Six top tips to prepare for the new EU Clinical Trial Regulation

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The European Union Clinical Trial Regulation 536/2014 (EU-CTR) aims to standardize and harmonize the conduct and management of interventional clinical trials across the European Economic Area (EEA), with legally binding rules on requirements and increased transparency.

This long-anticipated legislation uses one single electronic web-based Clinical Trial Information System (CTIS) to:

- submit, evaluate (scientific and ethical review) and authorize clinical trial applications (CTAs);
- submit any trial-related notifications, reports, and results, up to the clinical study report; and
- serve as the single communication channel between the sponsor and the Member States Concerned (MSC) in the clinical trial.

The EU-CTR goes into effect in January 2022, six months after the European Commission has published its notice in the Official Journal of the European Union. For the first 12 months after EU-CTR launches, sponsors can choose to submit CTA requests for new trials under the current EU Clinical Trials Directive 2001/20/EC (EU-CTD) or under the EU-CTR; after 12-months, all new CTAs must follow EU-CTR processes. Sponsors will have 36 months from the time of EU-CTR launch to transition ongoing trials to EU-CTR.

January 2022 is only a short period of time away, and preparing for the EU-CTR requires wide-ranging, cross-company initiatives. Companies should mobilize all stakeholders to analyze current business processes, upgrade information technology systems, and restructure operations to avoid disruptions to start-up, conduct, and maintenance of ongoing and new trials.

To reap efficiencies, sponsors must sow operational changes

The new EU-CTR promises a harmonized, simplified process designed to decrease the burden resulting from idiosyncratic interpretations of the current EU-CTD (Table 1).

Table 1. Current EU Clinical Trials Directive Versus New EU Clinical Trials Regulation

EU-CTD Current EU Clinical Trials Directive 2001/20/EC	EU-CTR EU Clinical Trials Regulation 536/2014
RA application and approval, country-by-country	One application via CTIS to all MSCs; one decision per MSC, including scientific and ethical evaluation, based on availability of: › Part I (core scientific data dossier) – Assessment report by RMS (with contribution by each MSC) › Part II (country-specific documents*) – Assessment report by each MSC separately *Informed consent documents, site suitability etc.
EC application and opinion, country-by-country	No separate EC applications and opinions (central or local), these are integrated into the process above
Response timelines to RFI vary across countries	RFI must be answered within 12 calendar days or the application is lapsed
Submission communication method is country-specific	Electronic communication via CTIS only
Trial sites or countries can be added, or protocols amended, at any time in a parallel process independent of ongoing applications	Ongoing review of an application (for example, substantial modifications within a MSC or the addition of a new MSC) prevents further applications
Assessment processes and deadlines vary by country	Ongoing review of an application (for example, substantial modifications within a MSC or the addition of a new MSC) prevents further applications

Key to acronyms: CTIS-Clinical Trial Information System; EC-Ethics Committee; MSC-Member State Concerned; RA-Regulatory Authority; RFI-Request for Information; RMS-Reporting Member State

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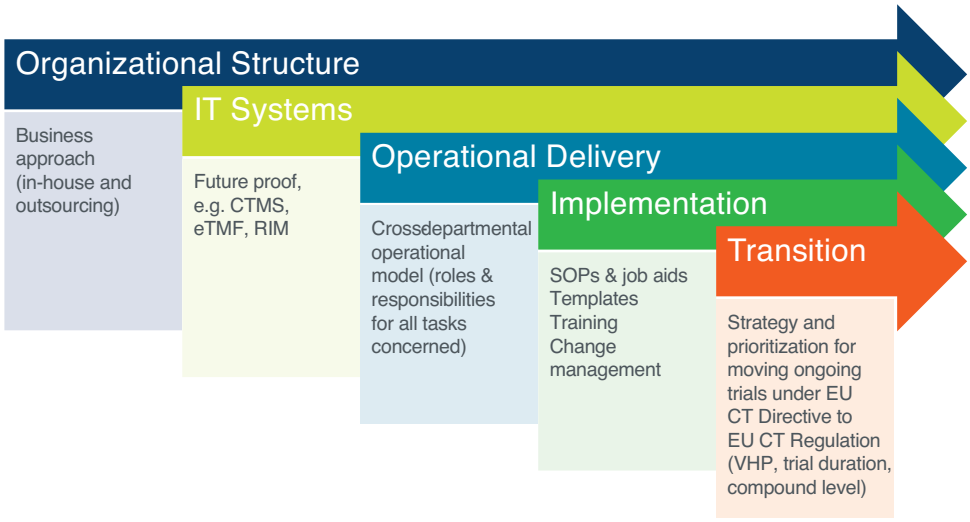

Figure 1: What sponsors should consider when preparing for the EU-CTR

Efficiencies promised by the EU-CTR include all-electronic submissions and communication, improved collaboration between MS, increased process transparency, and uniform review timelines. However, EU-CTR presents significant operational challenges for sponsors. Although core activities and datasets for trials in the EEA will not change, management of study start-up activities, RFI responses, and modifications to the CTA dossier need to change. For example, sponsors must establish processes for document redaction.

Here are essential preparations companies should undertake now:

1. Analyze processes across your portfolio

To maximize efficiency, sponsors need to assess processes across their portfolio lifecycle. Early on, sponsors should engage with internal stakeholders and external outsourcing partners to communicate clearly defined processes and workflows to ensure business-continuity and full compliance under the EU-CTR. They may need to employ different resourcing models to address varying circumstances.

Given the time to implement all required changes, sponsors must prepare for an EU-CTR future before they know all the pertinent details and may have to consider multiple contingencies (Figure 1).

2. Focus on first-time quality

Under the EU-CTR, a CTA's success depends on the first-time quality of the dossier to a greater extent than ever before. A CTA will not pass the validation phase in any MSC unless it receives clearance to proceed in all MSCs. The initial application authorization procedure and any Substantial Modification application must be completed before you can submit an additional MSC. This greater interdependency amongst MSCs in the trial demands that sponsors get applications right the first time.

3. Choose countries wisely

Under the EU-CTR, the study start-up strategy will need to change from "first EEA country ready" to a holistic approach to EEA country readiness. Part I of an EU-CTR CTA dossier evaluation is a joint assessment from all MSCs led by the RMS (sponsors propose the RMS). However if a CTA contains elements or provisions at odds with the RMS's national laws, a negative Part I conclusion will affect all MSCs. Experts with local knowledge can tailor the country list: choosing the right RMS and MSC will be critical.

4. Centralize CTA management

An industry-wide trend related to EU-CTR is the centralization of CTIS management. Communication exclusively via CTIS and the short RFI response timelines call for a focused team that monitors CTIS for incoming communications, handles document/data entry and download for trial master file compliance, and closely monitors timelines.

Anticipating the need for cost-efficient centralization, Parexel has already set up CTA Submission Hubs (CTA Hubs) in Europe, Asia and Latin America. This regional CTA Hub model has a proven track record and utilizes regulatory staff in low-cost geographies for CTA compilation, submission, tracking and archiving. CTA Hubs leverage the knowledge and expertise of Parexel's global regulatory network, wherever needed, to address complex regulatory scenarios. Parexel's CTA Hub model is well suited to handle CTIS management in a high quality and cost-effective manner.[1]

5. Upgrade IT infrastructure

Most companies will need to upgrade their electronic trial master file, regulatory information management, and clinical trial management systems to meet the new demands of EU-CTR. However, companies should realize that procuring and upgrading such systems can take anywhere from six to twelve months. And you can only upgrade effectively after a comprehensive impact assessment. It is vital to get the right insight and information about the current IT system and what will be needed going forward.

6. Tighten timing

Under the EU-CTR, sponsors will need to coordinate initial applications—and all modifications—closely. Missed timelines may result in legal consequences for sponsors, such as lapsed applications. Sponsors will need a strategic plan for management and oversight of timing of permitted and non-permitted overlapping initial, substantial modification, and additional MSC applications.

EU-CTR will require tight process coordination by sponsors' study teams: all contributors must synchronize activities, both lifecycle planning for each trial as well as across all studies with the same product because an ongoing assessment in one MSC will block further substantial modifications to Part I, or Part I and II, for all MSCs. Sponsors should attempt to minimize in-process changes to a clinical trial and ask: will this action impact the submission of another action?

If sponsors prepare well in advance, they will find that initiating and conducting clinical trials in a timely fashion will be manageable under the EU-CTR.

Now is the time to plan and pressure test the radical process changes mandated by the EU-CTR. Take advantage of Parexel's EMA CTIS product owner insights to review and refine your future operating model to avoid costly delays to overall development plans.

1 https://www.parexel.com/news-events-resources/news/current/parexel-announces-solution-eu-clinical-trials-information-system-regulation

"As an association representative and product owner for EMA's CTIS delivery model, I am able to help clients interpret and implement the necessary requirements for the EU 536/2014 clinical trial regulations."

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