The new European clinical trials regulation

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European Leukemia Net: Major Aim to Foster International Academic IITs in Leukemias

Major field: Treatment optimisation trials

- **Rare diseases, as leukemias**
- **Standard care and research done in parallel**
  (only way for progress in rare diseases)
- **Research questions without commercial interest**
- **Drugs with marketing authorisation**

Low Budget

(public funding, university budget, partly supported by industry)

High quality research

- **Excellent research infrastructure**
- **High international acceptance**

High potential costs

- **Multicenter, many hospitals (health care standard!)**
- **Long-term observation**
- **Toxicities in pts with life-threatening disease and comorbidities**

“History” of the EU Drug Regulation

ICH-GCP Guidelines

(Initiative of regulatory authorities / pharm. industry from EU / Japan / USA , 1996)

Clinical Trials Directive 2001/20/EG

(Later: EU GCP Directive (2005/28/EC) 08.4.2005)

Aims:

Improve patient safelty and quality of clinical research

Harmonize conditions within EU

Transfer into national legislation

Germany
AMG Novelle 6.8.04

Other Countries
Deadline: 2004

<u>Major consequence for academic research:</u>

Therapy optimisation trials (TOPs) and Investigator Initiated Trials (IITs) have to follow the same rules as registration studies of pharmaceutical industry

THE LANCET

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Who's afraid of the European Clinical Trials Directive?

Wouldn't it be nice if the approval and monitoring of clinical research done in the many, varied, and ever-increasing number of European countries could be simplified and streamlined? This deceptively simple idea was first mooted well over a decade ago and by 1995 the European Commission had published a concept paper for a European Directive on Implementing Good Clinical Practice. Several complex rounds of negotiation between the various European legislative bodies followed and the result, Directive 2001/20/EC, was officially adopted on April 4, 2001. The race is now on for Europe's member states to incorporate the Directive into domestic legislation, since compliance will be mandatory as of May, 2004. Most European countries published draft legislation earlier this year. Somewhat belatedly, some of Europe's academic clinical investigators have started to voice fears about how the Directive might stifle their research.

The essential aims of the Directive are to harmonise the various national administrative procedures necessary to start a clinical trial and to set pan-European legal standards of protection for all clinical trial participants, including healthy volunteers. Non-interventional trials will be exempt. The Directive was initially conceived and drafted as a way of facilitating commercial drug development to give Europe's pharmaceutical industry a competitive edge. Only in the later stages of negotiation was some acknowledgment of the different nature of non-commercial research made. The final text thus states that: "Non-commercial clinical trials conducted without the participation of the pharmaceutical industry may be of great benefit to the patients concerned", and notes that the Directive should "take account of the special position" of such trials with regard to the manufacture, packaging, and labelling of medicinal products. The catch is that in all other respects publicly funded clinical trials must fulfil the same requirements as their commercial counterparts.

According to the Directive no interventional research may be initiated without a sponsor—"an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial". The notion of a sponsor is familiar to commercial research. Publicly funded research ventures are by contrast collaborations where partners oversee different aspects of a trial but no one person or organisation is required to take overall responsibility. The inscription of this requirement into law will expose the single sponsor to the risk of litigation, a risk that charities, universities, and other publicly funded research bodies are unsurprisingly unwilling to take. It will be the sponsor's role to apply for trial authorisation and ethics-committee approval, activities currently the responsibility of the principal investigator.

Ethics committees will be obliged to give an opinion within 60 days of receipt of a standard trial application. The Directive provides the first European description and enforcement of the responsibilities of ethics committees, which include not only trial authorisation but also long-term monitoring. Serious concerns have been raised as to whether the ethics committees of Europe are sufficiently equipped and funded to take on these added responsibilities. Legal compliance with Good Clinical Practice for all trials will also be mandatory under the Directive, which means that publicly funded investigators face the same intensive site monitoring and source-data verification as are currently standard in industry.

Non-commercial research organisations claim that substantial new investment will be needed to put in place the infrastructure and staff—which the commercial sector already has—for the increased administration and documentation required by the Directive. Critics counter that this is knee-jerk panic at the threat of change and greater monitoring, and a convenient excuse to bemoan lack of funding. Who is right? The following quote about UK-based clinical trials is instructive. "Despite the stated purpose of the Directive it is clear that the planned changes in the UK and the rest of Europe will not simplify, and are unlikely to result in substantial harmonisation of, the current regulatory procedures for the conduct of clinical trials. There are many new requirements that will place an administrative burden on both sponsors of clinical trials and on regulators." This statement comes not from a UK academic body but no less than the Association of the British Pharmaceutical Industry. It follows that if the commercial sector, in whose interests the Directive is principally drafted, forecasts an intolerable increase in red tape, publicly funded investigators are right to be very afraid indeed.

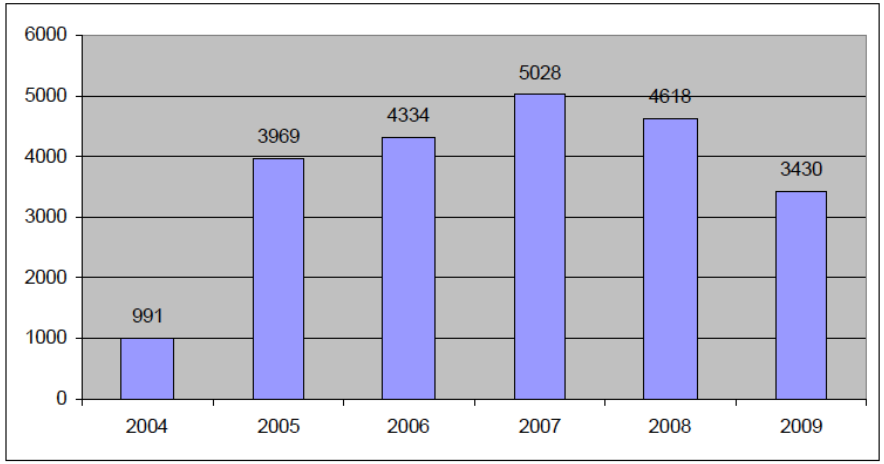
The Lancet

Lancet 2003: ……if the commercial sector, in whose interests the Directive is principally drafted, forecasts an intolerable increase in red tape, **publicly funded investigators are right to be very afraid indeed**

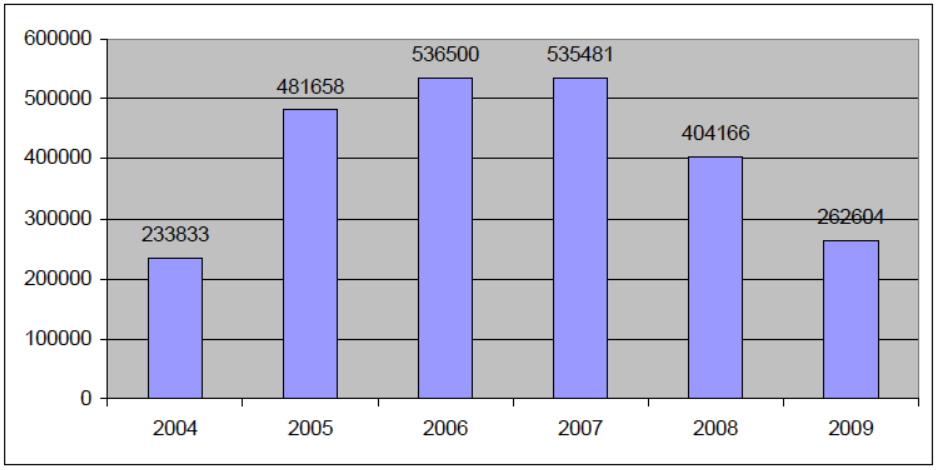
ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC

EUROPEAN COMMISSION, 2009

N° of clinical trials applied for in the EU



N° of planned clinical trials participants in EU



- **Reduction of applications from 2007 to 2011 by 25%**
- **Industry trials: +107% personnel costs**
  +800% insurance costs
  + 90% preparation time
- **Administration costs: 98%**

Source: EudraCT. Please note: 2004-figures only as of 1 May 2004. 2009-figures only until end Sept. 2009

Current Situation of Academic Trials: Summary

The EU Clinical Trials Directive: 3 years on

The EU clinical trials directive came into force in May, 2004, with the aim of simplifying the trial application process and providing a common set of regulations for member states. But some believe the directive has badly misfired, increasing costs and bureaucracy. Richard Hoey reports.

Lars Welzing will think hard before setting up another drug trial. Welzing, a specialist in paediatric intensive care at the University of Cologne, Germany, has just spent close to 3 years getting a modest, 20-patient study off the ground, and right now, he cannot face going through that grind all over again. His problem has been the EU Clinical Trials Directive, which was designed to streamline the trial application process and harmonise it across Europe, but in the view of some it has proven frustratingly counterproductive. Welzing says: "In the past, if you had an interesting medical question, you just needed the OK from the ethics committee. But now the administrative work is so huge. It took a long, long time".

The directive was passed in 2001, with a deadline of May, 2004, for its regulations to be enshrined into the national legislation of all EU member states. A key purpose was to make the European pharmaceutical industry more competitive, by simplifying the trial application process and ensuring that all member states played by the same rules. It also aimed to improve the quality and safety of trials, with extra scrutiny of methodology and stringent monitoring of adverse drug reactions.

The directive introduced the notion of a sponsor—an individual or an institution with legal responsibility for ensuring that the trial is run correctly. Sponsors are responsible for making sure the trial protocol is applied across all study sites and any severe adverse drug reactions are reported promptly and in full. Before the directive, these duties tended to be spread evenly among participating researchers. The sponsor also has to make sure investigators are covered by rigorous new insurance policies, which are reportedly more expensive than those that had been previously required.

Supporters of the directive claim it has been successful at driving up standards and point to the benefits of a single set of trial application procedures across the EU. A spokesperson for the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) insists that the aim of the directive was "to protect trial participants without hindering the development of new medicines". "It has raised the standards of clinical research and resulted in improved recording of data, making it easier to audit and more credible", the spokesperson argues.

But these claims are met with scepticism by many observers. Markus Hartmann, an independent consultant on medical and regulatory affairs based in Trier, Germany, believes the directive has largely failed to deliver. He says: "There were some promises in the clinical trials directive and the question is have they been fulfilled? One promise was to cut red tape, but I think most investigators believe the amount of red tape has increased. Another promise was harmonisation, but I am not sure this has been achieved. And I am not sure there have been many positive effects for safety [although] there have been some."

A key concern is that although the directive was supposed to introduce a single set of regulations, in practice EU states have implemented it in various of ways, some more rigidly than others. Countries differ in their interpretation of the sponsorship rules, the complexity of procedures for ethical approval, and the level of detail required for drug safety reporting.

One of the effects of the directive's stringent application processes appears to be an increase in trial costs, with fears the academic community will be most severely affected. Estimates of the impact on trial costs vary widely, but a recent paper published in the *European Journal of Cancer* suggested in the UK they had approximately doubled since the directive. Richard Sullivan, one of the authors of that study and director of clinical programmes at Cancer Research UK, one of Europe's biggest funders of non-commercial

The printed journal includes an image merely for illustration

- No harmonisation of trial regulations in Europe
- Excess of bureaucracy all over Europe
- Time delay in activation
- High costs
- Less independent trials, less centers, fewer patients within trials
- Commercialisation of clinical trials

EUROPEAN COMMISSION

Brussels, 17.7.2012
COM(2012) 369 final

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

... couching the legislation as a Regulation rather than a Directive will ensure the new rules, once finalised and adopted, will have an **immediate and binding impact across the EU, avoiding the fragmentation and vagaries of interpretation that have plagued Directive 2001/20/EC.**

Definition: Clinical Trial

'Clinical trial': Any of the following

- IMP not authorised
- IMP not used in accordance with the terms of MA
- Assignment to therapeutic strategy in advance and not within normal clinical practice
- Decision to prescribe an IMP is taken together with the decision to include the subject in the clinical study
- Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects

‘Low-intervention clinical trial’: All of the following

- IMP **authorised**
- IMP used **in accordance with the terms of MA** or use is a **standard**
- Additional diagnostics/ monitoring do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice

Low- Intervention Trials: Advantages

- Authorisation rapid
- No insurance
- Reduced monitoring
- No / Reduced labeling

Authorisation

Problems:

- **Separate application in each country; multilingual**
- **Different time-lines and opinions**

EU regulation:

- **Central application portal** (technical solution?)
- **Clear responsibility**
- **Harmonised dossier; 'commonly understood language'**
- **Clear but very narrow time-lines**

Validation

+6 d: Reporting state, scope, completeness,low-intervention

Assessment part I:

+10 d: low intervention trials

+25 d: other trials (except advanced therapies)

Assessment part II

+10 d: **national requirements**

Considerations for Authorisation

The anticipated therapeutic and public health benefits

The risks and inconveniences for the subject

- characteristics / knowledge about the IMP
- characteristics of the intervention vs normal practice
- safety measures
- **risk to subject health posed by the medical condition**

IRB Approval

Problems:

- Large number of independent IRBs
- No harmonisation on national or international level
- Focus on administrative issues e.g. CVs, GCP, FD
- Costs not predictable
- **IRB approval is the major workload for trial application**

EU regulation:

- **Responsibility of each country***
- **Within time-lines**
- **<u>But</u>: according to international guidelines, including patients/lays, qualified persons, independent**

* patient informed consent, reimbursement for investigators/patients, patient protection, data protection, qualification of investigators and sites, insurance, biobanking

Sponsor Role

Problem:

- **One sponsor takes the ‘responsibility’ for the whole trial**
- **Academic sponsors are overchallenged**
- **Complex contracting system as only chance**

EU regulation:

- **Co-Sponsoring will be allowed**
- **Each co-sponsor is responsible for the trial**
- **Responsibilities may be divided between cosponsors**
- **Need to name one responsible sponsor**

Insurance

Problem:

- **Increased costs and administrative burden**
- **Neither number of damages or amount has increased**

EU regulation:

1. **Minimal interventional trials**

- No additional damage compensation
- Medical practitioner, the institution, or product liability insurance provides sufficient coverage

2**. Other trials**

- Member States under obligation to set up a national indemnification mechanism on a not-for-profit basis
- Free for non-commercial sponsors

Monitoring

Problem:

- **High costs**
- **Administrative efforts for sponsors / investigators**
- **Undefined benefit**

EU regulation:

Monitoring shall be determined based on all characteristics of the trial, including the following:

- low-intervention clinical trial
- objective and methodology
- degree of deviation from normal clinical practice

Summary - I

- **Many of the suggestions from academica have been considered**
- **Flexible approach**
- **Chance to perform TOPs as low-interventional trials**

Caveat:

- **Deadlines**
- **Electronic systems**
- **Details like drug costs, auxilliary products, citations**
- **Problem of ‘rare diseases’**
- **Unrealistic transparency** (e.g. registration of all cited trials)
- **No ‘realistic’ definition for non-interventional trials**
- **Interest groups have started activities**
- **Most exhausting procedures (IRB) remain national!!**
- **Outcome after parliament discussion open**

Frankfurter Allgemeine

Feuilleton

Aktuell Feuilleton

Relapse into medieval research ethics?

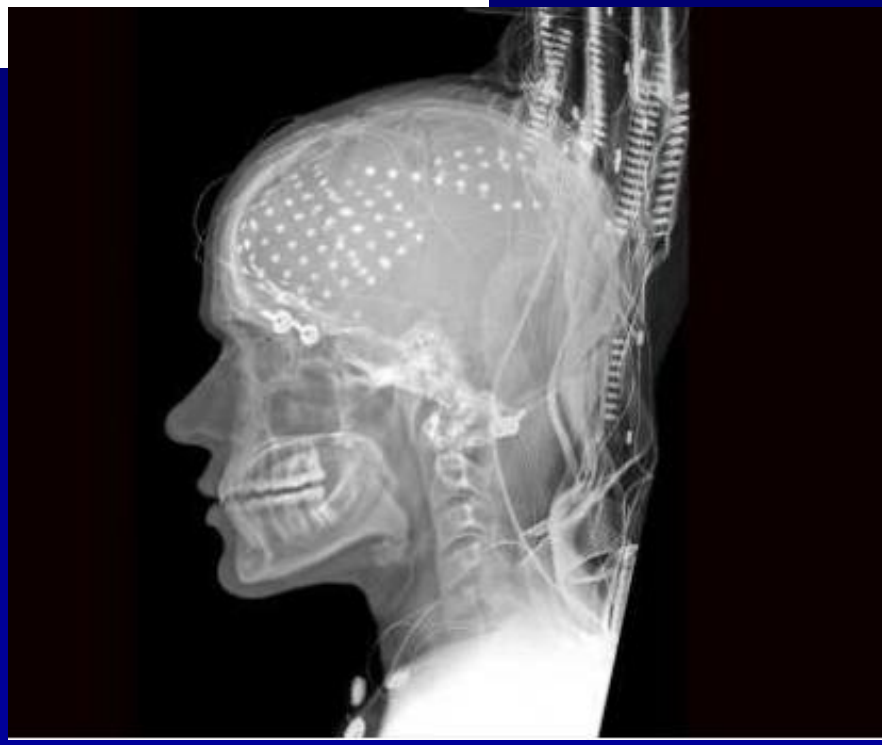
Europäische Pläne

Rückfall in mittelalterliche Forschungsethik

24.09.2012 · In Zukunft möchte die EU bei medizinischen Tests an Menschen auf die ethische Prüfung verzichten. Der Schutz des einzelnen Probanden gehört für die Europäische Kommission anscheinend nicht zum Gemeinwohl.

Von STEPHAN SAHM

Soon without IRB Approval?



Next Steps

17.7.2012 **Legislative proposal submitted**

11.9.2012 **Committee referral**

European Council (health ministeries)

Parliament: Committees

- **ENVI** (Environment, Public Health an dFood Safety
- **IMCO** (Internal Market and Consumer Protection)
- **ITRE** (Industry, Research and Energy)

24.4.2013 **Vote scheduled in commission**

10.6.2013 **Plenary sitting date**

Next vote for European Parliament: June 2014

Committee responsible	Rapporteur
ENVI Environment, Public Health and Food Safety	S&D WILLMOTT Glenis
	Shadow rapporteur
	JUVIN Philippe
	PARVANOVA Antonyia
	AUKEN Margrete
	CABRNOCH Milan
	SOUSA Alda
Committee for opinion	**Rapporteur for opinion**
IMCO Internal Market and Consumer Protection	BUŞOI Cristian Silviu
ITRE Industry, Research and Energy	RIVASI Michèle

Health and Consumers Commissioner: Tonio Borg

ENVI Environment, Public Health and Food Safety

69 members

Matthias GROOTE

Chair

Group of the Progressive Alliance of Socialists and Democrats in the European Parliament

Germany Sozialdemokratische Partei Deutschlands

Gerben-Jan GERBRANDY

Vice-Chair

Group of the Alliance of Liberals and Democrats for Europe

Netherlands Democraten 66

Carl SCHLYTER

Vice-Chair

Group of the Greens/European Free Alliance

Sweden Miljöpartiet de gröna

Dan JØRGENSEN

Vice-Chair

Group of the Progressive Alliance of Socialists and Democrats in the European Parliament

Denmark Socialdemokratiet

First Political Feed Back

- Role of IRBs under discussion
- Transparency of research results

- Time limits for authorisation of trials
- Duties of regulatory authorities and IRBs
- Automatic acceptance of authorisation if authorities do not keep to the time-lines

Summary - II

Needs in independent clinical research

- **Multinational trials: subgroup /targeted therapies**
- **Trials in rate diseases / subtypes with many centers**
- **Long-term follow-up**
- **Post-marketing observation**
- **Trials in older / comorbid patients**
- **Evaluation of treatment strategies / not drugs**

Speak to your national political decision makers i.e. members of the EU parliament to support a reasonable regulation