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European Clinical Trials Regulation: A need for change to improve efficiency and competitiveness

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In April 2014, the new Clinical Trials Regulation 536/2014/EC (the ''Regulation''[1]) was published, after nearly two years of negotiations within the legislative process, involving the legislators (Council of Ministers and the European Parliament), the European Commission and stakeholders such as the industry, patient organizations and academia. The Regulation likely will not apply until May 28, 2016, at the earliest, replacing Directive 2001/20/EC (the ''Directive'').[2]

The Directive was adopted 10 years ago (after nearly 10 years of gestation), and has been viewed as a cause for administrative burdens, inefficiency and high costs for initiating clinical studies in Europe. The Commission's Explanatory Memorandum for the legislative proposal states that the number of clinical trials conducted in the EU fell 35 percent from 2007 to 2011, while the costs related to insurance fees increased by 800 percent for industry sponsors.[3]

That said, certain national agencies have been known to be very efficient in approving clinical trials. For example, the U.K. Medicines and Healthcare products Regulatory Agency (''MHRA'') recently has been praised for approving the clinical trial for an experimental Ebola vaccine with extraordinary speed, recognizing the significant public health impact of the vaccine. In September 2014, the clinical trial application was assessed and authorized in just four working days. This illustrates the point that regulators have the powers to apply the rules flexibly if they want to. The same efficiency, however, needs to be replicated across the rest of Europe to make the region competitive and attractive as a serious global player for conducting clinical trials, especially multi-center studies. There is no question that the new regulatory framework has been

[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of April 16, 2014, on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

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[2] Directive 2001/20/EC of the European Parliament and of the Council of April 4, 2001, on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

[3] Explanatory Memorandum, section 1.

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adopted with this particular consideration in mind. In order to meet its over-arching aims, the Regulation must therefore deliver what it set out to do: provide a simplified and efficient regulatory framework for clinical trials in the EU.

Although the Regulation will not apply until 2016, the impact of the Regulation on the overall management of clinical development likely will be assessed by those who are involved in such activities.

As a general point, the Regulation seeks to consolidate, codify and simplify the existing rules and guidance concerning conduct of clinical trials. For example, the obligation on informed consent, a universally accepted ethical principle, is similar to that set out in the existing good clinical practice guidelines. That said, the Regulation has expanded considerably on the informed consent requirement to clarify how it is applied in clinical trials involving minors, and pregnant or breastfeeding women.

This article therefore discusses some of these key changes, and considers their regulatory impact on the overall management of clinical trials in Europe and the data arising from such trials.

Basic framework

Although the Regulation contains 19 legislative chapters and 8 annexes, its basic structure is underpinned by the following seven key elements:

- The scope of the Regulation as regards what studies are regulated by the Regulation and what products should be regulated as investigational medicinal products by cross-referencing to the definitions.

- The organizational structure overseeing the authorization, monitoring and communication of clinical trials.

- The procedures for managing the life cycle of a clinical trial authorization: from the initial regulatory submission and its modification to the end or termination of the clinical trial.

- The supporting data that should accompany an application for clinical trial authorization by cross-referencing to Annex I, which sets out the basic information for compiling the dossier.

- The good clinical practice and ethical principles that should be applied to lawfully recruit clinical trial subjects, taking full account of their individual circumstances and the nature of the clinical trials being carried out.

- The regulatory standard and expectation for manufacture, control, release and distribution of an investigational medicinal product.

- The enforcement powers conferred on the regulatory authorities in the event of regulatory breach.

Harmonization across Europe

The Directive was adopted originally seeking to harmonize the regulatory requirements for conducting clinical trials in the EU. However, because the framework was provided in the form of a directive, it left some flexibility for the Member States to implement the requirements (as the Commission put it, ''similarly but differently'') into their local laws. This has led to divergent national approaches and practices across the EU. The Regulation has now removed the need for the legal requirements to be implemented into the national laws. Therefore, the Regulation, which is directly applicable, provides greater consistency in the regulatory approach, and ensures a coherent procedure for submission and assessment of applications for authorization and their subsequent modifications.

The Regulation also introduces specific mechanisms to facilitate conduct of trials in more than one Member State, by streamlining the approval process. The process is largely based upon the documented success of the Voluntary Harmonisation Procedure (''VHP'') introduced in 2009 to coordinate the assessment of multinational trial applications across the EU. The new framework (discussed further below) enables Member States to cooperate in the assessment of a clinical trial with a single submission point for all EU trials. Such mechanisms should lead to cost and administrative savings for sponsors. Other harmonization provisions also are introduced, such as centralized reporting of adverse events to the European Medicines Agency (''EMA''), rather than the need to make multiple submissions to individual Member States.[4]

A Clinical Trials Coordination and Advisory Group (''CTAG'') will be set up to help coordinate the process and the conduct of clinical trials across the EU.[5] Its role is similar to the Clinical Trials Facilitation Group established by the EU Heads of Medicines Agency (''HMA'') to coordinate implementation of the Directive across Member States. The CTAG is tasked with supporting the continued harmonization of the requirements across the EU, and the exchange of information between Member States and the Commission on the proper management of issues that may arise from the authorization procedure. The CCAG should provide an appropriate forum to resolve disagreement, and to adopt agreed EU policy on authorization of clinical trials.

Streamlined approval process

One of the most substantive changes introduced by the Regulation is the process by which a clinical trial is approved. The Regulation introduces a single, electronic submission process through an EU portal hosted by the EMA, as well as joint assessment for certain parts of the application.[6] Similar to other EU regulatory procedures for granting a marketing authorization, a ''reporting Member State'' is responsible for leading the assessment to inform the decision to be taken by ''Member State(s) concerned.'' The system also allows substantial amendments to be submitted through the same process, and the trial can be extended to additional Member States if a trial site is added.

For applications involving two or more Member States, in Part I of the assessment process, Member States concerned can object to the approval of a trial by the reporting Member State only on certain specific grounds, namely: (a) participation in the clinical trial would lead to inferior treatment; (b) infringement of na-

[4] The Regulation, Article 42, 43.
[5] The Regulation, Article 85.
[6] The Regulation, Article 5.

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tional legislation, for example use of specific types of human or animal cells; or (c) disagreement with the conclusions of the reporting Member State based on safety and data reliability and robustness considerations submitted as part of the application.[7]

The Regulation imposes fixed time limits for completing the assessment to ensure timely authorization of the clinical trial. In general, this process will be:

- 10 days—validation of the application;
- 45 days—assessment report on Part I of the application, including assessment by the reporting Member State (26 days), coordination with the Member State(s) concerned (12 days) and a consolidation phase (7 days); and
- 5 days—notification of the decision.

This 60-day period can be extended by the reporting Member State in order to request additional information from the sponsor, or where, for example, the trial concerns advanced therapy medicinal products or novel medicinal products.

However, certain decisions are reserved for individual Member States and they are covered under Part II of the assessment procedure.[8] Part II covers matters that are of an ''*intrinsically national (for example, liability), ethical (for example, informed consent), or local (for example suitability of the clinical trial site) nature*.''[9] In particular, the liability and insurance provisions will remain under individual Member State control. Review of Part II also should take 45 days, that is, within the same time frame as the assessment of Part I. However, Part II decisions fall within the national competence. So it is possible that Member States may object to a clinical trial being initiated on national law grounds, for example, indemnification arrangements.

At this juncture, it is difficult to assess how this system will work in practice, or whether the current lack of harmonization will be significantly reduced.

Good clinical practice

The overall structure for clinical governance is not substantially different from that set out in the Directive and various guidance already adopted through the International Conference on Harmonisation. However, the Regulation now has introduced a self-reporting obligation for the sponsor in the event of a serious breach of the Regulation. The sponsor is required to report through the EU portal without undue delay, but not later than seven days of becoming aware of the breach. Consistent with the over-arching objectives of good clinical practice, a serious breach is defined in the Regulation as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial. This self-reporting requirement is based upon U.K. national measures under Regulation 29A of the U.K. Human Medicines (Clinical Trials) Regulations 2004 that seek to implement and enforce the requirements set out in the Directive.

[7] The Regulation, Article 8(2).
[8] The Regulation, Article 7.
[9] Explanatory Note to the Regulation, paragraph 3.2.

Definitional issues

New definitions have been introduced or existing definitions have been revised in order to clarify the scope of the Regulation.[10] These definitional issues had been in the past the cause for confusion in the Directive as regards to how the clinical trial rules could be workably put into practice.

- The term ''sponsor'' has been clarified to emphasize that financial support per se is not decisive on whether an individual, company, institution or organization is considered a sponsor. Rather, the definition makes clear that the sponsor is primarily responsible for initiating, managing and setting up the financing of the clinical trial.
- The concept of ''co-sponsors''[11] has been introduced. The concept reflects more accurately that clinical trials increasingly are initiated by loose networks of scientists, scientific institutions or commercial institutions in more than one country. Given the cooperative arrangements, for practical or legal reasons, there has been difficulty in identifying who among them should act as a single sponsor. Under the Regulation, all co-sponsors are responsible for the entire clinical trial and are responsible for managing the conduct of the trial in each Member State, ''*unless the sponsors decide otherwise in a contract setting out their respective responsibilities*.''
- The definition for ''low-intervention clinical trial'' (''LICT'') is introduced to reflect the need to regulate clinical trials proportionately to take account of the differences in risk between a clinical trial with an authorized medicinal product and that with an investigational medicinal product. LICTs have been viewed by the legislature as of crucial importance for assessing standard treatments and diagnoses, thereby optimizing the use of medicines and in turn contributing to a high level of public health. A clinical trial should be so classified if three conditions are met: (a) the product being investigated is authorized; (b) the study protocol requires the product to be used according to the marketing authorization, or there is supporting evidence on the safety and efficacy of the product; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the trial subjects as compared with normal clinical practice.
- The term ''auxillary medicinal product'' is defined to distinguish it from an investigational medicinal product. An investigational medicinal product is defined as a medicinal product that is being tested or used as a reference, including as a placebo, in a clinical trial. However, the auxillary product does not come within the scope of the Regulation. The term is defined as a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. For example, a product that is used to stabilize the clinical conditions of the trial subjects would not be considered as an investigational medicinal product. However, an active comparator is an investigational medicinal product.
- The Directive also caused confusion as to the role of the legal representative. Some Member States con-

[10] The Regulation, Article 2.
[11] The Regulation, Chapter XI.

sidered that the legal representative should assume legal responsibilities for the sponsor where the sponsor is outside the EU. While the Commission has sought to clarify this, some Member States stuck to their position. Article 74 of the new Regulation sets out the role of the legal representative where the sponsor is not established in the EU. Although this includes an obligation to ''*ensure compliance with the sponsor's obligations pursuant to [the] Regulation*,'' this does not materially change the current legal representative's role. In particular, Article 76 states that ''*this Chapter shall not affect the civil and criminal liability of the sponsor, investigator or persons to whom the sponsor has delegated tasks*.'' Therefore, liability should not be properly imputed onto a legal representative because the person (legal or natural) has taken on the role as the contact point for the sponsor with no involvement in any clinical-trial-related activities as delegated by the sponsor, for example, through contractual arrangements.

Insurance policy

The Directive is prescriptive about insurance. Such requirements as currently contained in the Directive are determined by the ethics committees in each Member State, which may take very different views of the risks of a trial. For example, in the U.K., ethics committees have required sponsors to take out specific insurance for a trial, and have been uncomfortable about accepting indemnities from, for example, a related or parent company.

In the Commission's assessment, this obligatory insurance or indemnity has substantially increased the costs and administrative burden of carrying out clinical trials. However, there is no evidence that the number or amount of damages has increased after the Directive came into force in 2004. Acknowledging that not all clinical trials pose an additional risk to human subjects when compared with treatment in normal clinical practice, the Regulation now states: ''*Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk*.''[12] The compensation arrangements as indicated in the Regulation are risk-based. What this means in practice is that in cases where a clinical trial poses an additional risk, the sponsor should ensure appropriate arrangements (whether in the form of insurance or an indemnification mechanism) are put in place. The Regulation therefore appears to accept that a separate insurance policy is not required, and allows Member States some flexibility in determining what is appropriate taking account of the nature of the clinical trial and the likely attendant risks that may arise.

Whether specific arrangements are considered appropriate likely will be influenced by the opinions of national ethics committees. In an area that has caused the most significant increase in costs under the Directive, this particular aspect will need to be carefully monitored to ensure that the costs associated with setting up the arrangements are not prohibitively high for clinical trials to be carried out across the EU.

That said, given the compensation arrangements are risk-based, Member States are not required to ensure additional use of any such insurance system for low-intervention clinical trials. By definition, these trials carry less risk for subjects. As a result, the Regulation acknowledges that general professional insurance should be sufficient to cover the minimal additional risks over and above normal medical practice, and no separate insurance ''system'' is required. This flexibility is introduced into the Regulation, recognizing that non-commercial sponsors have had, since the introduction of the obligatory insurance/indemnity with the Directive, great difficulties in obtaining compensation coverage.

Transparency of clinical trials and clinical trial data

Transparency in regulatory decision-making is a key feature of the European regulatory system. The EMA and the HMA are committed to continuously extending their approach to transparency. As declared by the EMA, a key goal is the publication of clinical trial data for products once the decision-making process on an application for an EU-wide marketing authorization is complete. The EMA says it has embarked on this process because it is important to establish trust and confidence in the regulatory system so that the public has a better understanding of the regulatory decision-making. This policy has received the support of academic researchers and patient groups through their related campaigns. On the other side of the divide, industry has been more cautious about the wholesale disclosure of its data, particularly where those data can be accessed by competitors.

The final publication policy was adopted by the EMA's Management Board on Oct. 2, 2014, following nearly 18 months of extensive consultations involving stakeholders with very divergent views on the topic. This policy will apply from January 2015 onwards for all new marketing authorization applications that are evaluated under the European Centralised Procedure. This policy will apply to all line extensions of approved products starting July, 1 2015.

Consistent with this EU-wide policy, the original proposal for the Regulation created a revised EU-wide database that will be accessible to the public. In particular, sponsors are required to register clinical trials on the database, and provide certain information about the trial, including a summary of the results once the trial is completed.

During the legislative procedure in 2013, the European Parliament, with the support of the Member of the European Parliament who was appointed as the MEP Rapporteur, proposed some additional amendments to the Regulation to require that the full results of clinical trials, together with the clinical study reports, be published on the database. These amendments coincided with the consultation on the EMA's proactive disclosure policy as referred to above. As a result, there has been intense debate about the wording of the Regulation (and the EMA policy and associated initiatives) and about what information arising from clinical trials should be made publicly available.

The final text of the Regulation states that, as well as the original provisions on registration of the trial, the

[12] The Regulation Article 76.

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sponsor should submit a summary of the results to the EU database within a year of the end of the trial. In addition, where the trial was intended to be used for obtaining a marketing authorization, the applicant should submit the clinical study report 30 days after the marketing authorization has been granted (or refused or withdrawn).[13] The Regulation also requires Member States to put in place penalties to cover noncompliance with these provisions.[14]

Although the recitals state that ''in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been *granted*'' (emphasis added), the Regulation states that the EU database shall be publicly accessible unless, among other things, confidentiality is justified on the grounds of ''*protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure*.'' The Regulation, however, provides no definition of commercially confidential information, but the term is defined in the EMA publication policy (see above) as any information contained in the clinical reports that is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant.

Operationally, the data-posting requirement will come into effect only when the EU electronic portal and the EU database are fully functional. At the time of writing, the EMA has initiated public consultation on the functional specifications for the EU portal and EU database following a series of meetings with the stakeholders. The functional specifications must be approved by the Agency's Management Board by the end of 2014 so that the IT platforms can be developed. In collaboration with Member States and the European Commission, the EMA will develop the rules of procedures on public access to data and information contained in the database.

Conclusions

The Regulation goes some way to addressing a number of the key concerns arising from the Directive, particularly in relation to greater harmonization between Member States on the authorization of clinical trials and clarity on the regulatory requirements, consistent with the single market principle. Although the Regulation has been adopted, it is subject to certain transitional arrangements and specific implementing measures such as the availability of a fully functional EU database to capture and facilitate exchange of clinical trial data.

On balance, the Regulation will greatly facilitate multi-center clinical trials. That said, it remains to be seen whether the 60-day assessment time line, which can be extended, or the continued review of certain aspects by national authorities, will have a significant impact on the delays currently being experienced by sponsors. Otherwise, this may dilute the many potential positive impacts of the Regulation.

[13] The Regulation, Article 36, 37.
[14] The Regulation, Article 94(2).