FEBRUARY 8, 2022

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Europe - Between The EU Clinical Trials Regulation And The UK Guideline On Clinical Trials

Last week the Regulation on Clinical Trials ("CTR") finally became effective in the European Union ("EU") and replaced the prior Clinical Trials Directive 2001/20 ("CTD"). The CTR was adopted in 2014 and was meant to enter into force a few years after; however, setting-up the EU portal, which is the spine of the new system, took significantly longer than initially expected.

The CTR primarily seeks (1) to better harmonize clinical trials rules across the EU and (2) to simplify the authorization procedure by replacing the parallel national procedures with a single "coordinated" procedure. The CTR introduces other changes into the conduct of clinical trials in the EU.

As a result of Brexit, the CTR does not apply in the United Kingdom ("UK"), but new, more dynamic rules on clinical trials are needed there as well. Two weeks prior to the CTR coming into effect, the UK launched a public consultation on proposals for legislative changes for clinical trials. The UK Government presented a series of proposals, most of which are more modern and flexible than the new EU rules. More importantly, they specifically take into account global clinical trials and innovation. The UK consultation closes mid-March 2022.

This alert focuses on a few new concepts and rules introduced by the CTR in the EU and compares them to those proposed in the UK.

IMPLEMENTATION OF THE CTR

Since 2014, the European Commission ("Commission") has had time to implement the CTR. It adopted a few related Regulations, in particular Delegated Regulation 2017/1569 on good manufacturing practices for investigational medicinal products ("IMP"), as well as many guidelines and forms that implement the CTR. The most recent form adopted by the Commission concerns compliance with national rules on the collection, storage, and future use of human biological samples. On February 1, the Commission also updated its Q&A on clinical trials.

Likewise, the European Medicines Agency ("EMA") adopted guidelines (on serious breach, archiving, etc.) and organized workshops for the various stakeholders. Under the prior CTD, the EMA's role regarding clinical trials was very limited. Under the CTR, the EMA manages the portal which, together with the database, forms the so-called "clinical trials information system" ("CTIS").

Like any regulation, the CTR must be implemented by the EU-wide Commission, but this does not leave the EU Member States without continuing powers in the area of clinical trials. The CTR expressly authorizes Member States to regulate several aspects of clinical trials at the national level. Moreover, ethics remain a national responsibility, at least for the time being.

TRANSITIONAL RULES

The CTR sets forth a fairly simple transitional regime:

- 2023: All new clinical trials are subject to the CTR. Until then, sponsors may still choose to rely on the CTD.
- 2025: All clinical trials started under the CTD, whether before or after 31 January 2022, must be transitioned to the CTR unless they have been completed.

Once a trial is transitioned to the CTR, the CTR rules apply (reporting, transparency, archiving, etc.).

NEW COORDINATED AUTHORIZATION PROCEDURE

The new procedure is quite complex but, overall, it should facilitate the authorization of clinical trials.

In a nutshell, for clinical trial to be conducted in one or more EU countries, the sponsor must submit a single authorization application through the new EU portal. The countries relevant to the application ("Member States Concerned") are chosen by the sponsor, as is the so-called "Reporting Member State," the country that will lead the assessment of Part I of the authorization dossier.

The authorization dossier has two parts. Part I, which is applicable to all the Member States involved in the procedure, generally concerns the scientific and methodological aspects while Part II, which is specific to each Member State, covers the ethical aspect of the trial. The CTR delineates the aspects of the trial that are covered by Part I and Part II, respectively. Annex I to the CTR enumerates specific information and documents to be provided for each Part.

The Reporting Member State assesses Part I of the application (initial assessment phase) and shares its draft assessment with the Member States Concerned so that they can make comments (coordinated review phase). The Reporting Member State then finalizes its assessment report (consolidation phase), taking the Member States Concerned comments into account. The consolidated assessment report is binding on all Member States Concerned, but a Member State Concerned may object to the conclusion of the report. The grounds for objection are limited to three: (1) participation in the trial would lead to receiving inferior treatment to normal clinical practice; (2) infringement of national rules on cells or narcotics; and (3) considerations regarding safety or data reliability and robustness raised during the assessment phase. On the other hand, if the Part I report is negative, it is negative for all Member States Concerned, without further discussion, and the trial may not be conducted.

Part II is assessed by one ethics committee in each Member State, in parallel to the Part I assessment. If the ethics committee issues a negative assessment report, the trial may not be conducted in the country at issue.

The procedure ends with a unique decision on Parts I and II in each Member State. The decision can be (1) acceptance, (2) acceptance subject to conditions, or (3) refusal. It will only be positive (i.e., acceptance or acceptance with conditions) if the two assessment reports are positive. Upon receiving the decision, the sponsor may start the trial in that Member State.

In short, there is a unique "coordinated" assessment report for Part I and several national assessment reports for Part II. The Part I assessment is driven by the Reporting Member State, while Part II is driven by each Member State.

New Member States may be added to the trial after the initial authorization decisions have been taken. The Reporting Member State will remain the same.

UK Proposal: The procedure would be very similar to that set out by the CTR, i.e., sponsors would submit a combined MHRA / ethics application through a single UK "front door" (the "Integrated Research Application System" or "IRAS"). Separate applications would remain possible but would be the exception. Of course, a procedure involving one country is much simpler than a procedure involving several countries.

Timeline. — The CTR sets strict deadlines for both Parts I and II of the procedure. After validation of the application (10 to 25 days), the assessment of Part I should last 45 days (plus 50 days for ATMPs). The assessment for Part II, which runs in parallel, should also last 45 days. Then, each Member State Concerned has five days to give its decision whether the trial may proceed. Overall, the shortest timeframe is 60 days, provided that there is no discussion from the Reporting Member States and that no additional information is requested from the sponsor.

Importantly, if a Member State does not provide its decision within the five-day timeframe, the decision is deemed to be the conclusion of the Part I assessment report. This tacit approval mechanism is meant to force national authorities to abide by the deadlines.

Deadlines are also imposed on the sponsor, and they are "sanctioned" if they do not comply. For example, if the sponsor does not provide the additional information required for the assessment within the period set by the Reporting Member State, the application is deemed to have lapsed in all Member States. This is a new challenge for sponsors because the deadlines for responding to the national authorities' queries are quite short: 31 days for Part I and 12 days for Part II.

UK Proposal: The maximum timeframe for the review and decision on clinical trial applications would be 30 days from acknowledgement of a valid application to approval or request for further information. Upon receipt of any requested information, a final decision would be made within a maximum of 10 days. Thus, as a rule, the timeline could be 30 to 41 days or more, depending on the time needed by the sponsor to respond to a request for information.

Other timelines may apply in specific cases:

- The current expedited timeframe for Phase 1 trials would continue.
- To facilitate multi-country trials, sponsors would have 60 days (but with flexible extension) to respond to any requests for information that would facilitate the harmonization of international protocols and better align requests for changes from multiple regulators.
- An additional 60 days would be added to the initial assessment timeframe where independent advice from the Commission on Human Medicines and/or its Expert Advisory Group(s) is required. This would apply, for example, for certain ATMPs.

Modification of the Trial. — The CTR also contains detailed rules on modifications of trials. The procedure for substantial modification is much more complex than the authorization procedure (due, in part, to the dual Part I – Part II structure), but the timeline is shorter (49 days).

Patient Recruitment. — If no participant is recruited within two years of an authorization, the authorization expires in that EU country unless an extension is requested by the sponsor.

UK Proposal: A sunset provision very similar to the EU rule would be introduced.

Withdrawal. — The CTR allows sponsors to withdraw an application at any time until the reporting date, but the application may only be withdrawn with respect to all Member States Concerned. The reasons for the withdrawal must be communicated through the EU portal. Sponsors may then resubmit a new application.

UK Proposal: The provisions on withdrawal would be very similar to the EU provisions.

NEW CONCEPTS

The CTR introduces new concepts into EU law, although some were already in practice in Member States.

Low intervention clinical trial. — The concept of a low intervention clinical trial existed in a few EU countries before the adoption of the CTR. It is now an EU concept. The CTR defines a low intervention clinical trial as a clinical trial that fulfills the following conditions:

- the IMPs, excluding placebos, are authorized for marketing;
- according to the protocol, (1) the IMPs will be used in accordance with the marketing authorization or (2) the use of the IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the Member States Concerned; and
- the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State Concerned.

Low intervention trials carry fewer risks to trial participants and thus are subject to much less stringent obligations, particularly in regard to the mandatory insurance coverage. Moreover, the specific nature of low intervention trials should be taken into account, for example, for purposes of monitoring or the content of the Trial Master File.

UK Proposal: Low intervention trials would be subject to notification rather than to an authorization regime. An ethical review would still be required, but the timeline would be much shorter overall.

Low intervention trials would be “trials where the risk is similar to that of standard medical care, e.g., they involve marketed product(s) either used in accordance with the marketing authorization or supported by (nationally accepted) published evidence and/or guidance and/or established medical practice.”

The criteria for a trial being eligible for notification would be the following:

- the trial meets the definition of low intervention trial;
- the IMP is authorized in UK;
- if the trial design includes prospective adaptations, all future adaptations need to be consistent with the definition of a low intervention trial;

- any placebo used in the trial is either a marketed product or has been manufactured under an IMP manufacturing license with a formulation that matches the marketed product except for the removal of the active substance. The use of placebo must not expose trials participants to a risk that diminishes their standard of care; and
- the primary purpose of the trial is not authorization.

The UK Proposal gives several examples of low-intervention trials. They include a new subtype or subpopulation or a new schedule of an authorized indication, but also off-label use and even a new indication (both subject to specific conditions).

With regard to the procedure, upon submission of the application, the sponsor would declare that the trial is low-intervention and complies with the criteria for the notification scheme. Once the ethics committee has issued a positive opinion, the combined decision would be an approval to proceed. Substantial amendments would not have to be submitted to the MHRA, provided that the modification does not change the status as a low-intervention trial or the eligibility for the notification scheme (submission to the ethics committee would still be required).

Serious breach. — A "serious breach" is a breach likely to significantly affect the safety and rights of a subject or the reliability and robustness of the data generated in a clinical trial. Article 52 of the CTR requires sponsors to notify the Member States concerned about a serious breach of the CTR or the protocol within seven days of becoming aware of that breach. This new obligation has been further explained and detailed in the EMA Guideline for the Notification of Serious Breaches of Regulation (EU) No 536/2014 or the Clinical Trial Protocol.

UK proposal: Regulators could refuse to approve a new study based on ongoing serious non-compliance with the applicable rules.

Co-sponsoring. — Before the CTR, most EU countries prohibited co-sponsoring of a clinical trial. A trial now may be conducted by more than one sponsor, provided that the sponsors enter into an agreement that defines the responsibilities of each sponsor. This new concept has been introduced to facilitate clinical trials by academia.

UK Proposal: The concept of co-sponsoring would also be introduced in UK law.

Emergency clinical trial. — When certain conditions are met, particularly in emergency situations (i.e., emergencies due to the nature of a disease and the participant's inability to receive the clinical trial information and provide consent), the information may be provided and/or the consent may be given after inclusion in the trial.

UK Proposal - Data Collection Before and After the Trial. — The UK proposes allowing certain data collection without a prior authorization for clinical trial. Sponsors would be allowed to collect the following data:

- Data after the MHRA has approved early access to a non-authorized medicinal product. An ethical review may still be required. The lack of regulatory approval would facilitate collecting "real world" data.
- "Non-interventional" long term follow-up information after the end of the trial.

UK Proposal – Patient Involvement. — The CTR does not expressly mandate sponsors to involve patients in clinical trials. On the other hand, the UK Proposal would include a requirement to work in partnership with individuals and communities (including patients and caregivers) in the design, management, conduct, and dissemination of a trial, or explain to the ethics committee why this is not appropriate.

MORE REPORTING FOR INCREASED TRANSPARENCY

Reporting. — The CTR imposes much more reporting than the CTD, thereby maintaining some administrative burden that the CTR was expected to remove. In addition to safety reporting, sponsors must notify each Member State through the EU portal (generally within 15 days) about the start of the trial, the end of recruitment, the end of the trial in all countries worldwide, and other information. Moreover, sponsors must submit a summary and lay summary of the results, an annual report on safety for each IMP, and, if the data are used for regulatory purposes, the clinical summary report (within 30 days of the granting of marketing authorization).

Public Disclosure. — The CTD expressly provided for the confidential nature of trial-related information and documents submitted by sponsors through EudraCT, the former database of clinical trials. This requirement was partly '"circumvented" by the disclosure of some protocol-related and result-related information in the EU Clinical Trials Register. The CTR goes further and facilitates increased transparency through the EU portal. All clinical trial-related documents and information going through the EU portal are meant to become public on the EU database, beginning from the decision on the trial.

Exceptions, however, will apply, such as for personal data or commercially confidential information. This last concept, which has been the subject of intense debate in recent years, will have the same meaning as it has under the EMA's current policies on access to public documents and to clinical trial data (so-called "Policy 0070"). In 2015, the EMA adopted an Appendix on disclosure rules and functional specifications of the EU portal and EU database that sets out rules and criteria for application of the exceptions. In essence, the Appendix provides for deferrals of publication (rather than exemptions), depending on the category of clinical trials.

UK Proposal: The UK focuses on three aspects.

- Trials would have to be registered in a World Health Organization- ("WHO") compliant public register before starting. The CTR does not include this requirement, but it specifies that clinical trial data may only be submitted in support of a clinical trial application if that clinical trial has been recorded in a publicly accessible, free of charge database which is a primary or partner registry of, or a data provider to, the international clinical trials registry platform of the WHO (WHO ICTRP).
- Sponsors would have to publish a summary of results within 12 months of the end of the trial unless a deferral is agreed to by the ethics committee.
- Sponsors would have to share clinical trial findings with participants in a suitable format within 12 months of the end of the trial or explain why this is not appropriate.

DATA PRIVACY

The CTR does not deal with data privacy but rather generally refers to the General Data Protection Regulation ("GDPR") and expressly allows sponsors to ask participants' consent to use their personal data outside the protocol of the clinical trial exclusively for scientific purposes (secondary use).

The CTR and GDPR requirements apply in parallel and yet may sometimes be difficult to reconcile. The best example is probably the participant's consent as legal basis for processing personal data. GDPR compliance, however, is very important, since it is part of GCP inspections. In January 2019, the European Data Privacy Board adopted an opinion on the interplay between the CTR and the GDPR. This document does not cover all the issues, and sponsors often face unexpected situations that trigger data privacy questions.

One key aspect to pay attention to is the qualification of the investigator/investigating site(s) under national law since it determines the investigator/site's obligations regarding data privacy and thus the content of the clinical trial agreement between the investigator/site and the sponsor.

NON-EU SPONSOR OR INVESTIGATING SITE

The CTR impacts sponsors and investigating sites located outside of the EU.

Legal Representative of the Sponsor. — As under the CT Directive, a sponsor that is not established in the EU must appoint a legal representative in the EU. Unlike the CT Directive, the CTR specifies that the legal representative is responsible for ensuring compliance with the sponsor's regulatory obligations. However, it leaves to the Member States the choice to replace, for their respective territory, the legal representative with a mere contact person.

Use of Non-EU Clinical Trial Data. — The clinical data from non-EU sites may only be submitted in the application dossier if the trial has been conducted in accordance with principles equivalent to those in the CTR. The Commission may apply controls to verify whether a foreign regulatory system on clinical trials meets that standard.

Data privacy. — The processing of personal data undertaken by a sponsor triggers the application of GDPR, even when the sponsor is located outside of the EU because the sponsor is effectively monitoring the behavior of data subjects within the EU. As a result, a non-EU sponsor must appoint a legal representative in the EU who may (or may not) differ from the legal representative for clinical trial purposes.

Archiving. — The mandatory archiving period not only becomes 25 years but also covers the Trial Master File ("TMF"), which extends application of the EU archival period to non-EU investigating sites. The TMF must at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial. The TMF kept by the investigator and that kept by the sponsor may have different content, if this is justified by the different nature of the responsibilities of the investigator and the sponsor.

UK Proposal: UK law would also require that sponsors keep a trial master file, but the focus would be on proportionality to the clinical trial. The TMF would also have be retained for a minimum of 25 years.

CONCLUSION

In the eight years since adoption of the Clinical Trial Regulation, EU and national regulators had time to adapt their rules, guidelines, and practices and become accustomed to the new clinical trials rules. Companies likewise have had time to adjust their SOPs and agreements. Yet, clinical trials rules are complex, and issues will undoubtedly arise.

Further areas of analysis will be required to streamline international studies. For example, the concept of low intervention clinical trials has long been applied in the United States, although the application in specific scenarios may vary from country-to-country. In an example of disparity, the U.S. regime anticipates clinical trials under an IND to have a single sponsor; hence, a trial allowed to have multiple sponsors in Europe may have to designate a sole sponsor for U.S. activities. Finally, reconciling evolving and expanded recordkeeping and disclosure requirements will continue to be a challenge across borders—at a minimum to ensure consistency and timeliness of information.

Many lawyers in our FDA & Life Sciences Practice Group have extensive experience dealing with clinical trial issues. They can help companies understand and adapt their clinical trial-related documents to the new European rules, ensure compliance with the EU rules, and navigating between CTR and GDPR, among other facets.

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