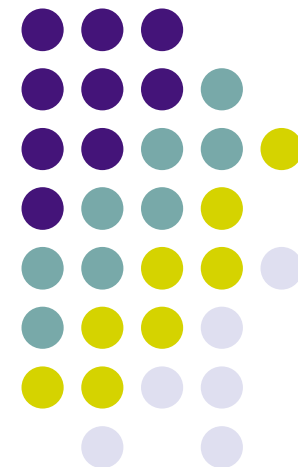


INTERPRETING THE CLINICAL TRIALS DIRECTIVE

A commentary for publicly funded researchers

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Introduction

- The content of this demonstration is taken from a lecture presented to the Scottish Stroke Research Network in Glasgow in September 2007.
- This shortened version is intended to supplement a demonstration given to the NHS R&D Forum in Newcastle on 13th May 2008.
- The argument is advanced that the principal difficulties arising from the implementation of the 2001 Clinical Trials Directive into UK clinical research derive not from the Directive itself but rather from errors of interpretation and application by R&D Leads within the UK Clinical Research Community.
- It is hoped that by drawing these matters to the attention of researchers, they can be encouraged to see the potential benefits of regulation in the Health Sector and adopt a more reflexive approach to its application.



A New Approach to Law and Regulation

- Use the Law to facilitate shared objectives
- Engage the legal community in collaborative action in research as you would amongst yourselves
- Maximise opportunities within permissible boundaries set by law
- Read what the Directives actually say and not what R&D think they mean
- Do not view the Law as a hurdle to surmount or an administrative bolt-on
- Do not repeat the mistakes made after the introduction of the 2001 Clinical Trials Directive

What follows derives in great part from Professor Rory Collins in his *Sensible Guidelines*:

http://www.crash2.lshtm.ac.uk/Audio/SensibleGuidelines_RoryCollins.pdf



Watching the Directives: Is NHS R&D a law unto itself?

The prophecy of doom for the 2001 Directive included the following predictions:

- Increased bureaucracy due to requirement for single sponsor
- Burdensome drug authorisation and labelling processes
- Rigid approach to pharmacovigilance in on-site monitoring

These are all errors of interpretation.

Have guidance errors by R&D leads contributed to an added cost for trials?

What the Directives really say: Single or Multiple Sponsors?



- The singular includes the plural in the absence of express prohibition
- The 2001 Directive never prohibited multiple sponsors
- The Medicines for Human Use (Clinical Trials) Regulations 2004 expressly permit multi-sponsor arrangements on a joint or several basis
- There was no substance to this objection



What the Directives really say: Data monitoring 1

- ICH GCP Topic 6 effective January 1997 stated:
 - *The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. **In general there is a need for on-site monitoring**, before, during, and after the trial; however **in exceptional circumstances** the sponsor may determine that **central monitoring** in conjunction with procedures such as investigators' training and meetings, and extensive written guidance **can assure appropriate conduct of the trial in accordance with GCP.***
 - ***Statistically controlled sampling may be an acceptable method for selecting the data to be verified***

ICH GCP allows for alternatives to on-site monitoring

Statistical methods can be used in data quality and to counter fraud

Was this a 'green light' for specific modalities in non commercial trials?



What the Directives really say: Data monitoring 2

The UK response in July 2004 lacks direction:

MRC/DH joint project to codify good practice in publicly funded UK clinical trials with medicines

Workstream 4: Trial Management and Monitoring: GCP in non-commercial trials

- **ICH GCP** is applicable principally to trials that produce data for submission to regulatory authorities but **may be applied to other clinical investigations**
- **ICH is not a legal requirement in the UK** but is the standard that MHRA expect for trials for drug licensing
- **ICH and MRC guidelines do not offer advice on adapting monitoring to different types of trial and the level of risk**
- **A main objective of the Joint Project is to give advice on adaptive monitoring standards**



What the Directives really say: Data monitoring 3

UK further guidance is issued on 30th June 2006
In response to EC Consultation on Specific Modalities

Monitoring of Clinical Trials: a summary of the outcome of the Trial Management and Monitoring Workstream of the MRC/DH Joint Project

In large, multi-centre studies, central monitoring of data using statistical techniques is particularly useful for identification of unusual patterns of data, and can be used to identify sites or contributors that may be deviating from the protocol.

Data monitoring modalities should be determined by reference to a risk assessment

NHS Final Guidance on Specific Modalities for non-commercial trials is awaited

Was this delay justifiable in the view of the content of the Directives?



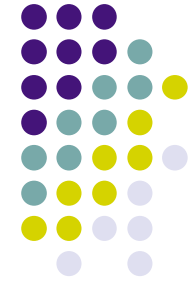
What the Directives really say: The Specific Modalities 1

2001 Clinical Trials Directive acknowledged the special status of non-commercial trials

- (14) *Non-commercial clinical trials conducted by researchers without the participation of the pharmaceuticals industry may be of great benefit to the patients concerned. The Directive should therefore take account of the special position of trials whose planning does not require particular manufacturing or packaging processes, if these trials are carried out with medicinal products with a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directives 75/319/EEC and 91/356/EEC, and on patients with the same characteristics as those covered by the indication specified in this marketing authorisation. Labelling of the investigational medicinal products intended for trials of this nature should be subject to simplified provisions laid down in the good manufacturing practice guidelines on investigational products and in Directive 91/356/EEC.*

Clinical trials within the existing marketing authorisation of a medicinal product should be subject to modified procedures and simplified labelling

What the Directives really say: The Specific Modalities 2



2005 Good Clinical Practice Directive extends special status to:

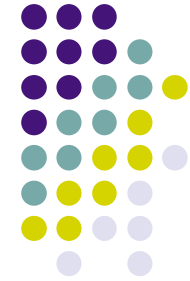
- CTIMP involving a new indication or patients with different characteristics outside the scope of the existing marketing authorisation should also have the benefit of special status

Specific Modalities should deal **in particular** with:

- the manufacturing or import requirements for authorisation and documentation
- archive requirements for the master trial file,

The wording of the Directive suggests that there may be other specific modalities that can be adopted.

What the Directives really say: The Specific Modalities 3



The current guidance on Specific Modalities:

June 2006: EC draft guidance on specific modalities for non commercial clinical trials;

- Document requirements
- Shipping
- Trial monitoring modalities to be subject to risk assessment

September 2006: MRC NHS joint response;

- EC draft fails to deal with CTIMP of a new indication
- Specific Modality advice is under construction

Is this delay justifiable in the view of the content of the Directives?

How much of the original prophecy of doom remains valid?



The Verdict

Enhanced Regulation will give you:

- Better consistency in clinical research conduct
- Networked Research Governance in Europe
- Common values rights and research systems
- Streamlined working in organisation and clinical research practice



END

DISCLAIMER

The content of this presentation is believed to be correct at the date of its publication. You should be aware however that changes in the law or other guidance may affect the accuracy of the material set out herein. This material is intended as a general introduction to the matters under discussion and is not intended as a definitive statement of the law or policy with a universal application. It should not be used as a substitute for legal, policy or operational advice upon real circumstances. The seminar and its associated documentation do not establish legal relations between the parties involved. No liability is accepted for any loss or damage arising from reliance on this document or upon the verbal seminar content that is associated with it.