

E-ALERT | Food & Drug

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NEW RULES FOR CLINICAL TRIALS PROPOSED IN EUROPE

On 17 July, the European Commission released the long-awaited proposal for a Regulation on clinical trials on medicinal products for human use (the Proposal). The future regulation will replace the Clinical Trials Directive 2001/20/EC, the revision of which has been advocated by the pharmaceutical industry, academia, and patients for years. Directive 2001/20/EC aims at harmonising the requirements throughout the EU but has not prevented divergent national requirements that, especially for multinational clinical trials, substantially hinder a swift handling of clinical trial applications and generate a very burdensome and costly administration. The Proposal primarily seeks to cut the red tape and to facilitate the conduct of multinational trials and restore competitiveness in clinical research in Europe.

The future Regulation will be more complete and detailed than Directive 2001/20/EC (more than 90 articles and five annexes) and will revise current rules, in particular as regards the authorisation procedures, and introduce new principles, such as co-sponsoring. Overall, the new regime should reduce administrative costs for industry and better reflect the variety of clinical trials. The Commission chose a Regulation as legislative instrument to ensure that identical rules will apply throughout European Union. This will increase harmonisation of the rules, but certain issues, such as ethics and sponsor liability, will remain governed by national law.

The submission of the Proposal to the European Parliament and Council is the first step of the legislative process. The Proposal will probably be heavily debated and substantially amended, in particular by the Council as the Member States are keen on preserving their powers over clinical trials conducted in their territories. It is difficult to determine how long the legislative process will last. The Commission expects the new rules to come into effect in 2016 after a transitional period of two years.

Scope

The future regulation has the same scope as Directive 2001/20/EC, i.e., interventional clinical trials and investigational medicinal products (IMPs). The Proposal, however, amends the existing definitions (clinical trial, non-interventional clinical trial) and introduces new definitions, such as “clinical study”, “low-intervention clinical trial”, or “auxiliary medicinal product” (to replace the concept of “non-investigational medicinal product”).

The concept of “normal clinical practice” at the Member State level is key for distinguishing between a clinical study and a clinical trial and between a standard clinical trial and a low-intervention clinical trial. Although legally defined, the term refers to the clinical practice as it exists in each Member State and could lead to national divergences on the qualification of a study.

Risk Categorization

The proposed new rules show a risk-based approach to clinical trials and distinguish between low-intervention clinical trials and other clinical trials. A “low-intervention clinical trial” is a clinical trial where the IMPs are authorised and used in-label (or their use is a standard treatment in any of the Member States concerned) and any additional diagnostic or monitoring procedures pose minimal additional risk or burden for the subjects compared to normal clinical practice in “any” Member State concerned. The reference to “any of the Member States concerned” suggests that a trial which qualifies as a low-interventional clinical trial in one Member State should also qualify

as such in other Member States, but that does not seem to be the intention (as illustrated by the German version of the Proposal).

Because of their very low risk profile, low-intervention clinical trials benefit from less burdensome requirements (safety reporting, labelling, and insurance) and shorter authorisation timelines.

Streamlined Authorisation Procedures

Currently, a clinical trial is approved by a competent national authority and an ethics committee in each Member State where the sponsor wants to conduct the trial, and the authorisation procedure is conducted in parallel in all the Member States. These parallel national procedures are replaced by a form of decentralised procedure, which also applies to purely national trials.

Authorisation

The key features of the new authorisation procedure for clinical trials are the following:

- Submission of a single and harmonised application dossier through an EU portal linked to an EU database. The content and format of the dossier are defined in an annex to the Proposal (which can be amended by delegated acts).
- Choice of a Reporting Member State (RMS) by the sponsor. The RMS is the interface between the sponsor and the other Member States for the assessment of Part I aspects of the trial.
- Validation of the application by the RMS.
- Two-part assessment of the application:
 - Each part covers specific aspects that are exhaustively listed in the Proposal.
 - Part I covers general aspects, such as the anticipated therapeutic and public health benefits, the risks and inconveniences for the trial subjects, or the investigator brochure. It is to be assessed by the RMS in coordination with the other involved Member States.
 - Part II covers ethical, local, and national aspects, such as the informed consent or the arrangements for compensating investigators or recruiting trial subjects. It is to be assessed separately by each Member State.
 - Parallel assessment of Part I and Part II.
- Single decision by each Member State, which covers Part I and Part II and must be notified to the sponsor within 10 days of the assessment.
- Tacit approval system based on the positive assessment of Part I by the RMS:
- The RMS assessment of Part I is binding on the other Member States unless they refuse the assessment (“opt-out”). The refusal can only be based on two, mainly ethical, grounds.
- In the absence of a notification of the decision within the deadline, the conclusion of the RMS assessment of Part I qualifies as the authorisation decision of the Member State on the application (also for Part II).
- The impact of a negative RMS assessment of Part I is unclear.
- Timelines are set out for each phase of the procedure. They vary depending on the nature of the clinical trial (shorter for low-intervention trials) or the medicinal product (longer for advanced therapy medicinal products). Except for low-intervention clinical trials, they are longer than under Directive 2001/20, but the tacit approval system provides for better compliance.
- The Commission manages the EU portal, and supports the cooperation of the Member States with the assistance of a Clinical Trials Coordination and Advisory Group (group of the national contact points). There is no role for the EMA.

Addition of a new Member States

The procedure for extending the trial to a new Member State is similar to the authorisation procedure, but with shorter timelines. The RMS is the same as for the authorisation procedure, but its role is limited as there is no additional assessment of Part I aspects.

Substantial Amendments

After having been authorised, a clinical trial may be modified. The modification is subject to authorisation where it has a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated. Non-substantial amendments should simply be entered into the EU database. The Proposal does not define or further describe what constitutes a substantial amendment, and the current Commission guideline may remain applicable. The deadlines for authorisation are shorter than for the authorisation procedure. The RMS is the same as for the main authorisation procedure.

Streamlined Safety Reporting

The rules on safety reporting are streamlined and simplified. So, reporting of certain adverse events by the investigator to the sponsor can be excluded in the protocol, and suspected unexpected serious adverse reactions (SUSARs) can be reported by the sponsor directly to EudraVigilance (EU pharmacovigilance database). More detailed rules on safety reporting, which partly codify the current Commission guidance, are contained in an annex to the Proposal.

Conduct of Clinical Trials Outside of the EU

An increasing number of clinical trials are conducted outside the EU and the results are also used to support marketing authorisation applications in the EU. Building on an EMA reflection paper, the Proposal implicitly requires that clinical trials conducted outside the EU comply with regulatory requirements at least equivalent to those in the EU. This obligation however is already included in Annex I to Directive 2001/83/EC. Also, it is unclear how the equivalence between foreign and EU clinical trial regimes will be assessed and, more importantly, how third countries will be convinced to adopt rules that are similar to the EU rules.

Indemnity and Insurance

Directive 2001/20 introduced an obligation for the sponsors to compensate trial subjects for damages resulting from clinical trials (in accordance with national law) by way of an indemnity or insurance. Under the Proposal, low-intervention clinical trials are exempted from the mandatory indemnity or insurance requirement. For the other (interventional) clinical trials, the sponsor must ensure compensation through an insurance or an indemnification mechanism, and the Proposal requires the Member States to set up a national indemnification mechanism that works on a not-for-profit basis (and may require payment of a fee by commercial sponsors).

Transparency

Under Directive 2001/20, clinical trials are registered in a central database (EudraCT). That database is not publicly available except for paediatric trials, but protocol-related information and trial results are indirectly made public through another database (EudraPharm). The Proposal makes EudraCT fully accessible to the public, subject to personal data, commercially confidential information, and the need for effective supervision of the conduct of the clinical trial by a Member State. This increased clinical trial transparency is in line with the general European trend in the pharmaceutical sector, but adequate attention is needed to protect business secrets.

Role for the Commission

The Proposal entrusts the Commission with a stronger role in relation to clinical trials, in particular as regards the authorisation procedures and inspections. The Commission may perform controls and, if need be, inspections in Member States and in third countries to verify compliance with the clinical trial rules or equivalent rules. It is the intention that the Commission will use its own staff for this, which will require training of a dedicated team. This illustrates a new trend that the Commission starts playing a more active role in regulatory matters.

Other Aspects

The Proposal covers other aspects of clinical trials, such as:

- Co-sponsoring: The Proposal expressly allows co-sponsorship. Each co-sponsor is responsible for the entire clinical trial unless the co-sponsors agree by contract to “split” the responsibilities amongst themselves.
- “Contact person” instead of “legal representative” for sponsors located outside of the EU.
- Obligation for sponsors to report “serious” breaches to the clinical trial rules or the protocol to the Member States within seven days of knowledge (through the EU portal).
- Specific conditions for clinical trials in emergency situations.
- Revised rules on manufacturing and importation of IMPs.
- Revised rules on labelling of IMPs (detailed in an annex).

What is missing?

The proposed rules do not address specific topics, in particular the following:

- *No centralised authorisation procedure* by the European Medicines Agency or another EU authority. The industry is favourable to such centralised procedure, but the Commission anticipated a strong opposition by the Member States and opted for a coordinated procedure instead.
- *No mention of ethics committees*: The Proposal makes no division of roles between ethics committees and national competent authorities, and does not even mention ethics committees. Ethical aspects are included in Part II and thus are assessed separately by each Member States act individually.
- *No specific rules for non-commercial trials* except for the free participation in national indemnification schemes.
- *No interface with scientific advice*: Certain parties advocated a system closer than the U.S. system where the same team is entrusted with a medicinal product, from the design of the clinical trials to the approval of the product. The Proposal does not establish a connection between scientific advice and clinical trial authorisation because the regulator’s involvement in scientific advice is conceptually very different from the authorisation of a clinical trial and clinical trial rules in the EU addresses clinical trials in the abstract (i.e., independently from whether the results are intended to be used in a future marketing authorisation application, or for any other purpose).

Next steps

The Proposal will now be reviewed by the European Parliament and the Council. Both institutions will undoubtedly propose amendments to the text, and this process provides an opportunity for interested parties to suggest specific provisions.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our firm:

Genevieve Michaux

+32.2.549.5247

gmichaux@cov.com

Peter Bogaert

+32.2.549.5243

pbogaert@cov.com

Grant Castle

+44.(0)20.7067.2006

gcastle@cov.com

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