The new European clinical trials regulation

Dr. N. Gökbuget

Head of Study Center
Department of Medicine II and Goethe University Cancer Center
Frankfurt, Germany
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
ICH-GCP Guidelines
(Initiative of regulatory authorities / pharm. industry from EU / Japan / USA, 1996)

Clinical Trials Directive 2001/20/EG
Aims:
Improve patient safety and quality of clinical research
Harmonize conditions within EU

Transfer into national legislation

Germany
AMG Novelle 6.8.04

Other Countries
Deadline: 2004

Major consequence for academic research:
Therapy optimisation trials (TOPs) and Investigator Initiated Trials (IITs) have to follow
the same rules as registration studies of pharmaceutical industry
Who's afraid of the European Clinical Trials Directive?

The 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.

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%

Current Situation of Academic Trials: Summary

- 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

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 backfired, increasing costs and bureaucracy. Richard Howel reports.

Lars Webling will think hard before setting up another drug trial. Weibling, a specialist in parasitic infectious care at the University of Cologne, Germany, has just spent close to 5 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 counterproductive. Webling 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 2003 and went into effect in May 2004, with a deadline of May 2006 for all 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 methodologies 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 adverse drug reactions are reported promptly and in full. Before the directive, these duties tended to be spread unevenly 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 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 ensured an 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 Harrahn, 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 reduce 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 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 process appears to be an increase in trial costs, with the academic community being most severely affected. Estimates of the impact on trial costs vary widely, but a recent paper published in the European Journal of Cancer suggested the savings (or 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
... 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
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
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
• But: 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
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
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, auxiliary 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
Relapse into medieval research ethics?

Soon without IRB Approval?
Next Steps

17.7.2012 Legislative proposal submitted
11.9.2012 Committee referral
European Council (health ministries)
Parliament: Committees
- **ENVI** (Environment, Public Health and Food 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**
<table>
<thead>
<tr>
<th>Committee responsible</th>
<th>Rapporteur</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENVI Environment, Public Health and Food Safety</td>
<td>WILLMOTT Glenis</td>
</tr>
<tr>
<td>Shadow rapporteur</td>
<td>JUVIN Philippe</td>
</tr>
<tr>
<td></td>
<td>PARVANOVA Antonyia</td>
</tr>
<tr>
<td></td>
<td>AUKEN Margrete</td>
</tr>
<tr>
<td></td>
<td>CABRNOCH Milan</td>
</tr>
<tr>
<td></td>
<td>SOUSA Alda</td>
</tr>
<tr>
<td>Committee for opinion</td>
<td>Rapporteur for opinion</td>
</tr>
<tr>
<td>IMCO Internal Market and Consumer Protection</td>
<td>BUŞOI Cristian Silviu</td>
</tr>
<tr>
<td>ITRE Industry, Research and Energy</td>
<td>RIVASI Michèle</td>
</tr>
</tbody>
</table>
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
Needs in independent clinical research
• Multinational trials: subgroup /targeted therapies
• Trials in rare 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