

Client Alert

Latham & Watkins Corporate Department

European Commission Proposes Overhaul of EU Clinical Trials Legislation

On July 17, 2012 the European Commission adopted a proposal to reform the existing EU clinical trials regulatory framework.¹ If approved, the Commission's proposal will replace the current EU Clinical Trials Directive, which has long been subject to criticism as unwieldy and inefficient.² The Commission's proposal still requires review by the European Parliament and European Council, which could amend it substantially, and it is not expected to come into force before 2016. The proposal also contemplates a transitional period in which both the regulation and the current Directive would apply in parallel.

The Clinical Trials Directive required the EU Member States to implement the Directive's provisions into their respective national laws, regulations, and administrative provisions no later than May 1, 2003. These national rules had to be in effect by May 1, 2004. As a result, if the proposed regulation is ultimately adopted, the Clinical Trials Directive will have been a short-lived experiment — and it seems unlikely that anyone will miss it. As recognized by the Commission's proposal, the Directive is “arguably the most heavily criticized piece of EU legislation in the area of pharmaceuticals.” Indeed, the Commission carried out two public consultations on the functioning of the Clinical Trials Directive and its revision, receiving multiple responses from pharmaceutical companies, industry associations, patient groups, investigators, hospitals and other key stakeholders, few of which had anything positive to say about it.³

Many public stakeholders identified the Member States' widely divergent implementations and interpretations of the Directive as one of the Directive's major shortcomings. They pointed to significant differences in Member State rules in key areas such as the reporting of adverse reactions, the definition of what constitutes a substantial modification to a clinical trial protocol requiring authorization or a non-interventional study falling outside the scope of the Directive, and insurance coverage requirements.

Another generally perceived shortcoming of the current regime is the need to obtain authorization from the various Member State national authorities in order to conduct clinical trials in more than one EU country. These authorities conduct their assessments entirely independent of one another, following their own procedures, and often reaching different conclusions. The need to make multiple submissions, to tailor submissions according to different content and format requirements, and to

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undergo divergent processes increases the likelihood of different outcomes across Member States, resulting in administrative burdens and unnecessary delays in the development of new drugs.

The Commission has acknowledged these shortcomings. According to a Commission-ordered study, the number of clinical trial applications in the EU has fallen drastically since the Directive came into force (between 2003 and 2007, the number fell by 25 percent), the administrative cost of conducting a clinical trial in the EU has risen dramatically and the staffing required by commercial sponsors has more than doubled.⁴ Since the adoption of the Directive, the cost of insurance for commercial sponsors has increased by 800 percent, and the average delay for launching a clinical trial in the EU has increased by 90 percent to 152 days.⁵

Main Changes to Address Shortcomings

Change in the Nature of the Legislative Act

To address the issue of the divergent implementation and interpretation of the provisions of the Clinical Trials Directive, the Commission proposes to replace it with a regulation. Unlike directives, where the provisions must be implemented into the national laws of the Member States, regulations are automatically applicable in the 27 Member States of the EU from the moment they enter into force. To further ensure uniformity, the provisions regulating some of the areas where national laws diverge the most, such as safety reporting, will be streamlined and simplified if the proposed regulation is adopted.

Further, the proposed regulation establishes only two categories of clinical trial post-authorization modifications requiring approval, namely those that have a substantial impact on (i) the safety or rights of the subjects or (ii) the reliability and robustness of the data generated in the clinical trial. Under the current Directive, in addition to those two types of modifications, authorization is required for "otherwise significant" modifications, an open-ended concept that enables Member States to require authorization for several additional types of protocol modifications.

Single Application

To streamline the clinical trial authorization process, and diminish the risk of divergent outcomes, the proposed regulation provides for a harmonized application dossier, which can be submitted to a single EU portal managed by the Commission. Once an application is submitted, the assessment of the clinical trial will be split into two parts.

Part I covers those aspects of the assessment in which the Member States in whose territory the trial sites are located must cooperate. These aspects include the assessment of the anticipated therapeutic and public health benefits of the trial; the risks and inconveniences imposed on the trial subjects; compliance with manufacturing, importation, and labeling requirements; and the completeness and adequateness of the investigator's brochure.

The Part I assessment will be carried out jointly by all the Member States where the trial sites are located, but with a single Member State appointed as the "reporting Member State" at the sponsor's request.⁶ The reporting Member State, taking into account the considerations made by the other Member States (the so-called "concerned Member States"), will carry out its assessment and draw up an assessment report reaching one of three conclusions: (i) that the trial is acceptable, (ii) that the trial is acceptable subject to conditions or (iii) that the trial is not acceptable.

A concerned Member State may only opt out of the conclusions reached by the reporting Member State based on two grounds: (i) significant differences in normal clinical practice with the reporting Member State that would lead to a subject receiving an inferior treatment than in normal clinical practice or (ii) infringement of national rules prohibiting or restricting the use of specific types of human or animal cells. The invocation of the first set of grounds must be justified based on scientific and socioeconomic arguments, and these justification will be communicated to the Commission, the Member States and the sponsor through the EU portal.

Part II covers those aspects of the trial with an intrinsic ethical or local nature, and will be carried out by each Member State individually with respect to their own territory. The Part II assessment areas include compliance with the requirements for informed consent; subject and investigator compensation; subject recruitment; data protection; suitability of the site, the investigator, and other individuals involved in conducting the trial and damage compensation.

Both the Part I and II assessments will be communicated to the sponsor through the EU portal, and both assessment processes are subject to clear timelines: the reporting Member State must submit the Part I assessment within 10 to 30 days depending on the type of trial at issue, and the concerned Member States must submit their Part II assessments within 10 days, though these periods may be suspended for specified amounts of time to allow for Member State requests for additional explanation and sponsor application amendments. To avoid undue delays, the trial will be tacitly approved if the deadlines are exceeded, a mechanism that is already included in the current regime.

Autonomy in the Election of the Assessing Bodies

The proposed regulation leaves it up to the Member States to decide the body in each Member State that will be involved in the Part I and II assessments. They must, however, ensure that the required expertise to carry out the assessment is available in these bodies, and that the persons involved in the assessment are independent from the sponsor, the site, and the investigator, and have the necessary qualifications and experience. Member States must also ensure the involvement of lay persons and patients in the assessment process.

Special Rules for Low-Risk Trials

The proposed regulation imposes less onerous requirements on low-intervention clinical trials. Low-intervention clinical trials are defined as clinical trials of authorized drugs, used within the approved indication or consistent with the standard treatment, and where additional diagnostic or monitoring procedures do not pose more than a minimal additional risk or burden to the safety of the subjects compared to normal clinical practice. Among other things, the approval of low-intervention clinical trials is subject to shorter timelines.

Co-Sponsorship

The proposed regulation introduces the concept of co-sponsorship to reflect the current practice of various pharmaceutical companies and/or research institutions joining forces to conduct clinical trials. The regulation provides that the co-sponsors are free to contractually determine between them how to split their responsibility, and in the absence of such an arrangement, responsibility will jointly lie with all of them. In all cases, the co-sponsors must designate one sponsor as the main contact point with the authorities.

Insurance

In an attempt to reduce the cost of insuring clinical trials in the EU, the proposed regulation explicitly excludes low-intervention clinical trials from the obligation to provide specific insurance or indemnification against any harm caused to the study subjects as a result of the trial. In these cases, the general insurance coverage of the medical practitioner, the health care institution or the sponsor is considered to provide sufficient coverage.

With respect to those trials that still require insurance, the proposed regulation obliges Member States to set up a national indemnification mechanism, which will be free of charge for studies that are not intended to obtain data to support a Marketing Authorization Application.

Inspections

The proposed regulation specifically authorizes the Commission to supervise Member State compliance with the regulation, and to control the regulatory systems of third countries to ensure compliance with EU legislation on clinical trials.

The mandate given to the Commission to control non-EU regulatory systems is meant to ensure the effective application of the provisions of the EU Code on Medicinal Products.⁷ The EU Code on Medicinal Products provides that, in order for clinical trials conducted outside the EU to be taken into account during the assessment of a Marketing Authorization Application in the EU, the clinical trials must “be designed, implemented and reported” on the basis of the ethical and good clinical practice principles of the EU Clinical Trials Directive and the Declaration of Helsinki. The Commission’s mandate also serves to facilitate application of the proposed regulation’s provision requiring that clinical trial data used to support a clinical trial application dossier must comply with EU standards.

Comparison to the US Clinical Trial Regulatory Framework

In the US, the Food and Drug Administration (FDA) regulates the conduct of clinical trials and the sufficiency of clinical trial data for marketing application approval through its enabling statute, the Federal Food, Drug, and Cosmetic Act,⁸ and its promulgated regulations and guidance documents. The primary difference between the US framework and the current EU framework is the existence of a single decision-making body. With the proposed regulation, the European Commission is aiming to move toward a similar, more streamlined decisionmaking approach, while maintaining the Member States’ autonomy in certain areas. Although FDA is no stranger to complaints of shifting interpretations, the European Commission’s proposed changes to its clinical trial framework are likely to result in more uniformity not only in clinical trials conducted in multiple EU countries, but in global trials conducted in both the US and EU as well.

Recent legislation amending the Federal Food, Drug, and Cosmetic Act explicitly authorizes FDA to work with foreign regulatory authorities, medical research companies, and international organizations to foster uniform, scientifically driven, global clinical trial standards.⁹ This legislative mandate and the new EU clinical trial regulation both signal a shift toward consistency and reduced burdens in the increasingly globalized clinical trial landscape, and medical product developers continue to hope that policies continue to move in this direction.

Conclusion

The European Commission's proposed regulation constitutes a renewed attempt by the EU institutions to harmonize and simplify the clinical trial legal framework after the current Directive's failings. However, it maintains a significant degree of Member State autonomy with respect to some important aspects, such as investigator and subject compensation and recruitment, and the assessment of the suitability of investigators and sites — areas where differences in standards and practices between Member States are perhaps more acute. If the regulation is ultimately adopted, only time will tell whether the Commission will achieve its objective of reducing the red tape to “bring patient oriented research back to Europe” and restoring the EU competitiveness in clinical research.

In our view, the regulation will not do away with the important differences that still exist between the countries of the EU on standards of medical treatment and patient care, quality of life or cultural attitudes to clinical trials. Its success will thus largely depend on the Member States' political will to cooperate in the achievement of the goals set out by the Commission.

Endnotes

- ¹ *Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC*, COM (2012) 369 final (July 17, 2012).
- ² Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, 2001 O.J. (L 121) 34.
- ³ The first public consultation was held from October 9, 2009 to January 8, 2010; responses received from the public are available at http://ec.europa.eu/health/human-use/clinical-trials/developments/responses_2010-02_en.htm. The second public consultation was carried out between February 9, 2011 and May 13, 2011; those responses are available at http://ec.europa.eu/health/human-use/clinical-trials/developments/ct_public-consultation_2011_en.htm.
- ⁴ Impact on Clinical Research of European Legislation (ICREL), Project Final Report, http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf.
- ⁵ *Id.*
- ⁶ The reporting Member State proposed by the sponsor is free to refuse the role, though it must work with another Member State to reach an agreement that the other Member State will be the reporting Member State. If no other Member State accepts the role, the Member State originally proposed by the sponsor must be the reporting Member State.
- ⁷ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, 2001 O.J. (L 311) 67.
- ⁸ 21 U.S.C. § 301 *et seq.*
- ⁹ Food and Drug Administration Safety and Innovation Act of 2012, Pub. L. No. 112-144, 126 Stat. 993.

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