The Situation of Investigator Initiated Trials in Europe

Dr. N. Gökbuget
1. Situation for academic clinical trials after the EU directive

2. Practical approaches to deal with the situation

3. Perspectives and next steps
Transfer into national legislation

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

Clinical Trials Directive 2001/20/EG

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
**Idea for a study and scientific concept**
- Therapy protocol
- CRFs / EDC
- Quality Management
- Qualified Staff
- Selection of Hospitals - Qualification

**Activation of a Study**
- Patient Insurance
- EUDRACT Application
- IRB Approval
- BfArM Confirmation
- Peer Review / Funding
- Local Authorities

**Study Hospitals**
- Information – Initiation – Study Meetings
- Randomisation - Advice – Monitoring

**(Study Medication)**
- Preparation, Labeling, Stocking, Dispatch

**Documentation**
- Data Base Design, Data Entry, Validation
- Software, Honorarium, Archivation

**Analysis**

**Improvement of Outcome**

**Sponsor of study**
- System of contracts
- Principal Investigator
- Pharmaceutical company
- CRO
- Hospitals
- Pharmacies

**Budget application**

**Registration**

**Internet Presentation Public Relations**

**SAE/SUSAR Reporting**

**Source Data Monitoring**

**Interim Reports**

**End of Study**

**Schematic Course of a Study**
## Major Aim to Foster International Academic IITs in Leukemias

### Major field
- Rare diseases, as leukemias
- Treatment and research done in parallel  
  (only way for progress in rare diseases)
- Questions without commercial interest

### Low Budget
(public funding, university budget, partly supported by industry)

### High potential costs
- Multicenter, many hospitals (Health Care Standard!)
- Long-term observation
- High patient numbers

### IITs in Leukemias:
Few industry-independent trials after the EU directive

**Danger:** Industry-dependence of academic research
Method: Eight specialised UK Clinical Trials Unit (CTUs) were interviewed

Topic: Consequences of CTD on information flow, start, conduct, finalisation and cost of clinical trials

Results:

- **Doubling of the cost** of running non-commercial cancer clinical trials
- **Delay to the start of trials in the order of 6 to 10 months**
- **Reduction / stop of international trials**
- Lack of central guidance
- Lack of clarity regarding the interpretation of the guidance notes
- Increase in essential documentation and paperwork

- **Staff is working beyond capacity and demoralised**
- Even experienced staff anxious about correct interpretation of CTD
THE LANCET
Volume 361 Number 9376

Who’s afraid of the European Clinical Trials Directive?

Wouldn’t be the time to approve and accredit a
clinical research done in the country, validated, and
over- increasing number of European countries could be
simplified and streamlined. This deceptively complex
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 July, 2001. Most European
countries published draft legislation earlier this
year. Somewhat belatedly, some of Europe’s academic
clinical investigators have started to voice fear about
how the Directive might affect their research.

The essential core of the Directive is to harmonise
the various national administrative procedures necessary to start a clinical trial and to set up
European high standards of procedure 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
governmental 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
read that: “Non-commercial clinical trials conducted
without the participation of the pharmaceutical
industry may be of great benefit to the patients
concerned”, and noted that the Directive should “take
account of the special position” of such trials with
respect to the manufacture, packaging, and labelling of medicinal products. The catch is that in all other
respects publicly funded clinical trials must fulfill the
same requirements as their commercial counterparts.

According to the Directive no investigational
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 remains as by contrast
collaborations where partners pursue different
goals but are part of the same programme in regulation as required to take overall responsibility. The introduction
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 unwell to take. It will be
the sponsor’s role to apply for that automation 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 for a European
description and enforcement of the responsibilities of ethics committees, which include not only trial
authorization 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 this added responsibility. 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 rigorous 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 staff—which the commercial
sector already has—for the increased administration and documentation required by the
Directive. Citizen groups have noted that this is not
part of the thrust of change and greater monitoring, and a
considerable source of concern is lack of funding: “Who is
going to pay?” The following quote about UK-based
clinical trials is instructive. “Despite the stated purpose of the Directive it is clear that the planned
costs in the UK and the rest of Europe will not
subsidy, and are unlikely to result in substantial harmonisation of the
the current regulatory procedures for the conduct of
clinical trials. There are many new requirements that
will place an additional burden on both sponsors of
clinical trials and on regulators.” This statement
comes from a UK academic body but not from the
Association of the British Pharmaceutical
Industry. It follows that if the commercial sector, to
which increases 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
Aim:

To collect information for each country on
- centers
- laboratories
- regulatory procedures (who can do what?)
- all types of costs which may occur
- practical procedures

Pre-requisite for
- contracts
- budget planning
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Current Situation of Academic Trials: Summary

- No harmonisation of trial regulations in Europe
- Different interpretation of laws and different attitude of authorities e.g. during inspections
- Excess of bureaucracy all over Europe
- High costs for academic trials
- No success on political level
The Good Clinical Practice Guideline: A bronze standard for clinical research
Grimes et al, Lancet 2005

GCP is not evidence-based
- Benefit not demonstrated
- Authorship and responsibility not clear
- Written for registration trials

Despite all this
1. It became a law and physicians are threatened with legal consequences
2. Scarce research funds are diversified to activities of unknown value
Investigator Initiated Trials in Europe - Difficulties and Possibilities

1. Situation for academic clinical trials after the EU directive

2. Practical approaches to deal with the situation
   - How to organise an academic international trial
   - Sources for support

3. Perspectives and next steps