The EU Clinical Trial Regulation: What’s on the horizon, and what can sponsors do to prepare?
Part 1 – Authorisations, substantial modifications and IT

The EU-CTR, (EU) 536/2014, was approved in April 2014 following extensive debate in the European Parliament and by the Council of Ministers, and published in the Official Journal on 27 May 2014.3 The earliest the EU-CTR will apply is from 28 May 2016, depending on timely development of the required IT by the EMA.

The EU-CTR is a Regulation and directly applicable in all MS, which ensures harmonised interpretation, although national systems will need to be adjusted to fit the EU system. It has seven Annexes which cover more detailed topics (such as the content of the clinical trial authorisation (CTA) dossier, investigational medicinal product (IMP) labelling and safety reporting), which can be updated via Delegated Acts.4 This article outlines some changes which sponsors can expect following implementation of the EU-CTR. Part 1 will also include recommendations on how to prepare for a seamless transition to the new regime. Please note, it is not an exhaustive analysis of all the content.

Definitions and scope
The EU-CTR applies to interventional clinical trials as defined in Article 2(2) (non-interventional studies are not in scope). The Article states: “‘Clinical trial’ means a clinical study which fulfils any of the following conditions: 
(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; 
(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or 
(c) diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects.”

A new low-intervention clinical trial (LiCT) definition has also been created, which will clearly identify clinical trials with a lower level of intervention, often performed by academic and non-commercial sponsors [Article 2(3)]:

“‘Low-intervention clinical trial’ means a clinical trial which fulfils all of the following conditions: 
(a) the investigational medicinal products, excluding placebos, are authorised; 
(b) according to the protocol of the clinical trial: 
(i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or 
(ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and 
(c) 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”.

Introduction
The EU Clinical Trials Directive (EU-CTD) was approved in 2001 and implemented in May 2004.1 The EU-CTD enshrined the principles of good clinical practice (GCP) in EU law and led to important improvements in the safety and ethical soundness of European clinical research. Unfortunately, the EU-CTD was also criticised by a range of stakeholders because of its disharmonised interpretation, increased associated costs, administrative burden and delays.

On 17 July 2012, following significant prior discussion, the European Commission published the draft EU Clinical Trial Regulation (EU-CTR).2 The draft EU-CTR attempted to address some of these issues including reducing unnecessary administrative burden, without compromising quality and improving the attractiveness of the EU as a location for clinical research.
Article 2 also includes additional new definitions, some of which are important for reporting the status of a clinical trial, such as: “start of clinical trial”, “end of clinical trial”, “early termination of clinical trial”, “temporary halt of clinical trial” and “suspension of the clinical trial”.

**Authorisation procedure for a clinical trial**

CTA dossier elements will be classified as either “general” (Part I) or “national” (Part II) (see Figure 1) – see EU-CTR Annex I for further details on dossier content. The language of the application dossier will be determined by the MS, although Article 26 states that they will consider accepting a commonly understood language in the medical field for documentation not addressed to the subject. It is hoped this opportunity for simplification is taken up by the MS.

The CTA submission and assessment process will be mediated via an EU portal and database that will be developed by the EMA with the MS. The MS will determine how to involve the appropriate bodies in the assessment process. Please note that although the views of both national competent authorities (NCAs) and ethics committees (ECs) are integral to assessment of this dossier, neither is mentioned in the EU-CTR in relation to this process to ensure MS-level flexibility.

Significant improvements to the way the CTA dossier is assessed will be introduced. Some of these include unified IT (a single EU portal and database), coordinated assessment of Part I and the concept of a single opinion per MS incorporating NCA and EC opinion (see Figure 2).

The key is compliance with the process and timelines to generate separate assessment reports for Parts I and II resulting in a single opinion per MS. The importance of EC is reinforced in Article 8(4), which states that a concerned member state (cMS) shall refuse to authorise a clinical trial if an EC has issued a negative opinion valid for that entire MS.

Assessment of Part I for multi-MS trials is coordinated via a reporting member state (rMS), proposed by the sponsor, with subsequent input from the MS if there is a disagreement (Article 5(1)). The rMS will coordinate the review of Part I with the remaining concerned cMS, consolidating feedback in a single Part I assessment report. The process will take between 45 and 76 calendar days, depending on whether additional information from the sponsor is requested. Please note that an optional additional 50 days can be added if an NCA requires scientific advice for advanced therapy medicinal products (ATMPs) or products that originate from recombinant DNA (rDNA); this provision is intended to be used sparingly. Individual cMS can only opt out under three specified scenarios (Article 8) (see Figure 2).

Assessment of Part II is not coordinated, but will occur in parallel to Part I along similar 45–76 calendar day timelines. If the MS fails to meet the timelines for Part II, the conclusion of Part I will be the MS decision (this is also called “tacit approval”). Failure by the sponsor to provide comments in time, eg, during validation, Part I or Part II assessment or during assessment of a substantial modification will result in automatic withdrawal from the process. Sponsors must therefore set up efficient systems to engage with the new approach. Withdrawal does not stop the sponsor from re-submitting a clinical trial application, however, and it is also possible for the sponsor to withdraw at any time, although this will apply to all MS in the process.
Figure 2: Outline of the EU-CTR CTA dossier assessment concept.

**Dossier (Part I & II) Submission to EU Portal**

**Part I – “General”**
Lead: reporting member state (rMS)

**Part II – “National”**
Lead: concerned member state (cMS)

**Confirmation of rMS and validation**

- 10–25 days

**Part I assessment report and conclusion**

- Acceptable (with/without conditions)
- Not acceptable

**Part II assessment report and conclusion**

- 45–76 days*

**EDASSESSMENT**

- rMS conducts review, drafts assessment report (AR),
  cMS comment, rMS incorporates input from cMS**

**DECISION**

- Default: No opt-out of cMS → cMS accepts positive conclusion of assessment report
- Exception: Qualified opt-out scenarios
  - Inferior treatment compared with normal clinical practice in cMS
  - Infringement of national legislation (on use of cells)
  - Disagreement with conclusion based on safety, data reliability and robustness

- 5 days

**EU portal – one single decision per cMS and notification**

**Start of clinical trial**

*Maximal timeline with clock stop for questions.
**rMS can extend assessment time by 50 days for advanced therapies and products derived from rDNA technology.

**Substantial modifications and addition of MS**
The process for a substantial modification of Part I or Part II is similar to the above CTA procedure but with slightly shorter timelines (EU-CTR Chapter III). The process for addition of an MS has similar timelines to the initial procedure and the application dossier can only be submitted after the notification date of the initial authorisation decision (Article 14) which will require sponsor discipline in the trial start-up phase and country selection process. Figure 3 gives a summary of the timelines. Importantly, the timelines are maximal, and MS can move more quickly, as some already do under the current Directive.

Although overall CTA timelines can be longer than the 60 days in the current EU-CTD, this must be balanced against the benefits of a single EU portal, unified IT concept and coordinated assessment of applications encompassing the NCA and EC opinions (single opinion per MS).

**EU portal and database**
The EMA, with the MS, will develop the previously mentioned EU portal and database, which will act as both the single interface for CTA dossier submission and associated processes and the single data repository for associated documents. Full functionality will be verified via an independent audit and the European Commission will publish a note in the Official Journal once this is complete. The EU-CTR will apply six months after this publication so any delay in developing the EU portal and database will delay the application of the EU-CTR.

This is therefore a key implementation step and EMA and the MS have already started to work on its development. In addition to its specified functionality, the database must supersede existing regional and national databases, consider EudraCT and link with EudraVigilance as the repository for adverse reactions and annual reports. A range of documents will be loaded on the database, including:
Figure 3: CTA timelines in the EU-CTR.

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Validation (from submission)</th>
<th>Assessment (from validation to questions and reassessment of responses)</th>
<th>Clock stop (sponsor to answer questions)</th>
<th>Decision (from assessment)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial procedure (Part I and Part II)</td>
<td>10–25 days</td>
<td>45–64 days</td>
<td>12 days</td>
<td>5 days</td>
<td>60–106* days</td>
</tr>
<tr>
<td>Additional cMS (Part I and Part II)</td>
<td>N/A</td>
<td>52–71 days</td>
<td>12 days</td>
<td>0 days</td>
<td>52–83 days</td>
</tr>
<tr>
<td>Substantial modification (Part I and Part II)</td>
<td>6–21 days</td>
<td>38–57 days</td>
<td>12 days</td>
<td>5 days</td>
<td>49–95* days</td>
</tr>
</tbody>
</table>

* The rMS can additionally extend assessment time by 50 days for advanced therapies and products derived from rDNA technology.

- The CTA application dossier (Parts I and II), and their assessment reports
- Notification of start, temporary halt and early termination of clinical trials
- Information affecting the benefit–risk balance of a clinical trial
- Serious breaches
- Inspection documents, including inspection reports from the EU and third countries.

The EU portal will also be used to post clinical trial result information (Article 37):
- Summary clinical trial results plus a lay-friendly summary (outline in Annexes IV and V): within one year of the end of the trial in all MS. Sponsors must justify in the protocol if this is not possible (eg, the trial may be ongoing outside the EU)
- Intermediate analyses in the protocol to be published within a year of analysis date
- Clinical study reports (CSR) are in general not considered to contain commercially confidential information (CCI) and must be published within 30 days of the marketing authorisation (MA) being granted, completion of the MA decision process or withdrawal of the MA application.

In addition to other stakeholders considering this topic, the European Commission will produce guidelines for voluntary raw data-sharing schemes.

The EU portal will also be used for the notification of each of the parameters below (defined in Article 2) to each MS, within 15 days, of:
- The start of the clinical trial and end of recruitment of subjects (Article 36)
- The end of a clinical trial, temporary halt and early termination of a clinical trial (Article 37)
- Temporary halt or early termination by the sponsor for reasons of subject safety.

The following additional reporting obligations will also be notified via the EU portal:
- Notification of “serious breaches” to the cMS within seven days (Article 52).
- Notification to the MS of unexpected events that affect the benefit–risk balance of the clinical trial that are not suspected unexpected serious adverse reactions (SUSARs) and all inspection reports of third country authorities concerning the clinical trial (Article 53).

This database will be publicly accessible unless confidentiality is justified, eg, to protect personal data, CCI, or communication between the MS (Article 81(4)). The documents and information on the EU database will contain a mix of publicly available data and personal data or CCI. In some cases, this categorisation will change as the development process progresses. At the same time, the database must effectively support MS cooperation, eg, in assessment of CTAs and safety data, as well as acting as a tool to make information available to the public in all EU languages. Much work is needed to develop a tool that effectively manages this information and also meets the needs of MS, sponsors, patients and the general public.

Conclusion

The original aims of revising this legislation included the reduction of unnecessary administrative burden without compromising standards and improving the attractiveness of Europe as a location for clinical research. Many of the provisions of the EU-CTR, including development of a single EU portal and database, unified application dossier, coordinated assessment of Part I of CTA/substantial modification applications and the single opinion per MS are big steps forward. Despite this, much work remains to be done to ensure this is a pragmatically implemented piece of legislation and it is important that all stakeholders work together (and are supported) to ensure the original vision for the revision is achieved.

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References