welcome address

Panel 1: The gold standard or fool's gold?

11.05 *Joel Lexchin - Introduction of Speakers and Overview of Topics*

11.10 Anita Hardon: Diversity in CT, design, Institutional changes

11.30 Joan-Ramon Laporte: Disclosure, Access, Selective data, Impact on safety

11.50-12.30 (up to 12.40): **Debate 1**

12.40-13.40: LUNCH

13.40- 14.10 **Afternoon Keynote address: Peter Lurie**

14.10- 14.35 Question and Answer session

Panel 2: Ethics in Clinical Trials

14.35 *Christian Wagner-Ahlf - Introduction of Speakers and Overview of Topics*

14.40 Wim Vandeveld: The Patient Perspective

15.00 Annelies den Boer: CT in Developing Countries

15.20-15.35 COFFEE BREAK

15.35-16.15 (up to 16.25): **Debate 2 Panel 2 continued**

Panel 3: Clinical Trials as marketing tools?

16.25 *Elina Hemminki - Introduction of Speakers and Overview of Topics*

16.30 Trudy Dehue: Clinical Trials as Marketing Tools

16.50 Petra Jonvallen: Case study on CT

17.10-18.00: **Final Debate and Closing Remarks**



SPEAKERS

KEYNOTE SPEAKER (13.40)

Peter Lurie, MD, MPH is Deputy Director of Public Citizen's Health Research Group, a Ralph Nader-founded advocacy group in Washington, DC. During his academic career he wrote about needle exchange programs, ethical aspects of mother-to-infant HIV transmission studies and HIV vaccine trials in developing countries and the impact of economic development policies upon the spread of HIV. At Public Citizen, he has been involved in efforts to ban or relabel multiple drugs and has petitioned to ban certain unsafe medical needles, to ban candles with lead wicks, to reduce worker exposure to beryllium and to lower medical resident work hours.

PANEL ONE

Joel Lexchin, MD (Moderator) received his MD from the University of Toronto in 1977 and has been an emergency physician at the University Health Network for the past 21 years. He is currently a Professor in the School of Health Policy and Management at York University and an Associate Professor in the Department of Family and Community Medicine at the University of Toronto. He has been a consultant on pharmaceutical issues for the province of Ontario, various arms of the Canadian federal government, the World Health Organization, the government of New Zealand and the Australian National Prescribing Service. He is the author or co-author of over 90 peer-reviewed articles on topics such as physician prescribing behaviour, pharmaceutical patent issues, the drug approval process and prescription drug promotion.

Joan-Ramon Laporte is Professor of Clinical Pharmacology at the Autonomous University of Barcelona, and Director of the Catalan Institute of Pharmacology, a 25-year-old institution working on the teaching and training of clinical pharmacology and therapeutics, drug information and research in pharmacoepidemiology. The institute is a WHO Collaborating Centre for Research and Training in Pharmacoepidemiology.

Anita Hardon was appointed as a lecturer in the Anthropology Department of the University of Amsterdam, after completing her PhD on self-medication practices in the Philippines (1990). She was the principal investigator of a policy-oriented study commissioned by the Dutch Health Care Research foundation, which aimed at developing ways in which clinical research can become more diversity-sensitive. In 2000, Anita was appointed Professor in Anthropology of Care and Health. Anita has published several books including the *Social Lives of Medicines* (with Susan Reynolds Whyte and Sjaak van der Geest, 2002 published by Cambridge University Press), *Medicines out of Control* (with Charles Medawar, 2004 awarded the Prix du Livre in 2005 by Prescrire), and the manual *How to Investigate Drug Use by Consumers* (with Daphne Fresle and Catherine Hodgkin, 2004). Between 2000 and 2005 she was also a chairperson of Health Action International and director of the Amsterdam School for Social Science Research.

PANEL TWO

Christian Wagner-Ahlf (Moderator) is a Project Manager at BUKO Pharma-Kampagne. Christian's main working areas are national and international advocacy on access to medicine, patent systems and patient information. He has been a member of Health Action International HAI Europe Executive Board since 2005. Until 2008, Mr Wagner-Ahlf coordinated HAI Global members' activities related to the World Health Organization "Intergovernmental Working Group on Innovation, Public Health and Intellectual Property rights (IGWG)".

Christian is also editor-in-chief for the German magazine, Gute Pillen - Schlechte Pillen.

Wim Vandeveld has been committed to full time action on HIV, hepatitis and TB policy, education and medical research programmes for nearly a decade. Elected to the Board of Directors of the EATG in 2004, he has served as its Chairman since 2007. EATG is the foremost HIV patient advocate NGO in Europe, representing over 30 countries on treatment and policy issues. Wim is the co-founder and President of the Portuguese HIV treatment group, GAT, and a member of the Steering Committee of the European Community Advisory Board (ECAB). Wim is a member of the HIV/AIDS Civil Society Forum and Think Tank of the European Commission and, since 2004, he has served on the Steering Committee of AIDS Action Europe, the European network of AIDS Service Organisations. In July 2008, he co-founded the Civil Society Health Network of the Portuguese-speaking countries, Rede Saúde PLP. Wim represents the Community in the Core Group of the Stop TB Partnership's Working Group on New Drugs.

Prior to his treatment advocacy work, Wim worked as an economist and has 16 years' extensive experience in the banking industry in Belgium, Spain and Portugal.

Annelies den Boer is a Project Coordinator at the Wemos foundation in the Netherlands. She is currently working on ethical aspects of clinical trials in developing countries. Wemos is a Netherlands based organisation that contributes to structural improvement of people's health in developing countries. She was previously employed by Médecins Sans Frontières in The Netherlands and Cambodia, and worked as a policy advisor for Bureau Beleidsvorming Ontwikkelingssamenwerking (Institute for Advocacy in International Cooperation) in The Hague.

PANEL THREE

Elina Hemminki (Moderator) is currently a research professor at STAKES (National Research and Development Center for Welfare and Health) in Helsinki, Finland. She has a medical background and extensive experience in epidemiological and health services research. Her research interests include knowledge production in medicine and its regulation as well as the role of ethics in decision making.

Trudy Dehue is a full professor of Theory & History of Psychology. She recently published the book *De depressie-epidemie [The depression epidemic]* with Augustus in Amsterdam that became a bestseller in the Netherlands. See www.rug.nl/gmw/boeken and for her website in English www.rug.nl/staff/g.c.g.dehue.

Petra Jonvallen received a PhD in Technology and Social Change from Linköping University in 2005 and currently works as assistant professor of Gender and Technology at Luleå University of Technology. Broadly, her research focuses on social aspects of various technologies in medicine and health care, mainly in pharmaceutical clinical trials and in practices of childbirth. Her main concern is the tensions and possibilities enabled by the intermingling of health care, the pharmaceutical and medical technologies industry, and medical research.



Overview

Clinical trials are considered the 'gold standard' for scientific research and the most reliable tool to obtain evidence on a medicine's effectiveness. But, just how much do we know about the way they are designed, conducted and presented?

Some argue that the influence of pharmaceutical companies' marketing departments and private contract research organisations (CROs) has led to a profound shift in priorities. Access to data is restricted and there is selective publication of results, leading to a misleadingly positive impression of effectiveness. With the newer antidepressants, access to the full body of clinical trial evidence led to screaming headlines saying that "antidepressants do not work", a far cry from what most people thought, based on selected, incomplete results.

But problems do not only affect study designs and their results.

Clinical trials affect human lives, with more and more medicines being tested in developing and transitional countries, where regulations are lax, law enforcement is difficult and ethics of informed consent are often ignored. Is it ethical to test a medicine in a country where it is sure to be unaffordable once marketed? And in a worrying trend, clinical trials are increasingly being used as sophisticated marketing tools to promote specific prescribing by physicians and to advertise new medicines to a wider public.



Keynote Address

Keynote Speaker: Peter Lurie, Public Citizen, Health Research Group (address at 13.40)

This presentation will concentrate on a number of recent developments in the United States with potential relevance to Europe and elsewhere. Topics to be addressed will include clinical trials registries, access to data at the U.S. FDA, conflict of interest in FDA advisory committees, regulation of direct-to-consumer advertising and off-label promotions. The talk will close with a discussion of non-drug products regulated by the FDA: genetic tests and medical devices.

Panel 1: The gold standard or fool's gold?

Moderator: Joel Lexchin, York University

Speaker One: Anita Hardon, University of Amsterdam

Confronting diversity in the production of clinical evidence

The goal of evidence based medicine (EBM) has been to improve the quality of care through the standardization of clinical decisions. Whether this goal can be accomplished is highly dependent on the quality of the underlying evidence base. An important aspect of the quality of the evidence concerns the 'generalizability' of the results from underlying clinical trials. Traditionally, the general assumption seemed to be that clinical trials yielded universal knowledge. More recently, this assumption has been criticized. Increasing evidence shows that outcomes of treatment differ according to patient characteristics like age, sex or ethnicity. Moreover, endpoints need to acknowledge diversity in disease progress and manifestation between populations.

If EBM is to improve the quality of care for the *whole* population, it is imperative that this diversity in aetiology of disorders and efficacy of treatments is considered in the design of clinical studies. Regulatory reforms, particularly in the US, have drawn greater attention to this issue, especially in relation to sex, age and ethnicity. These reforms stemmed from calls for inclusion of women and minorities in trial populations. Despite this recognized need, several reviews have shown that these groups are still generally underrepresented. When represented, subgroup analysis is rare.

The challenge is great. More than fifteen years after regulatory reforms calling for representation of and analysis by age, sex and ethnicity, evidence on such diversity is still scarce. In this presentation, we put forward methodological suggestions and institutional mechanisms which can facilitate a more systematic and comprehensive production of diversity sensitive evidence.

Speaker Two: Joan-Ramon Laporte, Fundació Institut Català de Farmacologia (FICF)

RCTs – The gold standard or fool's gold?

This presentation will address four key areas of RCT related to its status as 'the gold standard'. The discussion of internal and external validity, publication bias and fraud will enable us to better assess whether RCT should be awarded this unique status.

Several questions should be considered regarding internal validity:

- Did the control group receive optimal treatment?
- Was the dose of the control group adequate?
- Was the sample size adequate to identify any relevant difference?
- Did the published results refer to the primary variable?
- Have all the trial results been published?
- Were the results presented as a relative risk reduction, or as an absolute risk reduction?

External validity addresses the transferability of the data to usual use. Patients in RCTs often differ from those in real practice in terms of age, comorbidity, other treatments taken concomitantly, dosage and compliance as

well as diagnostic criteria. Differences in duration, patterns of use of the medication and the exclusion of comorbidity will clearly make it more difficult to translate results into the clinical practice context.

The third key area is the role of publication bias in assessing the merits of medicines or therapeutic options. As the majority of RCTs on medicines are sponsored by the manufacturer, the results may not be published when they are not favourable to the study drug. Conversely, the results may be repeatedly published when they are favourable to the study drug. This has been shown recently for SSRI antidepressants. Selective publication of RCTs grossly distorts the image of the beneficial and adverse effects of medicines. Not only does under-reporting breach implied contracts with the patients who participate in RCTs (who assume that they are contributing to a growth in knowledge); it can also lead to biased and unnecessarily imprecise estimates of the effects of treatments. Because these unreliable estimates sometimes harm patients, under-reporting of research has been deemed to be a form of scientific as well as ethical misconduct.

Fraud is also common in clinical trials, particularly in the process of adjudicating adverse events, and also in the statistical data analysis. The recent public availability of internal company documents from Merck regarding rofecoxib shows that this was common with this drug, and it suggests that it may be common with other drugs and in other companies.

Finally, conflicts of interest taint the reputation of clinical research and increased incidences of authors' financial ties to industry challenge physicians' faith in the validity and reliability of RCT results and in medical publications. As a result, it is becoming more and more difficult to evaluate the true safety and effectiveness of medicines.

Though RCT may be the best epidemiological method for causal inference, it is usually performed in a way which favours the sponsor's treatment. Consequently, medical literature should no longer be considered reliable for valid information. Research should be entirely free from commercial interest. The status of RCT as the 'gold' standard should be reconsidered and RCTs should be viewed only as one of many pieces of evidence about therapeutic interventions, making more room for other evidence.



Panel 2: Ethics in Clinical Trials

Moderator: Christian Wagner-Ahlfs, BUKO Pharma Kampagne

Speaker One: Wim Vandeveldel, European AIDS Treatment Group (EATG)

Since the early days of the AIDS epidemic, the HIV patient advocates movement in the US and in Europe has organized Community Advisory Boards (CAB) to deal with issues such as, inter alia, protection of participants in clinical trials and research ethics. This presentation addresses the basics of community participation in HIV R&D in Europe today, starting from the point of view of the research candidate. Why do trial participants engage with research? How can communities directly participate in the design of studies? These questions continue to be relevant today as they impact on the way community groups collaborate with industry, researchers and regulators, and on their vision of the critical role that civil society should have and its responsibility towards research.

Speaker Two: Annelies den Boer, Wemos

Increasingly, drugs used in the European Union have been tested in developing countries. As a result of weak health systems and insufficient regulatory oversight, the rights of trial participants in these countries are insufficiently protected. European Directives state that drugs should be tested according to ethical guidelines such as the Declaration of Helsinki, before they are granted market authorization. However European medicines agencies do not routinely check whether drugs have been tested according to ethical guidelines. As a result unethically tested drugs have been granted market authorization. As a purchaser of drugs tested in developing countries, the European Union has a clear responsibility towards the test subjects in these countries. Therefore, Wemos strives for integrating ethical guidelines into the system of market authorization.



Panel 3: Clinical Trials as Marketing Tools?

Moderator: Elina Hemminki, STAKES

Speaker One: Trudy Dehue, University of Groningen

Merging trials and publicity: On clinical trial research as a marketing instrument

A considerable number of studies have been published demonstrating that clinical trials financed by pharmaceutical companies generate more positive results for medicines than independently-funded trials. Nevertheless, the distinction between testing and selling drugs is increasingly blurred. Immense interests are involved in clinical trials today as the pharmaceutical stock market soars or plunges on the basis of even interim test results. As a consequence, pharmaceutical companies in need of positive test results turn to commercial research organizations (CROs) that are dependent upon their clients for their very existence. Slogans such as 'Your partner from bench to market' openly express the mission of CRO's to serve their customers' interests. This presentation will discuss some methodological handbooks from the CRO branch, showing how the privatization of clinical trials research changes its methodological protocols and the meaning of words such as 'research', 'article' and 'author'. In addition, CRO's are now merging with pharmaceutical marketing companies that are now opening clinics for conducting trials as well. In this way, the difference between attempts to get new drugs through the licensing process and attempts to get new drugs into the bodies of as many people as possible, is completely vanishing.

Speaker Two: Petra Jonvallen, Luleå University of Technology

This presentation concerns different forms of "market configuration" and "market orientation" in pharmaceutical R&D and is based on ethnographic research on a large scale clinical trial on a potential obesity drug performed in a Swedish clinic in 2001. My case study provides an illustration of how markets are configured throughout a trial: from the trial participant recruitment practices performed by a contract research organization; via the work performed by nurses, dieticians and doctors in the clinic once the trial had started; to the discussions by the pharmaceutical company's monitoring board after the trial was terminated.



BACKGROUND READING

N.B. This seminar pack includes copies of the 2008 Helsinki Declaration and ISDB's Declaration of Paris

Science: Special Online Collection: Clinical Trials and Tribulations. <http://www.sciencemag.org/clinicaltrials/>

In the 10 October 2008 issue, Science explored the increasingly complex clinical trials landscape. News stories reported on the growing costs of moving drugs from lab to market, the expansion of clinical trials overseas, efforts to make clinical data more accessible, balancing male and female participation in trials, and new interventions designed to prevent heart disease. An online video presentation discusses progress in regulating and testing medicines for children, and a podcast segment highlights some of the current challenges of conducting clinical trials including rising costs, complicated paperwork, and poor management.

The Buenos Aires Declaration on Ethics and Clinical Trials. Buenos Aires. May 13th, 2008.

<http://www.boletinfarmacos.org/download/Buenos%20Aires%20Declaration%20on%20Ethics%20and%20clinical%20Trialsfinal.pdf>

"The Buenos Aires Declaration on Ethics and Clinical Trials" was unanimously approved at the First Latin American Workshop on Ethics and Clinical Trials and endorsed by the Latin American organizations that are listed at the end of the Declaration.

Both the Workshop and the Declaration were a response to the rapidly increasing number of clinical trials that are taking place in the region and to the questions being raised as a result of the many alleged violations of ethics during the approval and implementation of the trials.

The Benefits and Savings from Publicly-Funded Clinical Trials of Prescription Drugs. Dean Baker. March 2008. Center for Economic and Policy Research. <http://www.cepr.net/index.php/publications/reports/the-benefits-and-savings-of-publicly-funded-clinical-trials-of-prescription-drugs/>

This paper proposes publicly funding prescription drug trials as an alternative to the present system wherein pharmaceutical companies often finance and conduct tests of their drugs themselves. The report posits that in addition to substantial savings for the government, independent companies working under long-term federal contracts would result in full and accurate disclosure of the results of drug testing.



CLINICAL TRIALS IN THE MEDIA

The Guardian. Ben Goldacre. Listen carefully, I shall say this only once. Published October 25, 2008.

<http://www.guardian.co.uk/commentisfree/2008/oct/25/medical-research-science-health>

Financial Times. Nicholas Timmins. Nice questions drug test methods. Published October 17 2008.

<http://www.ft.com/cms/s/0/c694ffaa-9be3-11dd-ae76-000077b07658.html>

The Independent. Professor Sir Michael Rawlins. Michael Rawlins: Statistics can help, but doctors must also use their judgment. Published 16 October 2008. <http://www.independent.co.uk/opinion/commentators/michael-rawlins-statistics-can-help-but-doctors-must-also-use-their-judgement-962607.html>

The Independent. Jeremy Laurance. Boss of drug watchdog attacks testing method. Published 16 October 2008.

<http://www.independent.co.uk/life-style/health-and-wellbeing/health-news/boss-of-drug-watchdog-attacks-testing-method-962711.html>

International Herald Tribune. Stephanie Saul. Lawsuit alleges Pfizer manipulated drug studies. Published October 8 2008. <http://www.iht.com/articles/2008/10/08/business/drug.php>

Washington Post. Ken Getz & Doug Peddicord. Tuskegee, a Cloud Over Research. Minorities Are Not Participating Enough In Clinical Trials. Published September 30, 2008. <http://www.washingtonpost.com/wp-dyn/content/article/2008/09/26/AR2008092603126.html?sub=new>

Financial Times. Margaret McCartney: Reality Check. Published: September 27, 2008. Interview with Hazel Thornton (Co-founder of Consumers' Advisory Group for Clinical Trials in 1994)

The Guardian. James Randerson. More than half of US drug safety studies never see the light of day. Published September 23, 2008. <http://www.guardian.co.uk/science/2008/sep/23/clinical.trials>

Pharmalot. Ed Silverman: Most Failed Clinical Trials are never published. Published September 23, 2008.

<http://www.pharmalot.com/2008/09/most-failed-clinical-trials-are-never-published/>

The Guardian. Ben Goldacre. Missing in Action: the Trials that did not make the news. Published September 20, 2008. <http://www.guardian.co.uk/commentisfree/2008/sep/20/medical.research.cancer>

International Herald Tribune. Alex Berenson: A Popular Drug with uncertain benefits. Published September 2, 2008.

<http://www.iht.com/articles/2008/09/02/business/drug.php?page=1>

The Economist. Valuing New Drugs: NICE turns nasty. Published August 21, 2008.

http://www.economist.com/research/articlesbysubject/displaystory.cfm?subjectid=531766&story_id=11975428

World Medical Association (WMA) press release. Proposed revisions to the Helsinki Declaration at the next WMA meeting in Seoul, October 2008. Published 20 June, 2008. http://www.wma.net/e/press/2008_8.htm

The Social Medicine Portal. FDA Abandons Declaration of Helsinki for International Clinical Trials. June 1, 2008.

<http://www.socialmedicine.org/2008/06/01/ethics/fda-abandons-declaration-of-helsinki-for-international-clinical-trials/>