Royal College of Physicians
Setting higher medical standards

11 St. Andrews Place
Regent's Park, London NW1 4LE

Telephone +44(0) 20 7935 1174
Textphone +44(0) 20 7486 5687
Facsimile +44(0) 20 7487 5218

www.rcplondon.ac.uk

From The Registrar
Rodney Burnham MD FRCP

Telephone extension 235
Direct facsimile +44(0) 20 7487 5218
rodney.burnham@rcplondon.ac.uk

Unit ENTR/F/2
BREY 10/114
BE-1049
Brussels

7th January 2010

Dear Sir or Madam

Re: Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC

The Royal College of Physicians is grateful for the opportunity to respond to the above. We would like to make the following comments.

General comments

We are very concerned that the revised Clinical Trials Directive (CTD) advocates a strategy that may be especially harmful for translational and experimental medicine. This would affect clinical pharmacologists (CPs) working in academia, Small & Medium-sized Enterprises (SMEs), Biotechnology companies, Clinical Research Organisations (CROs), and major industries.

The key issue is the definition of a Clinical Trial (CT). The Directive and Guidelines issued by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, and we presume by other Member States (MSs), are concerned with interventional trials (see 4.1.3) which, by exclusion, are studies in which the medicinal product in question is not prescribed in the usual manner, in accordance with the Summary of product Characteristics (SPC.). It also implies that the Directive is primarily, if not entirely focussed, on Investigational Medicinal Products (IMP) that have the potential to be new medicines or "old" products that are being revisited for variations to their licences or to be used in approved indicationsin novel CTs. However, this begs the question as to whether the term "interventional trial" includes studies that are exploratory and often preliminary in the course of translational evaluation of either a specific IMP or the concept testing of methodologies in different disease states. There are two classic classes of these types of studies. First, the use of naturally occurring molecules as agonists (or more rarely, antagonists) to evaluate a novel potential inhibitor or antagonist (e.g. LTD4 challenge against an LTD4 antagonist). The second class of translational/preliminary/proof of concept study is the study in volunteers or patients using medicinal products within the marketing authorisation to evaluate a test system that might be used in the future to measure the effects of an IMP. An example would be the use of anti-depressants or anxiolytics as validation tools in novel non-invasive techniques to measure patients'/volunteers' reactions to computer driven programmes.

In both these classes, no medicinal product outside the licence is being administered. The objective of both types of experiment is to pave the way for the testing of potential IMPs, when it would be appropriate for the "interventional trial" definition to be applied. But as of now, in the UK how can an investigator proceed to get approval from the MHRA for such studies? The

MHRA has devised its own Guidelines on its interpretation of the CTD. However, neither of the two classes referred to above are includable or excludable from the CT class system as so defined by this Guideline. They fall into no man's land. They are not audit. They are "trials" in the sense that they are objectively and critically evaluating responses to an intervention, using conventional study designs and analysis. This dilemma has, for many years, led to frustration for those involved in early evaluation of technologies.

The Consultation document, indirectly, makes reference to the "no man's land" scenario as follows:

- 2.5 last para: issues with Investigator driven CTs.
- 3.2 Administrative bureaucracy for academics and SMEs.
- 4.1.3 "Borderline" between observational and interventional studies.
- 5.3 penultimate para. "Clinical trials sponsored by academic/non-commercial sponsors are not necessarily performed with the intention to generate data to support an application for a marketing authorisation of a medicinal product"
- 6.0 and following. Peculiarities of paediatric and emergency situations. Many of the generic issues raised in this section apply to the CP studies described above.
- Consultation item No.18. Are SME aspects fully taken into account? Small biotech and CROs using the types of study described above do not have the financial or administrative resources to develop their Proof of Concept ideas.

We would therefore request that a separate class of clinical trial which could be called Clinical (or Investigational) Methodology Trials should be considered. Criteria would need to be worked up to differentiate them from audit, the classical Phase 1 studies of IMPs which are designed specifically to investigate tolerability, dose ranging and pharmacokinetics, and from Phases 2 and 3 trials.

Such methodology trials would still require ethics and MHRA approvals but in the latter case if the Methodology classification holds, approval should be swift.

<u>Specific comments</u>

2.5 Achievements but also short comings.

We are not aware of any other evidence relevant to this section.

3.1
Consultation No.2 – Is this an accurate description of the situation? What is your appraisal of the situation?
&
Consultation No.3 – Is this an accurate description? Can you quanitify the impacts? Are there other examples for consequences?

This is an accurate description of the situation. There needs to be clarity on the roles and responsibilities of ethics committees and research committees in the respective National Competent Authorities (NCAs).(See3.4.3). One of the major barriers to studies in the UK is that NHS Trust approval for the study can be over bureaucratic and time consuming. We wonder whether other MSs suffer similar time delays?

An important question is whether ethics and /or NCA research committee approvals for one MS could be obtained in another MS and then recognised by the first? For example, if a phase 1 study is sponsored and conducted in England, could a new, revised ECD permit ethics approval in, say, Belgium and NCA approval in Germany?

The options for "streamlining" NCAs approval and networking ethics committees, go some way to support the above option. The confusion over the interpretation of the CTD, as indicated in 4.1, is often due to the difficulty sponsors and investigators have in applying national Guidelines produced by their respective NCAs. NCAs could work together, and include input from industry and academia to produce European wide Guidelines. Fundamental to this approach is the definition of The Clinical Trial.

3.3.2.1 Streamlining the procedures

The practical proposals for NCA authorisation and approval by ethics committees seem to mimic the current system of study dossier assessment i.e. a Centralised and a Mutual Recognition (MR) procedure. Both routes have advantages and disadvantages for CT approval. For the UK with its NHS-based patient care system, it may be deemed unacceptable for an ethics committee in another MS to review and approve a UK based study.

We would support a 1-2 year pilot programme which permits sponsors to choose, for both ethics and research approval from either an MR or a centralised procedure.

Consultation No 6 – Is this an accurate description of the situation? Can you give other examplese?

Commented on above.

Consultations No. 7 – Is this an accurate description? Can you quantify the impacts? Are there other examples for consequence
&
Consultation No. 8 – Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical and legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?

We cannot comment on whether the safety of patients has been improved since the CTD came into force. However, if this aspect of the CTD is upgraded to a Regulation as suggested it could be in 4.3.2., we would need to ensure that this move does not hand over the authorisation systems as previously discussed, to the Commission.

Consultation No. 10 - Do you agree with the description?

We agree with the description.

Consultation No. 11 – Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

We have proposed above the need to revise the guidelines on definition and classification of Clinical Trials. If agreement can be reached on these proposed definitions, we see no reason why it should not be "vested in legislation" (see 5.4.1).

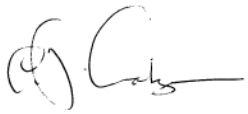
5.4.3. Review of existing Directive and excluding clinical trials of "academic" sponsors from the scope Directive

This could be broadened to include some CROs working closely with academia conducting methodology studies of the type we have described previously.

The text argues that if they are excluded from the Clinical trials scope of the Directive,then they cannot be referred to in an application for a MA. Does this matter? If the studies are ethical, scientifically approved, take forward Proof of Concept and translational studies, get published in peer reviewed journals and escape major bureaurocratic administration by working with national rules, this, surely, could be an advantage.

I trust these comments will be of use and propose some workable solutions.

Yours faithfully



Dr Patrick Cadigan
Registrar