Essential Considerations for a Successful Submission under EU CTR

The European Union Clinical Trials Regulation (EU CTR), which came into force in January 2022, was the biggest change to EU medicinal product legislation since 1995 when the European Medicines Agency (EMA) and the centralised procedure for marketing authorisations were introduced.

The EU CTR presents fundamental changes for clinical trials in all 30 countries of the European Union (EU) and the European Economic Area (EEA). The legislation has replaced the EU Clinical Trials Directive (EU CTD) and established a consistency-centred approach for clinical trial applications, assessments, and reporting. A key feature of the EU CTR is the introduction of a single electronic portal, the Clinical Trial Information System (CTIS), which is mandatory for all EU CTR submissions. CTIS enables harmonised and simplified end-to-end electronic application procedures over the lifecycle of clinical trials across the EU/EEA.

Submitting Applications Through CTIS

CTIS is the single-entry point for submitting, assessing, authorising, supervising, and reporting a clinical trial in all Member States of the EU/EEA. Through CTIS, applicants can submit a single, integrated clinical trial application dossier that covers all clinical trial applications submitted to EU/EEA Member States, national regulatory agencies and ethics committees. Through this single application, CTIS users also register their clinical trials in a public register.

The introduction of CTIS was the most significant hurdle for the introduction of the EU CTR. The journey towards this introduction has not been without challenges. Due to its pivotal role in the EU CTR process, delays to the release of CTIS led to multiple postponements of the overall introduction of the EU CTR. However, since the launch of CTIS on 31 January 2022, there have continued to be technical issues with the system – some more problematic than others. For example, some of the technology workflows have not acted as they are described. In some cases, this meant a resubmission was needed, even though the reporting member state (RMS) and sponsor had followed all the correct processes. This was a technical glitch that could not be passed. Even though the RMS wanted to progress the application to the next step, it was not possible due to the CTIS technology workflow.

The difficulties with the CTIS portal have been experienced by all users, including sponsors, regulatory agencies, and ethics committees. As a result, some countries have set-up CTIS specific working groups across sponsors, CROs, sites, etc., so that they can exchange training, learnings, and workarounds.

To resolve the portal issues experienced by users, there are regular CTIS updates being released and more information about these is published in the CTIS Newsflash, currently released weekly. It is important for all CTIS users to stay up to date on the new releases and workarounds since these can be critical to the success of an application.

Preparing for EU CTR Submissions

When planning for submission under the EU CTR in any EU/EEA country, there are a number of prerequisites for managing studies in CTIS that sponsors should consider. Access to CTIS requires a high-level administrator to manage and assign roles within the system. Sponsors must ensure the correct users/access rights are in place for CTIS activities to take place. Contract research organisations (CROs) are able to provide CTIS administration and submission support services to sponsors.

Data within CTIS relies on supporting systems to populate sections of the clinical trial information. All stakeholders that will be included in the application form, known as the structured data, must be registered in the Organisation Management System (OMS). These stakeholders may include marketing authorisation holders, sponsors, regulatory agencies, manufacturers/QP release sites, CROs, central labs, clinical trial sites, academia, hospitals, wholesale distributors, etc.

It is critical that sponsors place greater importance on site selection prior to the initial EU CTR submission. A cohort submission strategy that may have previously been possible under the EU CTR would significantly impact site activation due to the sequence of submissions and approval timelines. Therefore, it is practical to wait and ensure the site list is complete prior to initial submission to avoid any downstream delays to site activation for those sites that may not have been included in the initial submission.

Complete harmonisation of the protocol design across all EU/EEA countries is required. Therefore, any per-country nuances in the clinical approach that may impact protocol design would need to be incorporated into the global protocol. The protocol also needs to include the EU trial number. The protocol should include an unambiguous and clear definition at the start and end of the clinical trial. Unless described in the protocol, a document describing the procedures for the inclusion of subjects and detail of what the first act of recruitment is would need to be submitted. If the end of the trial is not the last patient's last visit (LPLV), a specification of the estimated end date and justification is required.

Requests for information (RFI) issued during assessment procedures are identified by the sponsor (or CRO) via the notices and alerts area and the RFI tab in the CTIS sponsor workspace. Responses to RFI are within a very short timeline, up to 10 calendar days (validation) and 12 calendar days (assessment), which cannot be extended. Responses to the RFI are required in CTIS, along with any applicable updates

made to relevant documentation in CTIS. This would include document(s) with tracked changes, translation(s), and redactions. Missed deadlines will lead to rejection and the need for resubmission.

Delegating to a CRO

CROs can support navigation of the CTIS system. This support can be provided independently of the organisation delivering the wider clinical trial and outside of the full-service delivery model.

It is generally acknowledged that the CTIS still presents challenges for users. The key benefits that working with a CRO can bring are knowledge and experience. For example, here at ICON, we've established a cross-functional initiative to ensure effective and timely implementation of the EU CTR across the organisation. Through close surveillance of the intelligence released by the European Medicines Agency (EMA) and national Regulatory Agencies and Ethics Committees, we've been preparing for implementation for many years.

Furthermore, at this point in its implementation, CROs have now been able to gather direct experience with preparing and making EU CTR submissions, in collaboration with sponsors and other key stakeholders. By capitalising on this knowledge and experience, they can address challenges and mitigate risks at the time of submissions. This enables sponsors the time to focus on their clinical trial overall and provides peace of mind that the submission process will be executed efficiently.

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