The Situation of Investigator Initiated Trials in Europe

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European Leukemia Net 2004: 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 potential costs

- **Multicenter, many hospitals (health care standard!)**
- **Long-term observation**
- **High patient numbers**

High quality research

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

“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)

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

Major Problems for the Conduct of Academic Trials after the CTD

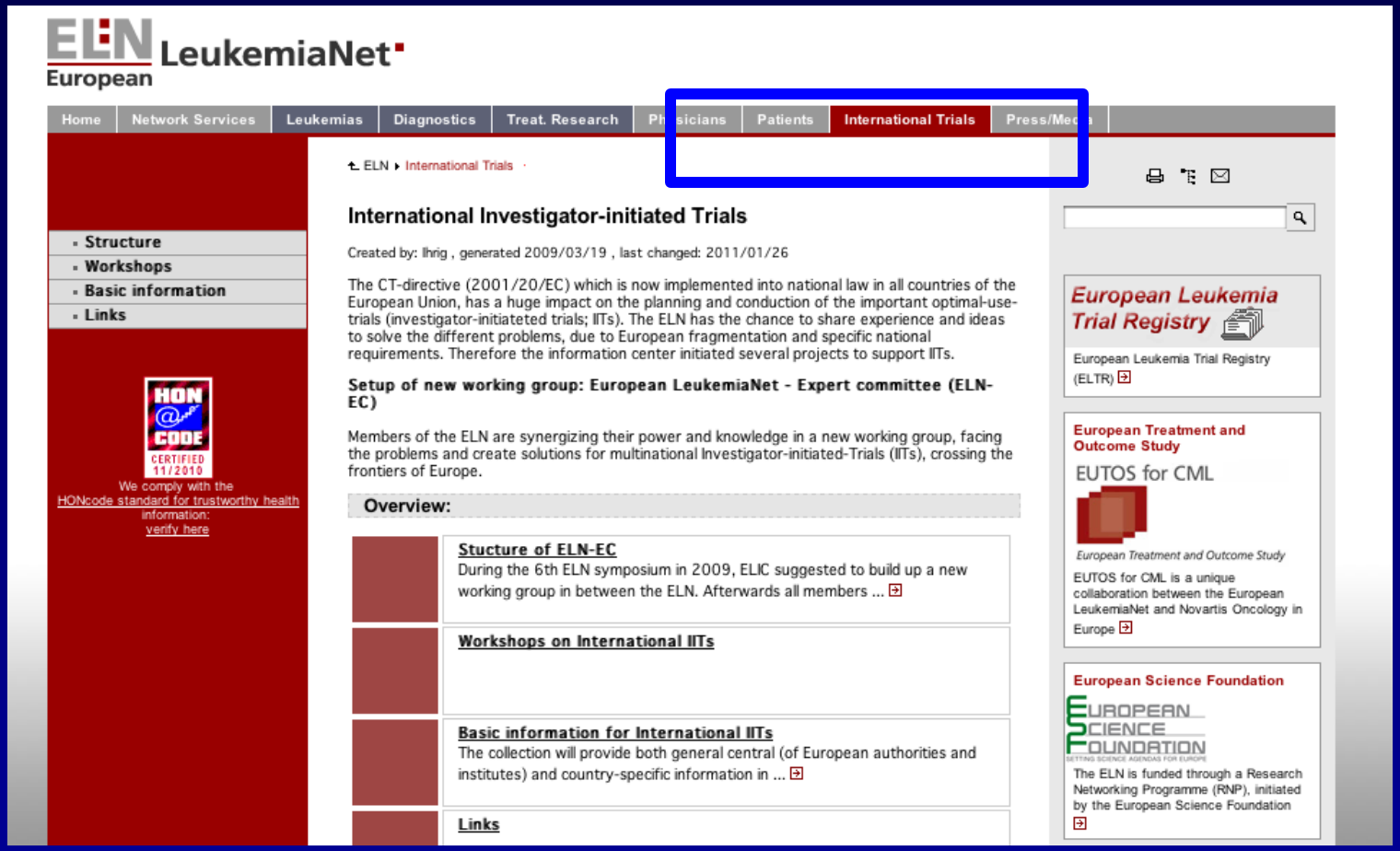
- **IRB approval**
  - most time consuming and buerocratic part of trial application
  - multi locations, multi language, multi opinions, fees
- **Qualification of centers and investigators (Germany!)**
  - CV, GCP certificate, financial disclosure from each investigator with up to date signature
- **Insurance**
  - **Cost factor, probably never pays in oncology trials**
- **Inspections of investigators**
  - Most findings formal, expectations cannot be fulfilled in standard healthcare circumstances

Major Problems for the Conduct of Academic Trials

- **Sponsor responsibility for international trials**
  - Academic institutions and investigators are reluctant
- **Authority application process**
  - multilanguage, multi locations, multi opinions
- **Monitoring**
  - Multilingual team, travel costs, financing impossible
- **Safety reporting**
  - variable from country to country, exhausting paper-work particularly in hematology trials with large numbers of SAEs
- **Non-interventional trials: Nearly impossible**

Independent international trials in rare diseases nearly impossible

Activities of the ELN



- **Participation in Roadmap Initiative**
- **Participation in Public Consultation Process**

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

Jonathan Hoey

- No harmonisation of trial regulations in Europe
- Excess of bureaucracy all over Europe
- High costs for academic trials
- Less independent trials, fewer patients within trials
- No success on political level

Next steps regarding Clinical Trials Directive

- **Proposal for modified CTD will be prepared until IV/2011 (Responsible: S.Fuehring, DG Enterprise, European Commission)**
- **Public discussion?**
- **Discussion in EU parliament and European Commission**
- **Proposal maybe completely changed during this process**
- **Finalisation and integration into national laws may take 5 years**