# A Reflection on the European Regulatory Framework

Historically gaining regulatory approval across multiple countries within the European Union (EU) was segmented, excessively bureaucratic, and challenging to navigate. Sponsors had to submit clinical trial applications separately to national competent authorities (NCA) and ethics committees (ECs) in each country to gain regulatory approval to run a clinical trial. Individual countries dictated their own set of national submission requirements and gave local opinions on the trial design. The result of inconsistent feedback left Sponsors with the challenge of unifying recommendations within a single global protocol often leading to multiple protocol amendments or country-specific versions of the master protocol. These challenges subsequently resulted in inflated costs and long start-up timelines and the perception that the EU was a difficult place to run clinical research.

On 31 January 2022 the EU Clinical Trial Regulation (EU CTR) No 536/2014 came into effect and repealed the Clinical Trials Directive (CTD) 2001/20/EC and national implementing legislation in the EU Member States.[1] The EU CTR is focused on ensuring high patient safety standards, collective decision-making on clinical trials and greater public transparency of clinical research, and aims to make the EU a more attractive place for conducting high-quality large-scale trials. There is a requirement to transition all clinical trials to the EU CTR by 31 January 2025 if they are still ongoing.

**Streamlining the Regulatory Process**

The EU CTR enables Sponsors to submit one multi-country application via a single online platform through the Clinical Trials Information System (CTIS) for approval to run a clinical trial in the EU and European Economic Area (EEA), making it more efficient to gain regulatory approval for multinational trials. The CTIS provides a single point of entry for clinical trial application procedures and publication of trial results over the life cycle of clinical trials run across the EU/EEA.

For multi-country clinical trial applications, a single, harmonised submission dossier is presented. The dossier is reviewed in two parts with the scientific assessment of the core documentation harmonised across all member states being led by one reporting Member State (part I) and ethical assessment of the country- and site-specific documentation (part II) completed by each country where the trial is to be conducted, creating a combined review and assessment process.

One of the principles of the EU CTR is that all submitted documents will be publicly available and the CTIS allows for searchable clinical trial information. CTIS enables redaction of documents as the method to protect personal data (PD) and commercial confidential information (CCI), if those are included in the documents. Having a single portal where the whole regulatory and ethical dossier of a trial is available has led to greater transparency of information.

Although the new submission process may have increased or decreased the overall timelines in some countries, it brings an increased predictability for clinical trial start-up timelines in the EU countries.

As with any new regulation, Sponsors, regulators, and ECs have faced challenges navigating the new requirements and process. Approximately one year on, Catalyst Oncology reflects on the impact this regulation has had on attaining approvals to run trials in the EU Member States and EEA countries and our experience to-date.

**Reforming Operational Considerations**

Data retrieved from CTIS, as of 19 February 2024, showed 3,872 clinical trial applications have been submitted since its launch and 2,473 have received a decision.[4] The therapeutic areas mostly investigated are neoplasms (tumours).[4]

The EU CTR establishes an overall timeline of 60 days for the member states to evaluate an initial application. This deadline may be extended if requests for information (RFIs) are raised by a Member State Concerned throughout the evaluation process. Timelines can be extended up to 15 days for RFIs raised in the validation phase and up to 31 days for RFIs raised in the assessment phases. In total, the initial application type assessment takes up to 106 days.

**Harnessing CTIS Submissions**

Technical problems with CTIS have led to delays in study approvals, unnecessarily raised RFIs, and duplication of work. A significant challenge is the requirement for manual data entry and the duplication of efforts to upload two versions of documents: redacted version for publication and non-redacted version for authorities' review, which results in a significant resource burden.

Another challenge is that the CTIS does not send alerts to users' emails, forcing users to daily monitor incoming RFIs and notifications within the portal. Considering the 12-day response requirement for RFIs, it is critical to become aware of an RFI immediately.

Another issue is certain information is not received in a document format, such as query letters or acknowledgments of application, which prevents such documentation from being included in the electronic trial master file.

**Meeting Deadlines**

It is important to understand the implication of not meeting RFI timelines. If a Sponsor fails to meet a deadline for a response to an RFI for a country, the RFI lapses, the whole application withdraws automatically in the system for all countries, and part I and part II must be resubmitted.

As Catalyst Oncology, we dedicate significant time with the preparation and review of the submission documents to ensure quality and minimize potential RFIs. We implement a risk mitigation strategy with our Sponsors to anticipate potential RFIs and pre-prepare responses where possible while the assessment is underway. Close collaboration between Sponsor and the dedicated regulatory or site activation team is critical to success.

**Documentation Needs**

While approval timelines should be shorter with EU CTR compared to CTD, timelines and the number of documents required for

submission have increased (mainly for part II). Examples of new documents previously not required in many countries are:

- individual site feasibility forms
- CVs
- declarations of interest for all investigators
- recruitment arrangements
- financial arrangements
- data protection statements
- description of use of biological samples

Their inclusion in the submission dossier increases the number of required documents to be prepared, reviewed, and potentially queried, increasing preparation and review timelines.

**Modifications of Submissions**

It is possible to make substantial and non-substantial modifications to a trial after study approval, including changes to the protocol, other study documentation, and to add new sites in a country (part II substantial modification). Adding a new country is considered a new application for both part I and part II or only part II, if there was a partial application previously and can take up to 83 days. New sites can be added via a substantial modification (SM) and must be approved by both NCA and ECs before the site can start enrolling patients (EU CTR, Chapter III, Article 15). Where modifications are made, each SM can take from 60 to 95 days and this should be factored into site and country strategies.

**Transparency**

One of the principles of the EU CTR is that all submitted documents will be publicly available unless their confidentiality are justified. Deferral rules for varying amounts of time depending on the category of the clinical trial and document type were in place for Sponsors submitting in CTIS. The European Medicines Agency (EMA) also notes that PD and CCI should not be included in the structured data fields or uploaded documents within CTIS, as structured fields are meant for publication.

However, during May and June 2023, a public consultation was held with stakeholders to gather insights from the previous year. One key finding was that the transparency and associated deferral rules were too complex. The goal of these rules, which aims to strike a harmonious balance between informing patients and protecting their data, is inherently complex and ambitious. The European Medicines Agency has subsequently decided to eliminate deferrals for clinical trial information publication.

Because of the ongoing changes, contract research organisations must have dedicated teams staying updated on changes in guidelines and regulations. Sponsors should consider how this change might impact their strategy, especially when identifying in-scope documents.

**Additional Considerations with the CTIS Application Process**

Although the submission process is a two-part package, clinical trial applications can be submitted as a full application with both parts together for all countries. Or a partial application with a part I submission to the reporting Member State and part II, the country packages, submitted later for the national assessment.

A mixed application where a part I package and an initial country part II package is submitted, followed by a second part II package to add additional countries later is also a possible strategy with risks and benefits to consider.

It is important and critical for success of a planned CTIS submission to have the sites in a country pre-selected as part II

packages (country and site level) require the collection and review of site-specific documents signed by the principal investigator or institutional board (CVs, Declaration of Interest, site suitability forms, GCP certificates, etc.). We recommend expediting and streamlining the site feasibility and selection process to get all sites selected four to six weeks before the planned CTIS submission timeline.

**Conclusion**

The changes brought about by EU CTR have shifted the clinical trial landscape in the EU. While challenging regulatory segmentation has receded, the EU CTR and CTIS have yet to completely smooth out all the challenges. As Sponsors and contract research organisations continue to embrace the changes the EU CTR is working towards, the EU regulatory landscape will become an even more welcoming place for conducting high-quality large-scale trials.

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