EU Shake-Up

Elisabethann Wright and Wim Nauwelaerts at Hogan & Hartson LLP offer their thoughts on improving clinical trials legislation in the EU

Conducting clinical trials is a crucial activity for pharmaceutical companies wishing to develop new medicinal products and treatment therapies. However, the risk involved in clinical trial activities must be balanced with the medical benefit for patients, both specific and general. Thus it is important that clinical trials be regulated.

The legislative framework governing EU clinical trials has changed substantially in recent years. Before May 2004, there was no legislation at EU level. As a result, pharmaceutical companies were required to deal with the varying rules of each EU Member State in which they wished to conduct clinical trials.

The Clinical Trials Directive 2001/20/EC (CT Directive) was adopted on 4 April 2001 (1). The intention of the Directive was to ensure the protection of public health and safety of clinical trials participants, the ethical soundness of the clinical trials, the reliability and robustness of data generated in clinical trials, and also to simplify and harmonise the administrative provisions governing clinical trials. On 1st May 2004, the provisions of the Directive became effective and binding in all EU Member States. To complete this framework, a Directive setting out the principles of Good Clinical Practice (GCP) and a number of guidelines have been adopted by the European Commission (2,3).

Five years have elapsed since the implementation into national law of the CT Directive. It is now considered to be an appropriate time to consider ways to improve on current EU legislation. This was the view behind the European Commission's launch, on 9th October 2009, of a public consultation on the assessment of the functioning of the CT Directive (4). In its consultation document, the European Commission identifies a number of shortcomings that have become apparent since the implementation of the CT Directive, and puts forward various options to address these. The consultation process is to be welcomed as it permits stakeholders to make known their views on the European Commission proposals.

In the consultation document, the European Commission proposes to address the multiple and divergent assessments of clinical trials by the national competent authorities of the EU Member States and the absence of rules governing emergency clinical trials. However, some stakeholders might be disappointed that other issues affecting the CT Directive are not discussed. The role and responsibilities of the sponsor's legal representative and the need to include clinical trial-specific data protection rules in the Directive (as opposed to referring to the general framework for EU data protection) could arguably also have been included in this consultation document.

TOWARDS EU PROCEDURES FOR AUTHORISATION

According to Article 9-2 of the CT Directive, before commencing any clinical trial, the sponsor is required to submit a valid request for authorisation to the Competent Authority of the EU Member State for which the trial is planned. While this requirement is simple for a clinical trial conducted in a single Member State, the situation is more complex for multinational clinical trials. This is because the sponsor must await the approval of an Ethics Committee and the authorisation from the national Competent Authority of each individual Member State in which the clinical trial is to be undertaken. This situation leads to delays in the approval of the clinical trials protocol and administrative costs that are particularly difficult to support for small- and medium-sized enterprises (SMEs).

Bearing in mind these weaknesses of the current CT Directive, the European Commission has identified different options to streamline the clinical trial authorisation process across all national EU Competent Authorities. These options reflect the marketing authorisation process provided for medicinal products in EU law and known to pharmaceutical companies marketing products in the EU.

Decentralised or Mutual Recognition Procedure

The first option proposed by the European Commission is based on the model of the decentralised procedure/mutual recognition procedures currently established in the EU for the marketing authorisation of medicinal products.

According to this option, concerned EU Member States would be required to reach an agreement on the authorisation of a clinical trial to be conducted in sites in their territory. One Member State, referred to as the Reference Member, would undertake an assessment of the clinical trial in consultation with and assisted, if needed, by the other concerned Member States. This assessment by the Reference Member State would be relevant to the clinical trials to be undertaken in all concerned Member States. A clear decision-making procedure (arbitrage procedure) would be established to address disagreement amongst the concerned Member States. A decision authorising a clinical trial would be issued either by the national competent authorities individually or by the Community for the concerned Member States.

The intention of the European Commission is to ensure an application for authorisation of a clinical trial was based on an identical interpretation and application of the Clinical Trials Directive in each Member State.

Centralised Procedure

The European Commission also proposes to establish a procedure whereby a single clinical trial authorisation would be valid throughout the entire EU. This proposal is based on the model of the centralised procedure currently existing for the marketing authorisation of medicinal products. In line with this procedure, the assessment of a clinical trial application would be performed by one body, with the authorisation being issued at EU level. The scientific expertise of the European Medicines Agency (EMEA) would be used and decisions made by the European Commission in close cooperation with the Member States. Following an EU-wide authorisation, the clinical trial could be expanded across the entire EU without additional follow-up authorisations in the Member States.

For the European Commission, this proposal constitutes a genuine one-stop shop for authorisations of clinical trials performed in the EU while at the same time closely involving national competent authorities.

Which Route for Clinical Trial Authorisation?

One question raised by the European Commission in its proposal is how to determine which route to approval would be most appropriate for individual products, whether any decision as to appropriate procedures should be optional, and whether the choice of route should be left to the sponsor. There is also a question as to whether the procedures should cover all clinical trials performed in the EU or whether they should be limited to only some clinical trials, such as multinational trials.

The pharmaceutical industry is expected to react favourably to these proposals. Such procedures are expected to reduce administrative work considerably and therefore the costs for the periods that precede the beginning of the clinical trials. The Competent Authorities of the EU Member States may not, however, share this view. Experience demonstrates that the CT Directive requirements are applied very differently in the Member States. The proposed changes to the framework may, therefore, require more authoritative rules or guidelines.

TOWARDS HARMONISED RULES REGARDING EMERGENCY CLINICAL TRIALS

Clinical trials in the EU are based on the principle of informed consent of the trial subjects (5). According to Article 2 (j) of the CT Directive, informed consent is defined as a "decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks, and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation."

In practice, the information provided to a subject prior to informed consent is extensive, covering several pages and sometimes difficult to absorb. Consequently, obtaining informed consent such as it is defined in the CT Directive can present challenges in certain circumstances.

Aware of this issue, the European Commission underlines in its public consultation on the assessment of the CT Directive that one of the weaknesses of the current framework is the lack of EU rules regarding emergency clinical trials.

It is explained in the consultation document that, in emergency situations such as a stroke or a heart attack, obtaining informed consent from the patient or their legal representative for the conduct of a clinical trial may not be possible. However, according to the current CT Directive, unless informed consent is provided, a clinical trial can not be performed. This is true even if a clinical trial may be the only possible route to save a patient.

There is a paradox in this finding. In international guidelines such as the World Medical Association's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (as amended in 2008) (6) and the Guidelines on good clinical practice of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6) (7), it is acknowledged that emergency clinical trials are necessary. Moreover, as the European Commission explains, there is general agreement at EU level that, in principle, clinical trials of this kind are necessary in order to ensure a high level of human health, which is a fundamental policy aim of the Community (Article 152(2) EC Treaty). The European Commission, therefore, highlights that the EU needs to regulate clinical trials of this nature.

At the national level, some EU Member States have already attempted to address this issue by adopting rules or guidelines to help sponsors to deal with emergency clinical trials. However, while these national regulations are welcome, it would undoubtedly be simpler if harmonised rules were established at EU level.

The European Commission therefore invites stakeholders to provide comments on the need to address the issue of emergency clinical trials and on the appropriate rules that should be adopted. It proposes to introduce a regime which ensures the safety and ethical soundness of clinical trials while making it possible, where necessary, to perform emergency trials. In other words, a balance needs to be found between compliance with these principles and the impossibility of obtaining informed consent in certain circumstances. In practice, it would be necessary to include in the EU rules a waiver of the need to obtain informed consent from trial subjects or their legal representative. The conditions for this waiver should be subject to very strict conditions. Establishing rules on emergency clinical trials may therefore constitute a real challenge that the EU may have difficulties to take up.

THE NEED FOR MORE CLARITY IN THE ROLE AND RESPONSIBILITIES OF THE LEGAL REPRESENTATIVE

Stakeholders may regret that the question of the role and responsibilities of the legal representative of the sponsor is not raised in the public consultation. In the CT Directive, only one Article deals with the role of the legal representative. Moreover, the European Commission guidelines are of limited help.

Article 19, paragraph 1 of the CT Directive provides that "this Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community."

This Article provides that non-EU sponsors are required to appoint a legal representative in the EU or the European Economic Area (EEA) (which includes Iceland, Norway and Liechtenstein) when they wish to conduct a clinical trial. According to the European Commission Questions and Answers document on clinical trials, only one legal representative can act on behalf of one sponsor in one clinical trial (8). This means that, if a clinical trial is to be conducted at several sites, a single legal representative must represent the non-EU sponsor in relation to all sites.

Regarding the legal representative itself, the questions and answers document acknowledges that it is acceptable to use an established company as a legal representative. In other words, if a non-EU sponsor has a sister company established in the EU, this latter entity may act as the sponsor's legal representative for the purpose of the clinical trials.

There is, however, no provision, either in the Directive or in the European Commission guidance, which clearly addresses the role and responsibility of the sponsor's legal representative. This lack of information has raised concerns, particularly from entities appointed to play the role of legal representative. A clarification, either in the Directive or in the Commission guidelines, would, therefore, be welcome.

From a legal perspective, it may be considered that the role of the legal representative of a non-EU sponsor during a clinical trial is the sponsor's point of contact in the EU for the Competent Authorities and the Ethics Committee. In other words, where information or documents related to the clinical trial are requested, or where there are issues related to the conduct of the clinical trial, the legal representative is contacted on behalf of the sponsor.

However, there remains uncertainty as to the responsibility of this legal representative. As the existence of the legal representative is provided in the Article regarding the "civil and criminal liability of the sponsor", the question arises as to whether the legal representative is civilly and criminally liable.

The European Commission is aware of this issue but, so far, it has preferred to ignore it. In the questions and answers documents, it explains that "responsibility in terms of civil law (that is liability, for example compensation for damages occurred to a patient), or criminal law (that is punishment, for example criminal sanction of a bodily injury caused by negligence), is not governed by Directive 2001/20/EC. In this respect, the applicable laws of the Member States apply. […] While the existence of a legal representative within the EU/EEA might be supportive to ensure effective sanctioning under national civil or criminal law, the rules for civil and criminal liability remain governed by the national laws of the Member States."

In practice, this means that while the sponsor already has insurance to cover its civil and criminal liability, the legal representative may also be required to have its own 'supportive' insurance, increasing again the costs of the clinical trials.

THE NEED TO INCLUDE CLINICAL TRIAL-SPECIFIC DATA PROTECTION RULES IN THE CT DIRECTIVE

At one stage or another, conducting a clinical trial inevitably involves the processing of study subjects' personal data, including health-related information. These data are generally protected by the data protection rules of the Member State(s) where the trial is being conducted. In fact, the CT Directive currently states that a clinical trial may only be undertaken if the study subjects' rights to privacy and data protection of the data concerning them are safeguarded in accordance with the Data Protection Directive (Directive 95/46/EC) (9).

The main issue, however, is that the Data Protection Directive provides a general framework of principles for data protection and privacy only. It does not include specific provisions on the processing of personal data in the context of clinical trials. The Data Protection Directive does impose restrictions on the ability to process health-related data, but again these rules apply across the board and they are not specifically tailored for clinical trials. Moreover, the national data protection laws in some Member States (such as France and Spain) have put in place approval procedures for the processing of health-related data, which also apply to clinical trials. This means that, in practice, clinical trials can only be conducted in those countries if prior approval of the competent data protection authority has been obtained. In other Member States, a simple registration with the data protection authorities suffices – no prior approval is required.

Under EU data protection rules, approval and registration requirements are incumbent upon data controllers – the entities or persons who determine both the purposes and the means of personal data processing. Applying this principle to clinical trials can be problematic because of the divergent positions taken in different Member States on what constitutes personal data. If, for example, the sponsor of a clinical trial receives study data that have been encoded (typically by the investigator or institution), some national data protection authorities will no longer view these data as personal data. In that case, the sponsor would not be subject to approval and registration requirements under applicable data protection law. However, in other countries, data protection authorities will take the view that encoded study subject data still fall within the ambit of data protection law, even if it is not practically possible for the sponsor to identify the individuals in question. In spite of

recent attempts by the Article 29 Working Party – an independent European advisory body on data protection and privacy – to propose a harmonised, logical approach, country-specific differences still exist. As a result, sponsors that conduct clinical trials in several Member States must ensure that their data processing is compliant with the data protection requirements of each relevant country. This can be a time-consuming and expensive exercise.

EU data protection law can also cause unexpected obstacles when study data need to be transferred to a sponsor located outside the EEA. Transfer of personal data to countries outside the EEA is heavily restricted by national data protection rules. In principle, personal data can only be sent to a recipient outside the EEA on specific legal grounds (for example, unambiguous consent). In the context of a clinical trial, sending encoded study subject data outside the EEA may be restricted in those exporting countries where data protection authorities consider encoded data to constitute personal data. This can be particularly difficult when study results (including encoded study subject data) are sent to the US in the context of the EU/US Safe Harbor Scheme (10). According to the EU/US Safe Harbor's Frequently Asked Questions, a transfer from the EU to the US of encoded study subject data does not constitute a transfer of personal data (subject to the Safe Harbor Principles). However, not all Member State data protection authorities seem to agree with that interpretation.

The CT Community rules are intended to establish harmonisation of clinical trial requirements, including the regulatory framework for protection of clinical trial participants. This arguably extends to the protection of clinical trial participants' personal data. The existing data protection framework, however, is not always adapted to the practical requirements of clinical trials. It would therefore be beneficial to supplement the CT Directive with clinical trial-specific data protection provisions. Straightforward provisions that would clarify, for example, under what circumstances clinical trial participants' encoded data would be covered by general data protection principles. A uniform, less rigid approach across Europe would enhance legal certainty for companies and organisations involved in cross-border clinical studies. Moreover, it could make the EU more attractive as a forum for conducting clinical trials.

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References

1. **Directive 2001/20/EC of 4th April 2001 of the European Parliament and of the Council 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, *OJ* L121, 1st May 2001**
2. **Commission Directive 2005/28/EC of 8th April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products, *OJ* L91, p13, 9th April 2005**
3. **European Commission, Directorate General Enterprise and Industry, *Eudralex* Vol 10, clinical trials guidelines: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm**
4. **http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf**
5. **As an example, Article 3 (d) of the clinical trials Directive provides that a clinical trial may be undertaken only if, in particular the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial; if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation**
6. **Paragraph 29, www.wma.net/en/30publications/10policies/b3/index.html**
7. **Paragraph 4.8.15 http://www.ich.org/LOB/media/MEDIA482.pdf**
8. ***Eudralex* Vol 10, Chapter V: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_07_28-q%26a_v4.pdf**
9. **Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such datam, *OJ* L281, P0031-0050, 23rd November 1995**
10. **FAQ 14-7; Commission Decision 2000/520/EC of 26th July 2000, *OJ* L215/7, 25th August 2000**

About the authors

Elisabethann Wright is a Partner at Hogan & Hartson, Brussels. Elisabethann's experience in the area of European law has included both periods in private practice and working with international institutions. She focuses on EU law relating to life sciences, with particular emphasis on pharmaceutical law, medical devices, food law and the environment. Elisabethann has extensive experience in litigation before the European Court of Justice, the European Court of First Instance, and the European Free Trade Agreement (EFTA) Court. Prior to joining Hogan & Hartson, Elisabethann served as Senior Legal Officer and Hearing Officer at the EFTA Surveillance Authority.
Email: ewright@hhlaw.com

Wim Nauwelaerts is Counsel at Hogan & Hartson, Brussels. With almost 15 years of experience, Wim's practice focuses on data privacy and competition matters. Wim is a former Assistant Professor at Nyenrode University in the Netherlands, and a graduate of the European Commission's Executive Training Program in Tokyo, Japan. In the area of data privacy and security, Wim co-chairs Hogan & Hartson's Global Privacy Group. He advises on all aspects of data protection and privacy compliance. **Email:** wnauwelaerts@hhlaw.com