

European Clinical Trial Regulations Undergo a Slow Revolution

Philip Ward

Implementation of the EU Directive proves to be challenging as regulatory variations among member states continue and questions remain unanswered.

If you were to type the phrase “EU Clinical Trials Directive” into the Google search engine, you would get more than 780,000 items. This not only highlights the vast amount that has been written and said about the directive, but also suggests that some confusion remains about Europe’s clinical research regulations.

The history of the directive began nearly 20 years ago, when both industry and regulators first recognized that the requirements for starting and conducting trials needed rationalizing and harmonizing, not least because of the growing complexity of multicenter studies. EU guidelines on Good Clinical Practice (GCP) were drawn up in 1990, and ICH-GCP guidelines followed in January 1997. The pharmaceutical industry embraced these new guidelines, but they were not legally binding until 1 May 2004, when the EU Clinical Trials Directive (CTD, Directive 2001/20/EC) had to be implemented by member states.

The CTD lays down minimum standards for conducting Phase I–IV trials, and it has important implications for ethics committees, applications for starting trials, and instructions on the handling of pharmacovigilance data. Many of the regula-

tions are designed to protect the rights, safety, and well being of subjects; for instance, informed consent must be obtained, and the subject can withdraw at any time and must have a contact point for further information. The directive also aims to simplify and harmonize the provisions governing studies and to establish transparent procedures that will harmonize trial conduct and guarantee the credibility of results.

The new operational standards for clinical research are not just a duplication of the GCP guidelines. They cover aspects such as expectations about individual performance, and they aim to make sure that clinical research is conducted ethically, credibly, and efficiently in an increasingly challenging environment.

Under the CTD, ethics committees (ECs) are obliged to give an opinion within 60 days, provided an application is deemed valid. For multicenter trials, one opinion is given per member state, and each country must take measures to establish ECs. A sponsor may amend a request on only one occasion, and some studies (*e.g.*, biologicals) require written approval. A 30-day extension is allowed for gene therapy, and no time limits exist for xenogenic cell therapy.

Another key element of the CTD is to establish a database, Eudract, to share information on trial submissions, amendments, ethical approvals, end-of-trial notifications, and GCP inspections. Eudract is designed to interact with a pharmacovigilance database, which allows for a systematic exchange of information about suspected unexpected serious adverse reactions (SUSARs) between the regulators.

Eudract, the database of all EU clinical trials commencing from 1 May 2004 onward, is evolving steadily. Sponsors from within and outside of the EU must obtain a Eudract number and complete a clinical trial application form. A new guidance on applications was issued by the commission last November (see <http://dg3.eudra.org/F2/pharmacos/new.htm>). The upgrade to a new version of Eudract was due to take place during the second quarter of 2006, and was to include the adoption of a redesigned application form. Some new questions

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have been added and others renumbered. (A helpdesk is available at eudract@emea.eu.int or tel. +44 20 7523 7523.)

Implementing the CTD has not been straightforward, however. At least four EU nations—Czech Republic, Denmark, The Netherlands, and Slovenia—failed to implement it by September 2005. The Dutch implemented the CTD on 1 March 2006, and others have gradually fallen into line. Delays have been caused by uncertainty and confusion over the definition of an investigational medicinal product (IMP), requirements for investigational medicinal product dossiers, reporting of SUSARs, Eudract database issues, and other areas such as labelling. Some member states have implemented the CTD in a restricted way by defining IMP as all medicinal products used in a trial.

Investigator-led studies have faced an enormous administrative burden resulting from the new approval procedures and data management requirements. In general, these studies have lacked established structures of quality control, and costs have risen sharply due to the handling of medicinal products and insurance for subjects. To provide support, public funding has increased and training of investigators and study nurses has improved. Furthermore, clinical trial units have been established, and in Germany, coordination centers (so-called KKS) have emerged.

Evolution of GCP

A further directive (2005/28/EC) followed in April 2005, dealing specifically with GCP. This allows member states to introduce specific measures for noncommercial trials, and requires manufacturing authorization for the total and partial manufacture of an IMP. In addition, the sponsor and investigator must retain essential documentation for at least five years after completion, and documents must be made available to competent authorities upon request. Documents should be kept for a longer period when required by other regulations or by agreement with the investigator and sponsor.

The EU Directive's Main Consequences

The new regulations have had an impact, both within the EU and outside of the EU. Several thought leaders have expressed their concerns. Dr. Jean-Pierre Tassignon, chairman of the Brussels-based European Forum for Good Clinical Practice, believes that the CTD has had five main consequences inside the EU:

- The number of new academic research studies has fallen sharply across the EU.
- The location of some Phase I studies involving new medicinal products has switched from the EU to North America.
- Statistics about Phase II and III industry-sponsored studies are inconclusive, making it impossible to assess the impact of the directive.
- The cost of complying with the CTD is expected to have the greatest impact on industry-sponsored studies in Phase IV.
- Hundreds of startup biotech companies in Europe looking to initiate their first clinical trial have had to postpone their projects, beef up the IMP Dossier, and collect more funds to meet the higher costs of clinical trials and additional expertise.

The sponsor has to appoint individuals responsible for the archives. Access is restricted to named individuals, transfer of ownership must be documented, and medical records should be retained in accordance with national and institution timelines. Member states must establish inspectorates and address the training and experience of inspectors.

The GCP Directive has added weight to aspects of ICH-GCP. Further guidelines on current practice are expected to deal with GCP inspections, training of inspectors, archiving, and the Trial Master File.

Looking at the wider picture, GCP has developed from operational guidelines for industry-sponsored research to national legal and ethical frameworks against which all research involving human subjects is measured and appreciated. GCP has become the dominant

means of regulating, carrying out, and evaluating global research, and it has come to represent a common understanding of correct procedures for arriving at sound research conclusions for public health decisions while protecting the dignity and well being of trial subjects. The ability of GCP to successfully combine science and ethics in research makes it such an important factor for all parties involved in research.

Perhaps surprisingly, no provisions are laid down in either the GCP Directive or the CTD on penalties for noncompliance. In Germany, failure to comply may result in imprisonment for a period of up to 12 months, or a fine in the case of an administrative offense, but other legislators in other countries have been less precise. According to the CTD, a competent authority may suspend or prohibit a trial if conditions are breached, and they must inform the sponsor and ECs of the reason. If further action is required to ensure compliance, the competent authority defines this. Community inspectors can also inspect third-country sites.

Finally, Directive 2003/94/EC on Good Manufacturing Practice is also relevant to trial organizers. Clinical trial supplies must be manufactured in compliance with GMP, and if they are manufactured outside of the EU, checks must be performed to prove quality. Movement of supplies without retesting is permitted. Also, the particulars on a label must appear in a member state's official language.

Impact outside the EU

"The CTD is creating a stimulus for the globalization of clinical trials, as the more advanced FDA regulations created a stimulus for trials to be exported from the United States to Europe 20 years ago," notes Dr. Jean-Pierre Tassignon, chairman of the European Forum for Good Clinical Practice. "Central and Eastern Europe is adopting the CTD fast, and is increasing its clinical research output. Emergent countries like India and China are at the beginning of developing a clinical research capacity to world standards. A doubling of their GDP per capita within the next decade should bring them to the

level of clinical research productivity now observed in Central and Eastern Europe.” The World Health Organization is further contributing to extending the borders of the “GCP world” *via* programs destined to enhance the ethical review capacity of less developed countries and train investigators in GCP, adds Tassignon.

However, some industry representatives in Central and Eastern Europe have expressed concerns that the CTD has resulted in only limited harmonization of procedures in the region. “In practice, to a large extent it has increased the paperwork requirements—an increase also due to a more precautionary attitude among some competent authorities in the post directive era,” remarks Dr. Iwona Capala-Szczurko, compliance and training manager for Roche Polska in Warsaw, Poland. “EU Directive requirements were merged with existing regulations and review systems in CEE, resulting in implementation outcomes that differ between countries. All the countries concerned are still in a learning stage. It is not certain, however, that they will ever meet at the same point.”

Implementation of a single competent authority approval process across the EU would harmonize and simplify the administrative procedures that govern clinical trials, noted Capala-Szczurko. This would help eliminate some of the repetitive paperwork.

Furthermore, legal instability has increased in the new EU member states, leading to more uncertainty and greater need for legal advice. The changing clinical trial environment is not a transitional difficulty, but a long-term reality, fears Capala-Szczurko, and this is particularly noticeable for those operating on a regional level, such as project leaders.

Another problem area is the shortage of experienced inspectors, states Gunnar Danielsson, GCP inspector at the Medical Products Agency in Sweden. He is concerned that member states have different priorities, and local regulations, cultures, and traditions vary widely. However, the situation will improve when guidance documents are developed for performing, evaluating, and reporting trials. Key harmonization objectives include standardization of inspectors’ qualifications, quality assurance of

inspection procedures, joint inspections, shared training programs supported by the European Agency for the Evaluation of Medicinal Products (EMA), and a shared database of inspections, he said.

Dr. Beat Widler, global head of clinical quality assurance at Hoffmann-La Roche, is concerned about the overall lack of harmonization. Local forms are still being used, as well as EU-agreed-upon ones, necessitating the translation of documents. German regulators, for example, request full viral safety testing in early trials, while others do not. The definition of an IMP varies widely, and Spanish regulators are applying a very broad definition. Certification of third-party comparator products is often impossible, and EU member states do not have a common

view on how to apply Mutual Recognition Arrangements, or MRAs. “The SUSAR process dumps investigators and ethics committees with loads of unhelpful, relatively unfiltered, and uninterpreted information, resulting in no improvements in transparency or patient safety,” notes Widler. “Inspection manuals are not publicly available, and inspection findings seem to depend on the subjective opinion of inspectors.”

Widler feels the following questions must still be answered by the EU regulators:

- What is the EU position on risk management?
- Are the EMA and EU to be aligned with FDA on this approach?
- Were key performance indicators defined, and are they being tracked?
- Regarding Phase I, can umbrella protocols become an option to speed up the process while still ensuring the protection of subjects?

Widler favors better alignment of regulatory requirements at the EU level and across member states, no rushing through of future legislation, and greater effort in reaching compromises with the EMA.

Conclusion

Europe’s new regulatory landscape for clinical trials is still suffering from inconsistencies and gaps in clarity. Regulatory variations between countries have not been removed and are interfering with proper study conduct. Some states are keeping local requirements and adding EU requirements, causing delays in starting trials and increasing costs. Sponsors are concerned that requirements may change during the transitional phase, meaning that the same study is conducted according to different rules. Such problems are unlikely to be solved overnight.

Furthermore, there are ongoing concerns that supporting guidelines and guidance documents are still not universally available, and there is a lack of transparency about how documents get prepared. Precise details are also lacking about how the CTD is being implemented in each country. ★

EU MEMBER STATES

Founding members (1952)
 Belgium
 France
 Italy
 Luxembourg
 The Netherlands
 West Germany

Second-wave countries
 Denmark (1973)
 Republic of Ireland (1973)
 United Kingdom (1973)
 Greece (1981)
 Portugal and Spain (1986)
 East Germany (1990)
 Austria (1995)
 Finland (1995)
 Sweden (1995)

Newest members (2004)
 Cyprus
 Czech Republic
 Estonia
 Hungary
 Latvia
 Lithuania
 Malta
 Poland
 Slovakia
 Slovenia

Potential future members
 Bulgaria and Romania (2007?)
 Croatia and Turkey (in negotiations)
 Macedonia (candidate country)

Possible candidate countries
 Albania
 Bosnia and Herzegovina
 Serbia and Montenegro