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European Union Negotiations Reach Agreement on New Clinical Trials Regulation

By Shine Chen and Mark Barnes

The European Union (EU) recently has seen a flurry of regulatory reform activity on clinical trials, research uses of clinical data and data protection. From the EU's proposed amendments on the General Data Protection Regulation to the European Medicines Agency's (EMA) draft policy on access to clinical trial data, the clinical trials landscape in the EU is rapidly evolving. Exactly how the moving pieces of the various legislative measures will interact with one another in practice remains to be seen.

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Most recently, the EU has cleared the way for adoption of a new EU clinical trials regulation.[1] On Dec. 20, 2013, the Committee of Permanent Representatives of the European Union endorsed proposed revisions to a draft regulation originally developed by the European Commission (the Proposal). The Proposal is a product of compromise from the negotiations between the European Parliament and the Presidency of the Council of the European Union.

The ''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''[2] would replace an existing Directive that grants individual EU Member States considerable flexibility in drafting and implementing clinical trials legislation specific to their country. The new regulation would be binding in its entirety and, if approved, automatically incorporated into the national laws for all EU Member States on the 20th day following its publication in the Official Journal of the European Union.[3] This increased authority and consistency would be channeled toward the stated goals of establishing a streamlined approval procedure, but without sacrificing patient safety, and increasing data transparency for clinical trials conducted across Europe.

[1] European Commission, *Proposal for a Clinical Trials Regulation — Questions and Answers* (July 17, 2012).

[2] *See* Council of the European Union, *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* (December 2013), *available at*: http://register.consilium.europa.eu/doc/srv?l=EN&t=PDF&gc=true&sc=false&f=ST%2017866%202013%20INIT [hereinafter Proposal].

[3] Proposal, Article 93.

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To become law across the EU, the Proposal still must receive the formal approval of the European Parliament and of the Council of Ministers. Neither entity is expected to request major revisions at this stage, following the extensive negotiations that have occurred, and the Proposal likely will enter into legal force across the EU later in 2014.

Unified and Streamlined Assessment Process

The Proposal charges the EMA with establishing, developing and hosting a single Web-based portal (the ''EU Portal'') for submission of all applications to conduct a clinical trial (each an ''Application'' submitted by a ''Sponsor''), regardless of the number of Member States in which the Sponsor intends to conduct the trial (each an ''Implicated Member State'').[4] This is a significant departure from the EU's current Directive 2001/20/EC, which requires that Applications be separately submitted to, and approved by, each Implicated Member State, while tailoring the content requirements of each Application to the national laws of each Implicated Member State.[5]

The Proposal also imposes a consistent set of content requirements for every Application, regardless of where in the EU the clinical trial will be conducted. Upon submission, the Sponsor must propose from among the Implicated Member States one ''Reporting Member State.'' The Reporting Member State is charged with directing and facilitating review of the Application through a new, harmonized process.[6] If the Sponsor's nominated Reporting Member State does not wish to be the Reporting Member State for whatever reason, that State has three days after the Application submission to notify the other Implicated Member States through the EU Portal. The Implicated Member States can discuss among themselves which State is willing to assume the position of Reporting Member State; however, if the Implicated Member States cannot agree, the Sponsor's originally proposed Reporting Member State designation stands. The Reporting Member State decision must be determined within six days following the Application submission.

The EU Portal and the streamlined process are meant to eliminate any duplicative efforts on the part of the Sponsor throughout the assessment and notification process. The EU Council hopes the simplification will stimulate the number of clinical trials held in the EU, as well as the number of clinical trial sites across as many Implicated Member States as possible.

Initial Validation

New fixed timelines for Application review also are incorporated into the Proposal. Within 10 days of the Application submission, the Reporting Member State must perfunctorily review the Application for completeness and compliance and (a) validate the Application, (b) provide the Sponsor with 10 days to furnish additional information (which the Reporting Member State will then evaluate within five days) or (c) decline to validate the Application.[7] Utilizing the EU Portal, the Reporting Member State will notify the Sponsor of the Application's validation. The Notice of Validation triggers commencement of a full, two-part concurrent review.

Part I: Harmonized Review

Following validation, the Reporting Member State will supervise the assessment of the Application. Part I of this assessment typically consist of three phases:

1. *Initial Assessment*: Within 26 days of validation, the Reporting Member State will author a Draft Assessment Report to be circulated among all Implicated Member States.

2. *Coordinated Review*: Within 12 days of the end of the Initial Assessment phase involving all Implicated Member States, all Implicated Member States will review the Application and Draft Assessment Report, and raise any concerns with respect to the Application.

3. *Consolidation*: Within seven days of completion of the Coordinated Review—that is, within 45 days of the Application's validation—the Reporting Member State will produce Part I of the Assessment Report, which it will distribute through the EU Portal to the Sponsor and Implicated Member States.[8]

Assessment during Part I focuses on the following aspects of the Application: patient safety, the expected therapeutic and public health benefits resulting from the clinical trial, compliance with EU manufacturing and importation of investigational medicinal products and compliance with labeling requirements as set out in the Proposal.[9]

Part I of the Assessment Report must record all concerns raised during Coordinated Review, indicate whether and how these concerns have been addressed and reach a conclusion on the merits of the Application. This conclusion will indicate that the Application is one of the following: (a) acceptable, (b) acceptable subject to explicitly listed conditions or (c) unacceptable.

During Coordinated Review or Consolidation, the Reporting Member State may request additional information from the Sponsor; in such cases, the review deadlines may be extended by up to 31 days as a result.[10] If the Sponsor does not respond to the request for additional information within the time frame set forth by the Reporting Member State, the Application will be considered as withdrawn in all Member States.[11]

Part II: Autonomous Review

In addition to its role in the Coordinated Review, each Implicated Member State also must complete simultaneously an assessment of the Application's compliance with that Member State's domestic law and regulation, including the following conditions:

- compliance with the scientific and ethical review of the Application by an independent ethics committee (IEC) that measures whether the Application complies with Implicated Member State's laws regarding ethical review;[12]

[4] Proposal, Article 77.

[5] *See* Council Directive No. 2001/20/EC of 4 April 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, O.J.L. 121/34 [hereinafter ''2001 Directive''].

[6] Proposal, Article 5, paragraph 1.

[7] *See id.*, paragraphs 2–4.

[8] Proposal, Article 6, paragraph 5.

[9] *See id.*, paragraph 1.

[10] *See id.*, paragraph 6.

[11] *Id.*

[12] Proposal, Recitals 14. This review requirement was removed from prior drafts, against significant opposition, but

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- compliance with the qualifications and competence of all investigators—including Article 46 of the Proposal: ''*Suitability of individuals involved in conducting the clinical trial*'';
- compliance with Article 47 of the Proposal: ''*Suitability of trial sites*'';
- compliance with compensation and other recruitment arrangements for investigators and participants;
- compliance with requirements for informed consent as set out in Chapter V of the Proposal: ''*Protection of subjects and informed consent*'';
- compliance with applicable rules for the collection, storage and future use of participants' biological samples; and
- compliance with Article 72 of the Proposal: ''*Damage compensation,*'' in regard to any injury suffered from participation in a clinical trial.[13]

For Part II of this Assessment Process, each Implicated Member State may—like the Reporting Member State in Part I—request additional information and thus, extend review deadlines by up to 31 days.[14] Following the completion of its analysis and review, the Implicated Member State then must conclude within Part II of the Assessment Report that the Application is (a) acceptable, (b) acceptable subject to explicitly listed conditions or (c) unacceptable.

Final Decision

If both Part I and Part II conclude that the Application is approved or approved with conditions, the clinical trial may be conducted in accordance with conditions, if any, in all Implicated Member States.[15] The Proposal is silent regarding the timeline for when the trial can commence once Application approval is granted. If Part I of the Assessment Report concludes that the Application is unacceptable, then the Application is refused on behalf of all Implicated Member States and the clinical trial will not be conducted in the EU. If, conversely, Part I of the Assessment Report concludes that the Application either is acceptable or acceptable with conditions, an Implicated Member State nonetheless may refuse to approve the Application with respect to its own jurisdiction if: (a) it disagrees with the conclusion of Part I for one or more enumerated reasons (such as patient safety)[16] or (b) it finds the Application unacceptable in Part II of the Assessment Report.[17] In such case, the clinical trial may be conducted only within the Implicated Member States that approved or approved with conditions; the clinical trial would not be permitted within the Implicated Member States that refused the Application. For the rejected Applications, Implicated Member States must provide an appeal procedure for the Sponsor.[18]

Regardless of the outcome, extensions granted to submit and process additional information may prolong the review process—from submission of an Application, through satisfaction of additional requests for validation to receipt of Parts I and II of the Final Assessment Report—to more than 100 days. This extended period represents a significant change from the European Commission's initially proposed 41-day review period, and the potential delays allowed in commencing trials have led some industry groups to voice displeasure with the Proposal. The Proposal was, however, a product of compromise, and it seeks to allow the time necessary properly to assess Applications, particularly for patient safety reasons.[19]

Informed Consent for Future Uses

The Proposal explicitly addresses future uses of clinical trial data, allowing Sponsors to ask participants for permission to use their data ''outside the protocol of the trial exclusively for scientific purposes.''[20] The Proposal states that such permission may be withdrawn at any time, but prior results obtained through permitted use of the data remain valid and useable by the Sponsor.

Interestingly, the Proposal also asserts that these provisions on informed consent for future uses are subject to the applicable data protection legislation.[21] The applicable data protection legislation, Directive 95/46/EC (''1995 Directive''), currently is undergoing reform and the new proposed General Data Protection Regulation (''2013 GDPR'') is one step away from approval by the European Parliament. The proposed changes to the 1995 Directive (12 MRLR 752, 11/20/13) would complicate and limit the secondary uses of data from clinical trials, particularly in terms of the more stringent and specific consent required for processing health data[22] and the ''right to erasure''[23] of any data pertaining to a subject who has chosen to withdraw from participation in a trial. These proposed changes may be inconsistent with what appears to be the spirit of the Proposal's provisions on informed consent for future uses. Research institutions and clinical trial sponsors will need to pay close attention to how the provisions of these two new Regulations can be read together in regard to informed consent for future research uses of data collected in clinical trials in the EU.

Informed Consent in Emergency Situations

The Proposal addresses emergency situations and their impact on informed consent, such as when a patient suffers a sudden life-threatening medical condition requiring immediate medical intervention.[24] This new provision makes EU law more consistent with long-standing U.S. Food and Drug Administration regulations on emergency research. The Proposal allows informed consent to be obtained after the intervention in certain emergency situations, if all of the following conditions are met:[25]

- The subject and the subject's legal representative are incapable or unavailable to receive all the clinical trial information within the therapeutic win-

was restored in the final Proposal. The ethical review must be done within the same specified timelines for Part I and Part II.

[13] Proposal, Article 7, paragraph 1.
[14] Proposal, Article 7, paragraph 3.
[15] Proposal, Article 8.
[16] *See id.*, paragraph 2.
[17] *See id.*, paragraph 3a.
[18] *See id.*, paragraph 3c.
[19] Proposal, Recitals 8.
[20] Proposal, Article 28, paragraph 2a.
[21] *Id.*
[22] 2013 General Data Protection Regulations, Article 4.
[23] 2013 General Data Protection Regulations, Article 17.
[24] Proposal, Article 32.
[25] *See id.*, paragraph 1.

dow or to provide informed consent prior to the intervention because of a sudden life-threatening or other serious medical condition.

- The clinical trial poses a minimum risk to, and imposes a minimal burden on, the subject, as compared to the standard treatment of the subject's condition.
- The clinical trial is directly related to the cause of the life-threatening or serious medical condition, such that the intervention should have a direct clinically relevant benefit for the subject.
- The investigator certifies that he or she is unaware of the subject expressing any prior objections to participating in the clinical trial.

Following the emergency intervention, and as soon as possible thereafter, the subject's informed consent (or that of the subject's legal representative) to continue participation in the clinical trial must be obtained.[26] Additionally, if the subject or the legal representative does not provide consent, he or she must be informed of the right to object to the use of data already obtained during the trial intervention.

Simplified Informed Consent Requirements for Randomized Cluster Trials

The Proposal permits simplified informed consent requirements for randomized cluster trials conducted exclusively in one Member State.[27] The simplified informed consent process allows informed consent to be obtained without the subject's having a face-to-face discussion with a member of the research team. The simplified informed consent process may be utilized for cluster clinical trials, as long as all of the following conditions are met:[28]

- The simplified informed consent does not violate any national law in the Implicated Member State.
- The clinical trial is a low-intervention clinical trial, and if it involves a medicinal product, such product is used in accordance with the terms of the marketing authorization.
- There are no interventions other than the standard treatment of the concerned subjects.

The protocol must describe the scope of information provided to the subjects, identify the method of providing such information and justify the reasons for utilizing the simplified informed consent process.

Increased Clinical Data Transparency

The Proposal also contains provisions designed to increase the transparency and accessibility of clinical trial data from trials conducted within the Member States of the EU. First, the Proposal addresses the content submission requirements for new Applications. Specifically, all clinical trial data supporting the Application to commence a new clinical trial must originate from clinical trials that have been registered and recorded on a publicly and freely accessible database.[29] Registration and recordation includes the clinical trial protocol, the summary of the clinical trial, and the clinical study report, if applicable. An exception is made for supporting clinical trial data generated before the effective date of the Proposal (when implemented); those data, in order to be used to support an Application for a new clinical trial, must have been included in the World Health Organization's registry or a partner clinical trials registry; or the data must have been published in an independent, peer-reviewed scientific publication.[30] Any clinical data that do not comply with these registration or publication requirements will not be considered during evaluation of an Application to conduct a new clinical trial in the EU.

The Proposal also contains provisions related to the transparency of data generated from *approved* clinical trial Applications within the EU. The EMA must establish and maintain a publicly accessible and searchable database of all approved clinical trial data relating to medicinal products. This database must include:

- Detailed summaries of clinical trial data from approved Applications, including a summary drafted by the Sponsor in plain language and submitted (except where an exception is granted) within one year of the termination of the clinical trial (*e.g.*, last visit by the last subject or as otherwise defined in the protocol).[31]
- For medicinal products for which marketing authorization in the EU has been sought, full clinical study reports that have been submitted to support a marketing authorization, which should be posted within 30 days of the marketing application's authorization, rejection or withdrawal.[32]

Conclusion

Whether the Proposal with its streamlined application and assessment process will serve, as intended, to increase the number of clinical trials sited in the EU remains to be seen. This Proposal, along with the EMA's draft policy and the EU's 2013 GDPR, represents reform activity within the EU that requires close monitoring. It is unclear if all the proposed changes, as they near finalization, actually will coalesce together in practice to provide a smoother clinical trials process. The EU's clinical trial landscape is still shifting and it warrants particular attention in the next few months, as the European Parliament resumes its 2014 plenary sessions.

[26] Proposal, Article 32, paragraph 2.
[27] Proposal, Article 29a, paragraph 1.
[28] *See id.*, paragraph 3.
[29] Proposal, Recitals 20.
[30] Proposal, Article 25, paragraph 6.
[31] Proposal, Recitals 25b.
[32] Proposal, Recitals 52.

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