The Situation of Investigator Initiated Trials in Europe

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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
3. Perspectives and next steps

“History” of the EU Drug Regulation

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

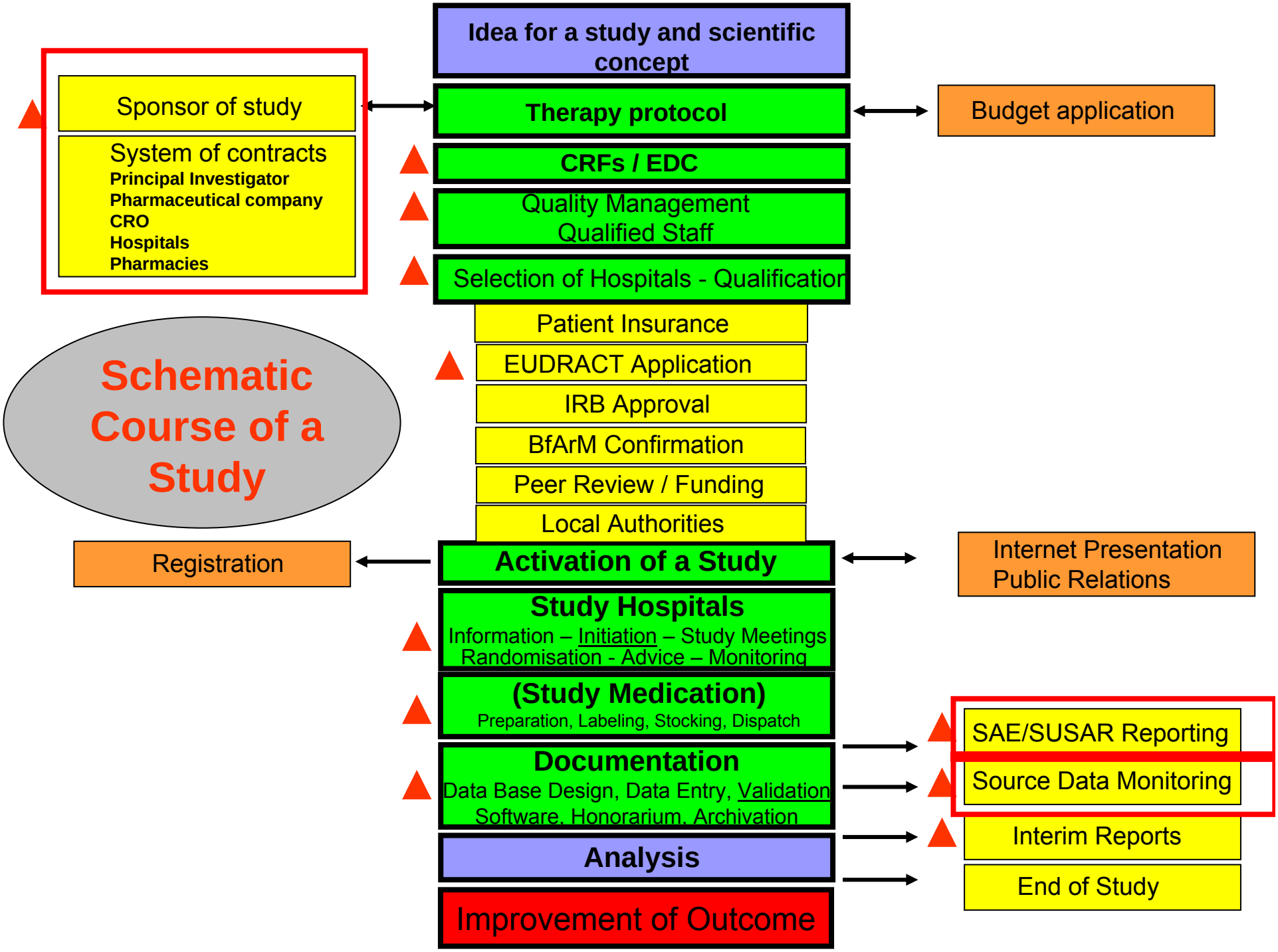
Clinical Trials Directive 2001/20/EG
(Later: EU GCP Directive (2005/28/EC) 08.4.2005)

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


Schematic Course of a Study
Idea for a study and scientific concept
Sponsor of study
System of contracts
Principal Investigator
Pharmaceutical company
CRO
Hospitals
Pharmacies
Therapy protocol
Budget application
CRFs / EDC
Quality Management
Qualified Staff
Selection of Hospitals - Qualification
Patient Insurance
EUDRACT Application
IRB Approval
BfArM Confirmation
Peer Review / Funding
Local Authorities
Registration
Activation of a Study
Internet Presentation
Public Relations
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
SAE/SUSAR Reporting
Source Data Monitoring
Interim Reports
End of Study

European Leukemia Net 2004: 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 akademic research

The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK ☆

J. Hearn, R. Sullivan*

EUROPEAN JOURNAL OF CANCER 43 (2007) 8–13

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

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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**

EWALL- Procedure for Planning of an IIT Questionnaire

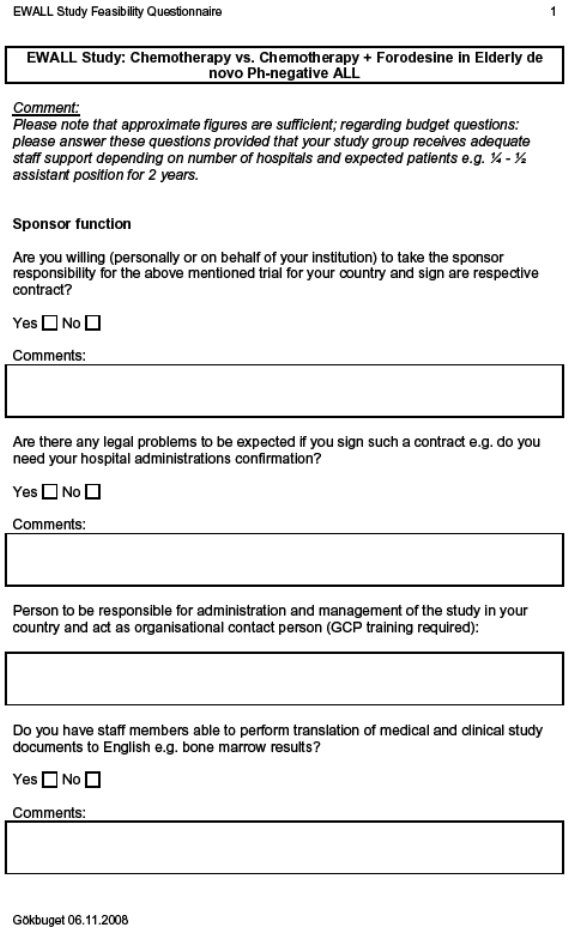
Aim:

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**



EWALL Study Feasibility Questionnaire 1

EWALL Study: Chemotherapy vs. Chemotherapy + Forodesine in Elderly de novo Ph-negative ALL

Comment:
Please note that approximate figures are sufficient; regarding budget questions: please answer these questions provided that your study group receives adequate staff support depending on number of hospitals and expected patients e.g. ¼ - ½ assistant position for 2 years.

Sponsor function

Are you willing (personally or on behalf of your institution) to take the sponsor responsibility for the above mentioned trial for your country and sign are respective contract?

Yes ☐ No ☐

Comments:

Are there any legal problems to be expected if you sign such a contract e.g. do you need your hospital administrations confirmation?

Yes ☐ No ☐

Comments:

Person to be responsible for administration and management of the study in your country and act as organisational contact person (GCP training required):

Do you have staff members able to perform translation of medical and clinical study documents to English e.g. bone marrow results?

Yes ☐ No ☐

Comments:

Gökbuget 06.11.2008

Clarification of Regulations and Costs per Country

Questionnaire

Country	Sponsor	Tasks to be taken	E-CRF	Lab	Centers	Pharmacy	Insurance	Doc.fees	National Language	Hospital Admin.	Monitoring
France											
Spain											
Italy											
Romania											
Germany											
Czech Republic											

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
- Different interpretation of laws and different attitude of authorities e.g. during inspections
- Excess of bureaucracy all over Europe
- High costs for akademic trials
- No success on political level

The Good Clinical Practice Guideline: A bronze standard for clinical research

Grimes et al, Lancet 2005

Viewpoint

The Good Clinical Practice guideline: a bronze standard for clinical research

David A Grimes, David Hubacher, Kavita Nanda, Kenneth F Schulz, David Moher, Douglas G Altman

Lancet 2005; 366: 172–74

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Clinical researchers throughout the world are having to abide by the Good Clinical Practice (GCP) guideline[1] developed by the International Conference on Harmonisation (ICH).[2] In today's evidence-based climate, little evidence supports this guideline. Moreover, the guideline diverts scarce research funds towards compliance activities of unknown value.

Although the guideline's goals of documenting informed-consent, safety of participants, and integrity of data are worthy, its development process was not ideal. Obsolete at inception, GCP lags at least 10 years behind the published work on research methods. Deemed a "gold standard" by some,[2] the guideline is at best a bronze standard. In this Viewpoint, we highlight some of these deficiencies, challenge the notion that GCP should be widely applied to clinical research, and offer practical solutions to the dilemma.

Background

Documentation of compliance with GCP is required for all submissions approved by regulatory agencies in the European Union, the USA, Japan, and Canada. A series of numbered ICH "efficacy" guidelines have been developed on various topics (E1 through E12A). This voluminous material (now totalling 367 pages) can be confusing (eg, when downloaded from different web sites, some identical documents have different titles and dates). The document on which we will mainly focus is "Good Clinical Practice: Consolidated Guidance (ICH-E6)." GCP "is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects."[1] Compliance is intended to assure that the rights, safety, and wellbeing of participants are protected, and that trial data are credible. We agree with these goals.

Deficiencies of GCP

The term "Good Clinical Practice" is a misnomer (table). This unofficial jargon refers to US Food and Drug Administration regulations and guidelines organised within the US Code of Federal Regulations.[3] Unfortunately, other organisations, such as the UK Medical Research Council, have adopted the GCP misnomer. "Good Clinical Practice" here does not relate to clinical practice, but, rather, to the conduct of clinical research.

Four general approaches to guideline development exist: informal consensus development, formal consensus development, evidence-based guideline development, and explicit guideline development.[4] "Good Clinical Practice" derives from the weakest approach, informal consensus.[2] The International Conference on Harmonisation states that "The ICH process [informal consensus] has achieved success because it is based on scientific consensus developed between industry and regulatory experts."[5] Contrary to this assertion, consensus-based guidelines are worse than evidence-based guidelines.[4] Although no methods for development of research-practice guidelines exist, GCP fails on most criteria when judged by reproducible instruments for development of clinical-practice guidelines.[6,11]

Despite expert consensus and external review by industry and regulatory bodies, ICH-E6 is missing important information.[2] For example, the need for adequate allocation concealment to avoid selection bias in randomised controlled trials was published in 1995,[8] a year before ICH-E6 was published (1996). But despite its supposed emphasis on scientific validity, the ICH-E6 guideline does not mention this key requirement for such studies. This shortcoming might result from the absence of a systematic up-to-date search for and categorisation of the relevant published work.[4]

ICH-E6 has other deficiencies. The document has no identified authors or contributors. Since it provides no references, the scientific basis for its recommendations is unknown. Not being included in PubMed, the document is fairly inaccessible to the biomedical research community. Guidelines, like grocery-store produce, have a limited shelf life, after which they should be discarded.[10] ICH-E6 has not been updated since 1996, and no timetable for revision is specified. Unlike some clinical practice guidelines,[12] this guideline has not been shown to be of benefit.

The GCP development process omitted important constituencies. Academic researchers did not participate in GCP guideline development.[4] ICH missed the opportunity to build trust with the medical profession or public-health advocacy organisations; indeed, "the international regulatory-network 'state' suffers acutely from a lack of public accountability."[4]

GCP emphasises clinical monitoring and data audits to confirm that clinical trial data are "verifiable from source documents."[1] Key objectives are detection of fraud and accurate transcription of data. We support both goals, but whether the methods of GCP achieve them is unclear. Although intensive monitoring of clinical sites and auditing of research could help prevent or detect fraud,[13] "fraud in clinical trials is so rare and … generally inconsequential, that the public may be far more misguided by studies that are poorly designed,

GCP is not evidence-based

- Benefit not demonstrated
- Authorship and responsiblity 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 akademic 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**