European Union Negotiations Reach Agreement on New Clinical Trials Regulation

The European Union ("EU") has cleared the way for adoption of a new clinical trials regulation within the EU. On December 20, 2013, the Committee of Permanent Representatives of the European Union endorsed proposed revisions to a draft regulation originally developed by the European Commission and then negotiated between the European Parliament and the Presidency of the Council of the European Union (the "Proposal"). To become law across the EU, the proposed regulation 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 proposed regulation will likely become effective across the EU later in 2014.

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" would replace an existing Directive that grants individual EU Member States considerable flexibility to craft implementing legislation specific to their country, with a regulation that is binding in its entirety and automatically incorporated into the national laws for all EU Member States. This increased authority and consistency will be channeled towards two goals: establishing a streamlined approval procedure and increasing data transparency for clinical trials conducted across Europe.

Integrated and Streamlined Review

Unified Application Process

The EU's current Directive 2001/20/EC requires that all applications to conduct a clinical trial (each an "Application" submitted by a "Sponsor") be separately submitted to, and approved by, each Member State in which the Sponsor intends to conduct the trial (each an "Implicated Member State"). By contrast, the Proposal charges the European Medicines Agency ("EMA") with establishing, developing and hosting a single web-based portal (the "EU Portal") for submission of all Applications, regardless of the number of Implicated Member States.

The Proposal imposes a consistent set of content requirements for every Application, irrespective 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" charged with directing and facilitating review of the Application through a new, harmonized process. If the Sponsor's nominated Reporting Member State does not wish to be the Reporting Member State, it 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 made within six days following the Application submission.

Initial Validation

The Proposal also includes new fixed timelines for review of the Application. The Reporting Member State must, within ten days, cursorily review the Application for completeness and compliance and (a) validate the Application, (b) provide the Sponsor with ten days to furnish additional information (which the Reporting Member State will then evaluate within five days), or (c) decline to validate the Application. Notice of validation is provided through the EU Portal to the Sponsor, and triggers commencement of a full, two-part concurrent review.

Part I: Harmonized Review

Once validated, the Reporting Member State will supervise the assessment of the Application. Part I of this assessment typically consists 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 (particularly respecting therapeutic benefits, risks to participants and labeling requirements).
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.

Part I of the Assessment Report, once complete, must record all concerns raised during the Coordinated Review, indicate whether and how these concerns have been addressed, and reach a conclusion on the merits of the Application. This conclusion may indicate that the Application is (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 and, in such cases, the review deadlines may be extended by up to 31 days as a result.

Part II: Autonomous Review

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

- 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 (this review requirement was removed from prior drafts but restored in the final Proposal);
- The collection, storage and future use of participants' biological samples;
- Informed consent arrangements for clinical trial participants;
- Compensation and other recruitment arrangements for investigators and participants;
- The collection and transmission of participants' data;
- The qualifications and competence of all investigators;
- The suitability of proposed clinical trial sites; and
- Arrangements for compensation to participants who suffer injury as a result of their participation in a clinical trial.

In performing this analysis, 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. On completion of its analysis, the Implicated Member State must then conclude—again, as with Part I—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. The Proposal does not

address the timeline for when the trial can commence once approval is granted. If Part I of the Assessment Report concludes that the Application is unacceptable, the Application is refused on behalf of all Implicated Member States. If, conversely, Part I of the Assessment Report concludes that the Application is either acceptable or acceptable with conditions, an Implicated Member State may nonetheless 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); or (b) it finds the Application unacceptable in Part II of the Assessment Report. In such case, the clinical trial may only be conducted 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.

Irrespective 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 concession from the European Commission's initially proposed 41-day review period, and has led some industry groups to voice displeasure with the Proposal due to the potential delays allowed in commencing trials.

Increased 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. These measures first apply to the content submission requirements for new Applications. Specifically, all 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. 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. 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); and
- 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.

Informed Consent

Informed Consent for Future Uses

Although U.S. Food and Drug Administration ("FDA") regulations and guidance are largely silent on this point, 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." Such permission

may be withdrawn at any time, but prior results obtained through permitted use of the data remain valid and useable.

However, the Proposal also states that these provisions on informed consent for future uses are subject to the applicable data protection legislation. The applicable data protection legislation, Directive 95/46/EC ("1995 Directive"), is currently 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 would complicate and limit the secondary uses of data from clinical trials, particularly in terms of the specific consent required for processing health data and the "right to erasure" of any data involving a withdrawn subject. 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.

Simplified Informed Consent Requirements

The Proposal allows simplified informed consent requirements for randomized cluster trials conducted exclusively in one Member State. The reduced informed consent process allows informed consent to be gained without a face-to-face discussion with a member of the research team. The simplified informed consent process may be used for cluster clinical trials, as long as all of the following are met:

- 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; and
- The protocol describes the scope of information provided to the subjects, the method of providing such information and justifies the reasons for utilizing the simplified informed consent process.

Informed Consent in Emergency Situations

The Proposal addresses informed consent in emergency situations, such as when a patient suffers a sudden life-threatening medical condition requiring immediate medical intervention, thus bringing EU law largely into line with long-standing FDA regulations on emergency research. The Proposal allows informed consent to be obtained after the intervention in certain emergency situations, if all of the following are met:

- The subject and the subject's legal representative are incapable or unavailable to receive all the clinical trial information within the therapeutic window or to provide informed consent prior to the intervention because of a sudden life-threatening or other serious medical 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; and
- 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.

Following the emergency intervention, informed consent to continue participation in the clinical trial must be obtained from the subject or the subject's legal representative as soon as possible thereafter. 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 from the trial.

If you would like to discuss the foregoing or any other related matter, please contact Mark Barnes, Eve Brunts, Al Cacozza or your usual Ropes & Gray advisor.