Where next for the European Clinical Trials Directive 2001/20/EC?

The voices of stakeholders were heard in London last October and again this month in Brussels. Changes to the clinical trial regulatory system are now required.

Changes to Directive 2001/20/EC should aim to improve harmonisation, as well as to simplify the requirements that have become a burden for competent authorities, commercial and non-commercial sponsors and ethics committees alike. However, there will be no quick fix. Harmonisation will be best achieved by a Regulation that replaces the current Directive. Such a process can be expected to take several years, bearing in mind that 10 years were required to finalise Directive 2001/20/EC.

It is unlikely that the Directive will be changed before the next Commission is installed in Brussels, Belgium, in autumn 2009. In the meantime, the excellent work of the Clinical Trials Facilitation Group – an operational group established by the EU Heads of Medicines Agency (<www.hma.eu/77.html>) – will bring about some of the much-needed changes. These include the agreement of a single set of core Clinical Trial Authorisation (CTA) requirements; the simplification of Member States’ specific requirements; the development of electronic CTA submission; the harmonisation of suspected unexpected serious adverse reaction (SUSAR) reporting using EudraVigilance; and the development of a Voluntary Harmonisation Procedure – same dossier, single repository, e-submission – to be piloted in 2009.

Impact of European legislation on trials

On 2 December 2008 a conference was held in Brussels to consider the impact of European legislation on clinical research.

The main piece of legislation under the spotlight was once again the European Directive 2001/20/EC (often known as the Clinical Trials Directive or CTD). Newsletter Editor Professor David Hutchinson was at the meeting – this issue is dedicated to summarising the meeting highlights.

The CTD applies to all interventional clinical trials conducted in the European Economic Area on medicinal products in humans. It was adopted in April 2001 for implementation by EU Member States by 1 May 2004. However, it took until 2006 for all Member States (at that time) to implement the Directive into their national laws. Implementation of the CTD has led to a further 34 legal acts, 59 application acts and 29 guidances in Europe. The CTD’s fundamental aims were to...
• protect the rights, safety and well-being of clinical trial participants
• simplify and harmonise the administrative provisions governing clinical trials
• establish a transparent procedure to harmonise the conduct of clinical trials in Europe and to ensure the credibility of research results.

The CTD was expected to harmonise the regulatory framework for clinical trials in Europe. It has partially achieved this aim. Before the CTD was implemented, each Member State had its own way of authorising clinical trials and there were wide differences in both the speed and quality of ethics committee review. Today there is a common authorisation (CTA) procedure, with applications to competent authorities and ethics committees being mostly standardised. In addition, timescales have been placed on these review processes. Furthermore, safety reporting requirements have been significantly harmonised.

Unfortunately, Directives can be ‘gold plated’ when implemented into Member States’ legislation. In this way some countries have added additional requirements, and the interpretation of the CTD therefore varies between Member States. This lack of complete harmonisation is seen as a problem by regulators, the industry, academic sponsors and ethics committees alike.

The CTD is also considered by many stakeholders to impose unnecessary administrative burdens and costs. Both the industry and academic stakeholders therefore want - for different reasons - changes to the CTD.

In October 2007, the European Commission (DG Enterprise and Industry) and the European Medicines Agency (EMEA) organised a conference at the EMEA in London, UK, to discuss possible changes to the Directive. The outcome of the meeting was reported in the newsletter (CRAvisor Issue 200, 12 November 2007).

At the same time, the European Commission’s DG Research funded the ‘Impact on Clinical Research of European Legislation’ (ICREL) project to provide metrics - and thus more objective arguments - for the need to adapt the current legislation.

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**What is ICREL?**

**ICREL is a 1-year project financed by the European Seventh Framework Programme (<http://cordis.europa.eu/fp7/home_en.html>).**

The project is co-ordinated by the European Forum for Good Clinical Practice. Collaborators in the project include the European Clinical Research Infrastructures Network (<www.ecrin.org>), the European Organisation for Research and Treatment of Cancer (EORTC; <www.eortc.be>), the Hospital Clinic of Barcelona and the Medical University of Vienna. ICREL’s co-ordinators were required to present results before the end of 2008. ICREL aims to measure and analyse the direct and indirect impact of the CTD and related legislation in the EU on all categories of clinical research and on the different stakeholders: commercial and non-commercial sponsors, ethics committees and competent authorities. This initiative fits in with the need to adapt the current legislation and will help to determine the most relevant pathways for improvement. More details about the project can be found at <www.efgcp.be/ICREL>.

ICREL’s methodology includes the collection, comparison and interpretation of figures from all EU Member States on all types of clinical trials on medicinal products. These include trials sponsored by pharmaceutical companies, biotechnology companies, small and medium enterprises, and academic institutions. The approach compares the situation before (2003) and after (2007) the implementation of the CTD. Detailed data were obtained through a series of questionnaires targeting the four stakeholder groups. The preliminary findings were presented and discussed during a conference held in Brussels on 2 December 2008.
ICREL has collected:

- information on positive and negative factors that have an impact on clinical trials of medicinal products and other types of clinical research
- figures on the impact of the legislation on the clinical research activity of big pharmaceutical companies, small and medium enterprises, and academia-sponsored trials
- data on the resource, cost and effectiveness implications of CTD implementation for all stakeholders
- data comparing the success of national CTD implementation.

ICREL has also consolidated conclusions on the findings amongst the stakeholders.

How were ICREL data collected?

Data were collected through a longitudinal, retrospective, observational and comparative survey involving the four stakeholder groups: commercial sponsors, non-commercial sponsors, the competent authorities of Member States and ethics committees in 27 countries. In addition, anonymised CTA application data were obtained from the EudraCT database for comparative purposes.

The questionnaires were specifically designed for each stakeholder group to include the minimum number of questions. The questionnaires were then tested in a pilot phase. Address lists were compiled covering all competent authorities in the EU, all ethics committees in EU countries, non-commercial sponsors in EU countries and commercial sponsors globally (many of which have head offices in the USA) that might have performed clinical trials in the EU between 2003 and 2007.

Some of the highlighted problem areas

Many of the areas requiring change were highlighted at the conference by representatives from the stakeholder groups. The lack of harmonisation in both administrative procedures and the interpretation of definitions appears to account for many of the problems. The objective of simplification and harmonisation has not been fully achieved.

- Documentation requirements are not always clear. There are differences in CTA documentation requirements between Member States (eg. specific national requirements). In addition, not all Member States accept documentation in English. Delegates called for an end to the bureaucratic hurdles, with quick decisions and a rapid information flow. The concept of a single multinational CTA was favoured using a single CTA dossier. This would help to avoid duplication and divergent assessments. A common, single CTA would allow for better predictability by sponsors (eg. trial design linked to EMEA scientific advice and Paediatric Committee decisions).

- Both commercial and non-commercial sponsors were concerned about the different interpretation between Member States of the definition of a substantial amendment. A number of other definitions also cause problems. For example, the definition of investigational medicinal product (IMP) is interpreted differently in different Member States, and in some countries marketed comparators are considered to be IMPs. There is a need for unambiguous definitions for items such...
as IMP, substantial amendment and label requirements.

- The CTD requires the application timescale clock to stop when there is a request for further information. The clock restarts when the information is provided. This requirement is not uniformly applied by the competent authorities.

- There are differences in the way that ethics committees are organised in the Member States. For example, some countries have a single ethics opinion (Cyprus, Denmark, Estonia, Greece, Finland, France, Hungary, Ireland, Luxembourg, Latvia, Malta, Portugal, Sweden, Slovenia), whilst others have a central ethics committee issuing a single opinion and a local ethics committee giving opinions on the protocol (Belgium, Czech Republic, Germany, Spain, Slovakia). The third type of ethics committee system involves a central ethics committee issuing a single opinion and a local ethics committee giving opinions on site feasibility (Austria, Italy, Lithuania, The Netherlands, Poland, UK). This means that there is no real single opinion in some Member States. Many stakeholders accuse the current systems of being inefficient. In some countries local governance approval (R & D) is also required and no timescale is defined for this process.

- Although the timescale for obtaining ethics approval is defined by the CTD, it does not take into account the often rigid dates of submission (application to be received some days before the meeting; date of meeting is often deemed to be the start clock time). Furthermore, when ethics approval is obtained, the EudraCT number is often not the unique trial reference number used.

- There is a genuine need for training on basic principles for ethics committee members, as well as quality assurance and the accreditation of ethics committees to develop greater harmonisation.

- Safety reporting requirements require streamlining. In particular, the reporting of SUSARs to ethics committees needs to be abandoned (as is the case in the UK).

ICREL findings: the facts

The sample consisted of 53 commercial sponsors, 106 non-commercial sponsors, 64 ethics committees and 23 national competent authorities. Two spontaneous responses from non-EU countries were also received. The size of some commercial respondents, a country bias in the ethics committee responses and bias caused by the non-respondents have been accounted for in the statistically adjusted data. Although the data are yet to be validated, the observed trends outlined below are of interest.

Competent authorities

- A total of 23 out of the 27 countries invited to participate provided data to the ICREL project. The non-respondents included three very small countries (few clinical studies) and one medium-sized country (estimate of 300–400 clinical trials in 2007). The responses received accounted for around 95% of CTAs in Europe.

- The number of CTA applications from commercial sponsors has increased in EU Member States by around 500 between 2003 and 2007 (2003, 7240; 2007, 7735).

- The number of CTA applications from non-commercial sponsors has decreased by 10% in EU Member States between 2003 and 2007 (2003, 1664; 2007, 1519). However, the number of regulatory submissions in 2004 was significantly higher, perhaps in an attempt to beat the new procedures.

- More CTAs were not approved in 2007 (242) compared with 2003 (94).

- The number of amendments submitted to the
competent authorities increased by around 153% between 2003 (7,597) and 2007 (19,267).
- The time for approval of CTA applications has not increased (mean of just under 50 days).
- The cost to the competent authority of administering CTAs has increased by approximately 230% between 2003 and 2007, due to the increased review workload.

There appears to have been an increase in the fees charged for a CTA of around 54% for commercial and 38% for non-commercial sponsors.

**Ethics committees**
- Ethics committees provided around 20–25% more positive opinions in 2007 than in 2003.
- Ethics committees received more substantial amendments (+64%) and serious adverse event reports (+139%) in 2007 compared with 2003.
- There were no significant differences in the timelines for providing an ethics committee opinion (days to receipt of application to opinion: original application, approximately 40 days; amendment, approximately 25 days) between 2003 and 2007.

**Commercial sponsors**
- Responses were received from nine (of 15 invited) top companies, 10 (of 81) ‘Top 85’ companies, 14 (of 195) medium and 19 (of 299) small companies.
- Commercial sponsors performed more trials in the EU in 2007 compared with 2003 (+29%). In particular, there was a sharp rise in the number of trials on biotechnology products (102%, unadjusted data).
- The mean number of trials in all phases increased between 2003 and 2007 (eg. more Phase III trials were performed by commercial sponsors, +20.9%). However, although the numbers of centres and countries used appear to have increased, the number of trial participants has not.
- Timelines (eg. protocol to first patient included) and the number of days to implement a substantial amendment appear to have increased (by around 30%, unadjusted data).
- There has been a significant increase in workload for commercial sponsors (CTA, 103%; pharmacovigilance, 56%; quality assurance, 16% (unadjusted data) – higher percentages in adjusted data). The cost of changing the pharmacovigilance system has markedly increased for most sponsors.
- The cost of liability insurance for sponsors has increased by 373% (unadjusted) from 2003 to 2007. When adjusted to take into account the bias caused by the larger companies, this figure increases to around 900%.

**Non-commercial sponsors**
- Most responses from non-commercial sponsors came from Spain, Germany, Italy, the UK and France. A high proportion of respondents were involved with cancer trials (42%) or defined themselves as multidisciplinary (43%).
- The number of trials performed by the non-commercial sponsors appears to be higher for observational studies and slightly lower for medicinal products.
- The number of days between protocol finalisation and inclusion of the first patient increased by 24% between 2003 (before CTD) and 2007 (after CTD). This suggests a delay in recruiting the first subject.
- The workload involved in co-ordination and monitoring has increased (+22%) between 2003 and 2007.
- Since CTD implementation, fewer countries (approx –27%) and fewer centres (approx –9%) participate in non-commercial trials.
- Non-commercial sponsors called for a risk-based approach to be applied to the regulation of trials (low risk, less regulation), simplified...
Editorial: don’t blame the Directive for everything

The ICREL results are still to be validated and thus should be interpreted with caution. However, the trends revealed do have some value and support the thoughts expressed at the October 2007 meeting held at the EMEA. Whilst there are clearly areas that have suffered adversely as a result of implementation of the CTD, some of the problems should not be directly linked to the CTD. For example, insurance costs have increased for sponsors. However, data were collected at a time when safety issues (such as that of Vioxx) were likely to have had an impact on premiums. Sponsors often complain about the increased workload, and the need to have staff dedicated to tracking national requirements and responding to multiple sets of questions. However, even before the implementation of the CTD each Member State had different systems, so surely the burden is no greater than it would have been then?

It is apparent, however, that there is a genuine desire to reduce the administrative load and simplify the requirements of the CTD. This will happen – eventually.