

## Implications of the Clinical Trial Directive for Academic Research

HealthWatch was directed to the website [www.saveeuropeanresearch.org](http://www.saveeuropeanresearch.org) and asked to add its support to a petition to have Directive 2001/20/EC reversed. The petition asserts that academic clinical research will be destroyed when the Directive comes into force, but does not explain why this position is taken.

The Directive is long and complicated; see Appendix 1 for a brief legal summary of its intentions and implications. HealthWatch sees that there is a great deal of additional work and documentation involved in its implementation, but agrees with the conclusions drawn in this summary.

This Directive has been in discussion for some 12 years; a number of European Commission documents have been released during that time and circulated via the UK Regulatory Agency to professional bodies (see Appendix 2). Comments have been received and the provisions greatly modified from their original form. The Directive has now been agreed and the UK is preparing legislation which will implement it into local law. It is late to object to this legislation and very good reasons would be required if HealthWatch is to support a petition to reverse it.

We make the following points:

- The petition exaggerates the scope of the Directive. It is not true that trials not involving drugs (such as screening, radiotherapy and surgery, which are the examples cited in the petition) will be nearly impossible to conduct as a result of the high administrative expenses. A trial does not need authorisation from the Regulatory Authority under this Directive unless it involves "a medicinal product for human use". However, as before, both drug and non-drug trials will require the approval of an Ethics Committee (see below).
- Ethics Committee approvals will be formalised by the Directive. The European Commission has drafted a standard application to be used throughout the EU. The situation in the UK has, of course, greatly improved from that described in 1992 by Julia Neuberger<sup>1</sup>, but it will surely be better to use a standard protocol for all Ethics Committee applications rather than the miscellaneous formats current. Attempts to achieve standardisation voluntarily<sup>2,3</sup> did not prevent individual committees going their own way. The use of a standard protocol every time a committee is approached will eventually make things easier. The present situation in the UK is still not satisfactory and standardisation is to be welcomed.
- Application to the Regulatory Authority (in the UK to the MHRA) will be necessary before starting a trial. As for Ethics Committee approval, a standardised application format has been drafted which will be the same for all member states of the EU. In the UK, this will replace the current methods, which *should* involve application for one of three approvals: Clinical Trial Certificate (CTC), Clinical Trial Exemption (CTX) or a Doctor & Dentists Exemption (DDX). CTC is obsolete; CTX application has been described by American experts as the most difficult procedure in Europe; the DDX is exceedingly easy and there is no doubt whatsoever that the new procedure will be more onerous than this. However, it is now a fact of life that everything requires increasingly complex documentation;

formalising the procedure will prevent some of the problems that Dr Peter Wilmshurst described to HealthWatch in his address at our AGM.

- The petition makes it an issue that we will be put at a disadvantage vis-à-vis American research. In fact the Americans have been subject to strict Institutional Review Board (Ethics Committee) and regulatory control since the 1970s<sup>4</sup>. In the EU, there are as many ways of starting a clinical trial as there are member states (more, actually: there are the 3 ways described above for UK alone, 2 each for Italy and Ireland). The UK found itself at a disadvantage soon after the 1968 Medicines Act came into effect because the Committee on Safety of Medicines (CSM) decided that the clinical trial subject was entitled to as much protection as any other citizen. This meant that trials could only be started after all information on the drug had been fully reviewed and a CTC issued. This procedure took 12-18 months and, since the investigators had to be approached at the start of the process then wait this long period, this put UK at a great disadvantage vis-à-vis e.g. Germany and The Netherlands, where trials could be started at once. In 1981 a subcommittee of the CSM devised ways around the situation: early clinical research (phase I) was exempted from control and the CTX procedure developed for later phase trials. This phase I exemption from control gave us a great competitive advantage over other EU member states and over the US, which will now be lost. But this is an example of the level playing field everyone is always asking for; we will not be put at a competitive *dis*advantage, just lose an unfair advantage. This is a major issue for pharmaceutical companies and specialist phase I units, but not for academic units, generally not involved in early phase research. The MHRA is running a programme to assist phase I units to deal with the changed situation and indeed always tries to be flexible with regard to process.
- The Medical Research Council (MRC) is cooperating with MHRA and seems to be receiving their assistance. At present, they may not intend to monitor and audit their research (if they did this, Dr Peter Wilmshurst's primary objective for validation of data would be met). However, they seem to have accepted the burden implicit in prior approval of research projects.
- HealthWatch sees advantages in having a central register of clinical trials available at the EMEA (the EU Regulatory Authority). The register of trial starts would prevent unnecessary repetition and would reduce publication bias, a long-standing and continuing problem. We emphatically believe that this register must be publicly accessible.

**In Conclusion: the Directive will impose an additional set of burdens upon academic research, but these are not out of line with those that are reasonable for professionals working with patients.  
HealthWatch cannot support the petition.**

## References

1. Neuberger J (1992). Ethics and Health Care. The role of research ethics committees in the United Kingdom. Research Report 13; King's Fund Institute. ISBN 1 870607 29 5.
2. Standards for Local Research Ethics Committees. A Framework for Ethical Review. Department of Health NHS Training Division; no formal citation.
3. Bendall C (1994). Standard Operating Procedures for Local Research Ethics Committees – Comments and Examples. McKenna & Co, London.
4. Code of Federal Regulations, Title 21: Part 50; Part 56; Parts 312.50-70.

Agreed by HealthWatch Committee 20<sup>th</sup> December 2003

Michael E Allen  
HealthWatch Secretary

## **Appendix 1: REGULATION OF CLINICAL TRIALS IN THE EUROPEAN UNION: THE NEW REGIME**

Abstracted by Michael Allen from an article written by Natasha Singarayer of Crowell & Moring, 180 Fleet Street, London EC4A 2HG: *The Regulatory Review* (2001): 4/5, 24-26

*On February 26, 2001 the European Council formally adopted a Directive relating to the conduct of clinical trials. On May 1, 2001 the Directive came into force. This new Directive is the first one aimed solely at clinical trials.*

### **Summary**

The rules and regulations governing clinical trials can be currently found in a variety of European and domestic legislation.

The new Clinical Trials Directive seeks to “simplify” and “harmonise” such trials by establishing a "clear, transparent procedure" and by "creating conditions conducive to effective co-ordination of such clinical trials" by the relevant authorities of each Member State.

### **Scope**

The Directive applies to the conduct of clinical trials including multi-centre trials on human subjects involving medicinal products. The Directive does not apply to non-interventional trials (as defined) but has adopted principles of good clinical practice. "Good clinical practice" is defined in Article 1(2) of the Directive as “A set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects”.

### **Definitions**

Article 2 of the Directive sets out a number of definitions including "clinical trial", "multi-centre clinical trial" and "non-interventional trial". Of special interest is the definition of a "sponsor" as “An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial". The wide scope of this definition could mean that a number of companies already involved in supporting clinical trials (for example in the provision of medicinal products, equipment or financial resources) could be open to be classified as a sponsor for the purposes of this Directive with the attendant potential liabilities.

### **Key provisions**

#### **Article 3 – Protection of clinical trial subjects**

It is a requirement of the Directive that a clinical trial may only be undertaken if certain criteria are fulfilled. These include the rights of the subject to mental and physical integrity, privacy, and the protection of data concerning himself/herself (in accordance with the Directive on the protection of individuals in the context of processing personal data) and the need for the subject to give written informed consent.

#### **Articles 4 and 5 - Clinical trials on minors and incapacitated adults not able to give informed consent**

Clinical trials on minors are strictly regulated and particular importance is attached to obtaining prior informed consent from the parents or legal representative of the minor. Additionally, the investigator has to take account of the explicit wishes of a minor who is capable of forming his/her own opinion. There is also a requirement to ensure that a minor has received adequate information on the clinical trial according to his/her capability and understanding. Similar provisions apply to incapacitated adults (for example, psychiatric patients) not able to give informed consent.

#### **Article 6- Ethics Committee**

An Ethics Committee is established by Article 6 which has the responsibility of protecting the rights and safety of the subject and assuring the public of that protection by playing a key role at the very early stages of the trial in the documentation evaluation process. However, there is a provision that allows a Member State to refer questions directly to the competent authority (that is, the authority responsible for regulating clinical trials in each Member State) in relation to three particular matters that are set out in Article 6(3) (h), (i) and (j). These matters include questions relating to the compensation/rewarding of investigators and subjects, compensation for injury or death and indemnity provisions.

#### **Article 9 - Start of clinical trials**

The sponsor is required to submit a valid request for authorisation to the competent authority of the Member State in which the clinical trial is being conducted before commencing the clinical trial. The competent authority has 60 days to consider the request. Following the expiry of this time period if the sponsor has not heard from the competent authority it can assume that there is no objection to the commencement of the trial.

This 60 day time period can only be extended if the trial involves certain specified medicinal products, for example products used in gene therapy. Full details of the medicinal products to which this exception applies is given in the Article.

There is also a requirement to obtain a prior written authorisation before starting clinical trials on certain medicinal products.

#### **Article 10 - Conduct of clinical trials**

Following the commencement of the clinical trial the sponsor is able to make amendments to the protocol without notifying the competent authority if those amendments are minor and unlikely to affect the safety of the trial subjects or change the interpretation of the scientific documents that support the conduct of the trial. If the above criteria cannot be satisfied, the Article details the procedure to be followed to obtain approval of the proposed amendments.

#### **Article 11 - Exchange of information**

In order to build up a central register of information of the various clinical trials being conducted throughout the European Union, there is a requirement for Member States to enter into a European database extracts of certain documents such as the request for authorisation, any amendments to the protocol and the favourable opinion of the Ethics Committee. The database is not public and will only be accessible to the competent authorities of the Member States, the European Agency for the Evaluation of Medicinal Products and the European Commission.

#### **Article 15 - Compliance**

The Directive contains provisions granting powers to the Member States to verify compliance with the provisions in the Directive by appointing inspectors to inspect clinical trial sites, manufacturing sites, laboratories used for analyses and/or the sponsor's premises. Following the inspection a report is prepared which is made available to the sponsor (subject to the protection of confidentiality) and also it can be made available to other Member States, the Ethics Committee and the European Agency for the Evaluation of Medicinal Products.

There is also provision for inspection of trial sites/sponsor's premises or manufacturer's premises in countries outside the European Union if the European Union has special arrangements with those particular countries.

#### **Articles 16-18 - Adverse events and reactions**

These Articles together legislate for the reporting of adverse events and adverse reactions.

"Adverse event" is defined in Article 2 as "Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment". "Adverse reaction" is defined as "All untoward and unintended responses to an investigational medicinal product related to any dose administered". "Serious adverse event" and "serious adverse reaction" are also defined in Article 2.

The investigator is obliged to report all serious adverse events (which are not identified in the investigator's brochure or the protocol) to the sponsor. The sponsor is required to keep detailed records of these reports which can be requested for inspection by the Member State.

The sponsor's obligations are extended in the case of adverse reactions to the reporting of suspected serious unexpected adverse reactions that are fatal or life-threatening to the competent authorities in all Member States and to the Ethics Committee within seven days after the sponsor's knowledge. Other suspected serious unexpected adverse reactions are required to be reported within fifteen days of the sponsor's knowledge. Article 17(2) requires the sponsor to provide a list once a year to the Member State in whose territory the clinical trial is being conducted and to the Ethics Committee of suspected serious adverse reactions and a report of the subjects' safety. Detailed guidelines on reporting adverse events and adverse reactions are to be drawn up by the European Commission in consultation with other interested organisations.

### **Conclusions**

The Directive is now in force and Member States are required to legislate nationally in order to comply with the provisions of the Directive before May 1, 2003 and apply the Directive's provisions at the latest with effect from May 1, 2004.

The new Clinical Trials Directive has provided (at long last) a comprehensive source of European law and guidance on implementation of clinical trials. One of the aims of the Directive is to bring a degree of consistency in the approach to the conduct of clinical trials across Europe. It is clear that one of the main purposes of the Directive is to treat as paramount the rights of clinical trial subjects in terms of safety and privacy. Additionally, the reporting procedures and obligations on sponsors are stringently controlled. Ultimately this will lead to higher standards for both the public and those sectors of industry involved in clinical trials. It is anticipated that the Directive will be welcomed by many sections of industry that are involved in this area of healthcare law and practice.

### **References**

1. Directive 2001/20/EC
2. Directive 95/46/EC
3. Directive 65/65/EC

## **Appendix 2: Discussion Papers and Consultation Process**

1. DISCUSSION PAPER on the Need for a Directive on Clinical Trials III/3044/91

Issued 23 January 1991, (before Directive 91/507) with comments from Member States of EU and EFTA, trade and professional bodies

2. CONCEPT PAPER on a Directive on the Implementation of Good Clinical Practice and Clinical Trials: III/5608/95 rev (1995)

Problems seen to be remaining in the EU:

- Delays in initiation of multi-centre (multi-national) clinical trials - delays up to 6 months as compared to US
- Manufacture and labelling - Member States have different legal requirements
- Investigational Medicinal Products legally exempt from GMP
- Compliance with GCP - inconsistent approach through EU (few inspections)
- Mandate for International agreements - still on hold
- Ethics Committees - delays being encountered

3. PROPOSED DIRECTIVE: Timetable for Consultation Process:

Comments received by November 1996  
Commission proposal - early 1997  
Council discussion - during 1998  
Parliament discussion - 1997/98  
Implementation - about 2004

There were two consultation cycles:

Commission ↔ Council ↔ Parliament