SynteractHCR

A Full-Service International CRO

The New EU Clinical Trials Regulation: The Good, the Bad, the Ugly

Dr. Martine Dehlinger-Kremer
Vice President, Global Medical and Regulatory Affairs

The original intent of Directive 2001/20/EC was to simplify and harmonize the administrative provisions governing clinical trials in the European Union. However, experience has proven that a coordinated approach to the regulation of clinical trials has been only partly achieved, making it difficult to perform a clinical trial in several Member States (countries).

Challenges of the Previous Clinical Trials Directive

The time and costs of conducting clinical trials in the European Union grew significantly.

- Staffing requirements for the clinical trial authorization process for sponsors doubled.
- Insurance fees increased by 800 percent for industry sponsors.
- There was a 98 percent increase in administrative costs for non-commercial sponsors.
- Delays for launching a clinical trial increased by 90 percent to 152 days[1].

Worse yet, there was little cooperation among the Member States and no pooling of expert knowledge. As a result, the number of clinical trial applications in the EU fell by 25 percent from 2007 to 2011.

A New Regulation for Evolving Needs

Looking to the future, scientific development suggests that future clinical trials will target more specific patient populations, such as subgroups identified through genomic information. In order to include a sufficient number of patients for such clinical trials it may be necessary to involve many, or all, member countries, so any new procedures for the authorization of clinical trials will need to include as many countries as possible under the same rules.

Therefore, the European Commission determined to develop a legal Regulation that would repeal the earlier Directive and both simplify the submission of an application dossier for authorization and harmonize the procedures for conducting clinical trials. The goals include:

- Making the European Union more attractive for clinical trial research
- Reversing the decrease in number of investigations of medicines conducted in the EU
- Maintaining high standards of patient safety

Regulation of the European Parliament and of The Council on Clinical Trials on Medicinal Products for Human Use, repealing Directive 2001/20/EC

The new Regulation directly applies to all individuals in the European Union. It was adopted by the European Parliament (02 April 2014) and by the Council of Ministers (14 April 2014) and signed off on 16 April 2014. It was published in the Official Journal on 27 May 2014 and is expected to become effective on 15 June 2016.

First Steps

Two preconditions need to be accomplished by the EMA by January 2016:

- An operational database for clinical trials
- A portal for submissions

Six (6) months after these two components are functional, the Regulation will come into effect.

There will be a transition period of one year, during which trials can be authorized according to the current CT Directive or the new CT Regulation. Trials already authorized in accordance with the current CT Directive will continue to follow the CT Directive until 3 years after the new Regulation comes into effect.

Core Components

The scope of the Regulation is extensive, with several primary components covered in the core text and multiple appendices, including:

- Authorization procedures
- Start of trial, suspension or temporary holds, early termination
- Protection of subjects, informed consent
- Conduct of trials
- Safety reporting
- IMP manufacturing, labeling and import
- Insurance

Country-specific Aspects

Certain aspects are not covered by the Regulation and remain country specific, including:

- Ethics
- Legal representative of the subject not able to provide informed consent
- Substantial rules of liability in the case of damages
- Requirements for investigators and site qualification
- Requirements for country/site specific documents such as originals and copies, notarization, language

Additional approvals might still be required for certain items as well, such as:

- R & D in the UK
- CNOM in France
- Radiation approval in Germany when applicable
- Local EC/Authorities
- Data Protection

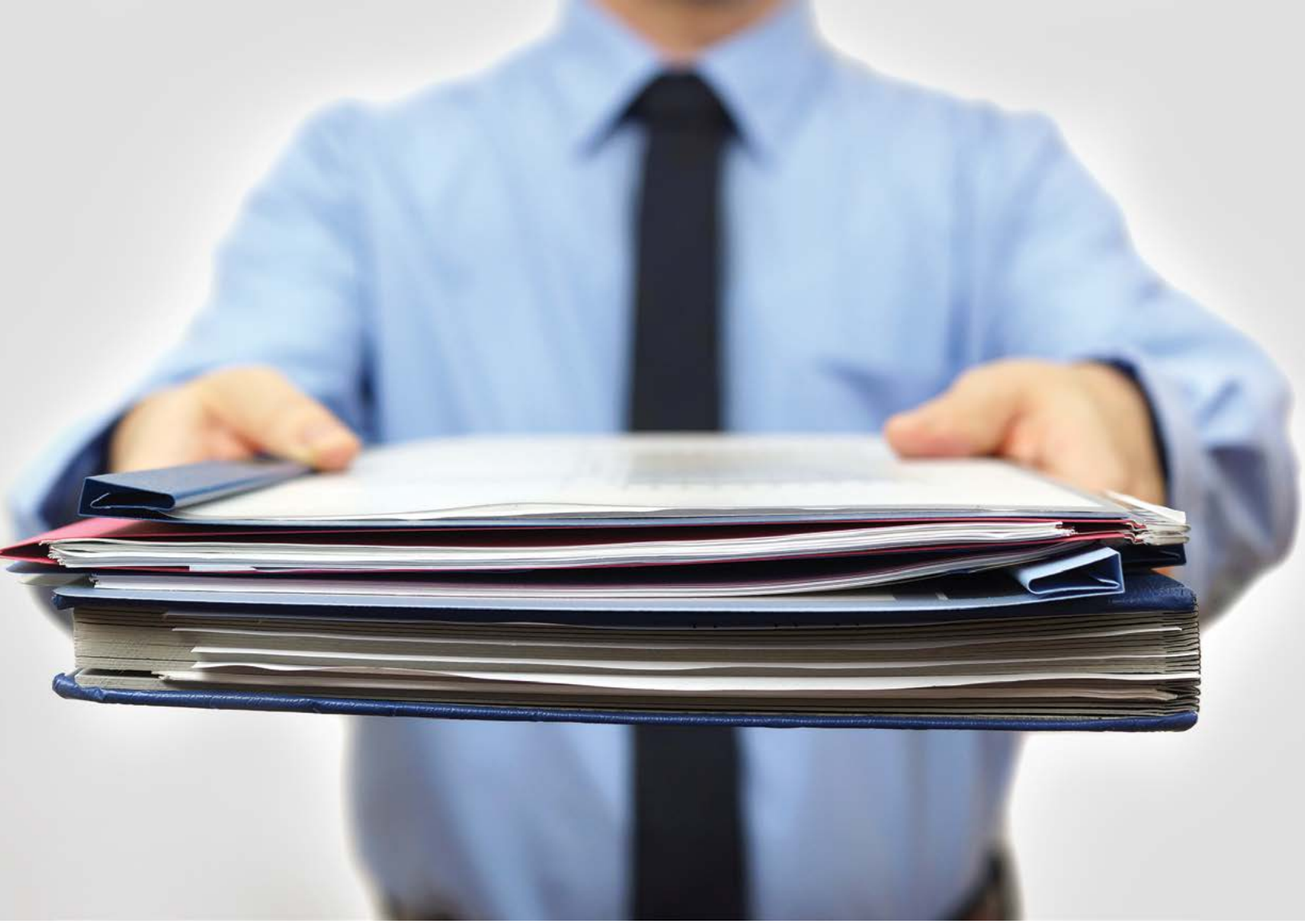
Advantages of the New Regulation

That said, there are several advantages and simplifications brought by the new Regulation. The most important of these are:

A harmonized application dossier that covers regulatory and EC approval.

- Part I – Study specific documents – The concerned Member States cooperate in the assessment of scientific, therapeutic and safety aspects
- Part II – Country/site specific documents – The assessment is made by each concerned Member State individually and would apply to items such as biological samples, clinical trial agreements, informed consent, recruitment of subjects
- Part I + II – can be reviewed in parallel or, alternatively, part I can be reviewed first followed by part II, depending on the sponsor's preference

A national level body will review the documents as per the national applicable law but with one contact point and one fee per country.



Efficiency has been enhanced through:

- A single portal for the submission of the clinical trial applications, no matter how many countries will be involved
- A single decision through the EU portal
- New Member States to be added assess only Part II, with Part I remaining valid as already approved, unless there is a disagreement on the basis of circumstances permitted by the Regulation, such as safety, data reliability and robustness of the considerations

Review timelines have been established, with a total maximum time of 106 days allowed for the initial submission, although advanced therapy trials can take up to 156 days.

Impact on Sponsors

By harmonizing the requirements, using a single application dossier and one central point for submission of all documents, submissions have been simplified from what might have been a total of 28 submissions to just one! This will streamline the functional processes and allow centralization of submission.

Co-sponsorship

Clinical trials are increasingly initiated by loose networks of scientists and scientific or academic institutions. Under the new Regulation, co-sponsorship is now permitted. Each co-sponsor assumes full regulatory responsibility of the entire clinical trial unless co-sponsors agree otherwise.

Monitoring

The extent and nature of monitoring shall be determined by the sponsor on the basis of all characteristics of the CT. Monitoring can be flexible based on the intervention level of the trial, the objectives and methodology of the trial, and the degree of deviation of intervention from normal clinical practice.

Safety Reporting

SUSARs are required to be electronically reported by the sponsor directly into EudraVigilance, instead of being submitted to each Member State. If, due to a lack of resources, an electronic report is not possible, then the SUSAR should be reported to the Member State where the event occurred. They are to enter it into EudraVigilance.

Transparency

There is an effort to make research transparent and open to the public. Results will be made publicly accessible in the EU database. Detailed summaries of the study results, including a summary in plain language, are to be submitted within one year of termination of the clinical trial. Final clinical study reports that were submitted to support a marketing authorization are to be uploaded onto the EU database within 30 days of authorization, rejection, or withdrawal of the marketing application. Sponsors are subject to penalties if they fail to adhere to these transparency obligations.

Some Cautions

Clinical trial data submitted in an application dossier must be based on clinical trials that have been registered prior to their start in a public registry that is a primary or partnered registry of the international clinical trials registry platform of the World Health Organization. For trials started before the Regulation applies, publishing in an independent peer-reviewed scientific journal is accepted as well. Typically in the US, registration can be made within 21 days after recruitment start and is not mandatory for Phase I. However, if trial data from the US is to be considered for the EU marketing application, then it must have been registered prior to start. US companies, not accustomed to doing this, will need to keep that in mind.

Serious breaches of the Regulation or of the protocol – meaning a breach likely to affect to a significant degree the safety and rights of the subjects or the reliability and robustness of the data generated – must be reported by the sponsor to the Member States concerned through the EU portal within seven days.

Conclusion

In summary, the new EU Regulation on Clinical Trials is expected to be a major improvement over the previous CT Directive and will:

- Streamline the approval process for studies conducted across multiple Member States
- Make one single application sufficient for conducting clinical trials in several Member States
- Harmonize the regulation of clinical trials throughout the Member States
- Simplify reporting procedures
- Increase the transparency of clinical trial results

References:
1. Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL version 17 Jul 2012