The intricacies of effectively transitioning active clinical trials to the EU Clinical Trial Regulation

European Union lawmakers designed EU Clinical Trial Regulation 536/2014 to heighten interest within the healthcare industry for planning and conducting clinical trials in the EU, which experienced a decline after implementing the EU Clinical Trial Directive 2001/20/EC more than two decades ago. Lawmakers hope to better harmonise processes to ease drug development for stakeholders who have worked with different requirements and timelines across EU member states for many years.

The CTR requires clinical trial sponsors to meet new process requirements and related timelines to ensure EU-based programmes stay on track.

Looming questions for active trial transition:

- How much information do we really need to take the decision to transition?
- What exactly does the application to transition active trials look like?
- What is a realistic project timeline to ensure the deadline is met without causing trial delays and added cost?
- How will we need to modify the active trial as we transition over?
- How will the transition application process impact plans for other changes we need to make?

What will happen to trial subjects if the trial is not authorised in a timely manner?

For those already working through the previous directive for a trial in progress, there was a nuanced set of questions to address to successfully transition to the EU CTR by the 30th January 2025, deadline. Further, sponsors were informed that for trials to be transitioned into CTR and reviewed by 30th January, to continue as planned, then all documentation had to be submitted by 16th October 2024.

How have sponsors met these requirements? Below, we discuss noteworthy core activities we found to be fundamental to help sponsors make the transition to the EU CTR.

Successful active trial transition: What helped

EU lawmakers provided sponsors and clinical research organisations eight years (2014-2022) to familiarise themselves with the ins and outs of the CTR. This gave sponsors and CROs the opportunity to map their existing processes and adapt accordingly.

It was critical to use the time to prepare updated submissions strategies and, in parallel, educate and train teams, including sites, about the inner workings of the new regulation and its Clinical Trial Information System portal, where all new and current trial information would be submitted and processed for review.

Transition to a completely new regulation in the midst of ongoing trials allowed sponsors and CROs to collect plenty of lessons learned and best practices for complying with the CTR in a timely manner, and eventually how to apply these experiences to new or other updated regulations.

Guiding sponsors from end-to-end

The European Medicines Agency estimated up to 6,000 ongoing trials would ultimately need to transition to EU CTR because they were expected to continue beyond 30th January 2025. However, many sponsors were initially hyper-focused on ensuring new trial applications were submitted on time, instead of transitioning active trials. This made it critical for CRO partners to ensure focus on active trial transition strategies by offering ongoing education and guidance to meet the deadline, especially considering the ongoing updates to EMA requirements (e.g., 2023 updated rules regarding publicly available trial documentation).

Study start-up managers, regulatory experts, local country-specific start-up specialists, operational leads, project managers, therapeutic experts, and potentially also medical writers, clinical supply, and pharmacovigilance specialists, were involved in guiding sponsor and recommending transition strategies to:

- Consolidate and explain ongoing EMA guidance to sponsors and team members to make sure all new guidance was accounted for and applied to submissions.
- Clearly communicate to all sponsors the consequences of not adhering to the EMA's transition deadline. In some instances, this meant several discussions between sponsors and project managers, regulatory leads, and individual clinical trial experts to explain that trials must transition to be able to continue in the EU.
- Reassure and advise sponsors in the absence of clear guidance. When implementing new regulations, the uncertainties can also be viewed as opportunities to create flexibility and allow exploration with authorities and ethics committees. Trial sponsors comfortable with exploring were able to learn quicker and become early adopters.

To alleviate sponsor hesitation to proceed with active trial transition, it helped to provide a quantitative impact analysis. For example, we conducted and prepared an impact analysis for 1,150+ studies for varying pharmaceutical and biotech companies, gathering details on therapeutic space, trial status, plans, and timelines, etc. We prioritised the trials by high-to-low risk of not meeting the transition deadline to then hold individual conversations with sponsors on what was necessary to drive trials ahead while transitioning to the CTR, including detailed project timelines. Part of this included developing guidance on clear communications to emphasise steps to effective transition for each trial.

Strategic roadmaps per trial

Each active clinical trial scoped to transition would need its own strategic roadmap, where stakeholders — sponsors, CROs, and sites — were on the same page at every step, including the following considerations.

Individual trial nuances

One key difference in submitting an active trial to the CTR as compared to a new trial was reviewing each trial's unique scenario and what was necessary to move forward effectively. For example, there were trials with different protocol versions authorised in different EU countries. Such variability may have dictated that "harmonisation" was necessary before transition was possible, and the details of each case would therefore need to be carefully outlined and accounted for to provide recommendations on direction. Other trials may have had plans to expand into new EU or non-EU countries, which would have a significant influence on transition plans. As of 31st January 2023, such trials would need to transition before adding EU countries, though adding non-EU countries during the transition may be more attractive. Often, many factors dictated increasing complexity for trial-related scenarios as the transition period drew on and additional variables became relevant.

Strategic structure from the start

Recognising the complexity of effectively transitioning trials by the deadline, it was critical to have a structured framework of action that addressed various needs from the sponsor and within CRO teams. A sample of key components includes:

- Clearly outlining and documenting roles and responsibilities among CRO teams and sponsors.
- Holding regular training sessions and developing and providing materials regarding transition needs, EMA updates, etc., for all relevant team members.
- Hosting open forums for CRO team members to discuss transition strategy pain points per individual trial, lessons learned, and best practices to reduce future unknowns and delays.
- Creating document templates for trial submission packages.

One key example of the need for structure from the start is requests for information, or RFIs, from regulatory authorities, which may arise during the transition. If a sponsor receives an RFI, they have up to 12 calendar days to provide a sufficient response and update any documents that may be impacted.

Though the transition application would not be expected to require re-assessment of the scientific documentation, many transition applications did result in RFIs and the availability of relevant expertise and effective collaboration proved crucial during that 12-day period. During planning stages for individual studies, CROs can help map timetables of assigned responsibilities and roles for each day after receiving an RFI to facilitate timely responses. Also, as CRO teams gather knowledge from other trial submissions and regulators' questions, they can help build a database of collective insights to better anticipate potential question scenarios according to study type or other factors. This will further facilitate a sponsor's ability to respond swiftly.

Ongoing engagement with regulators

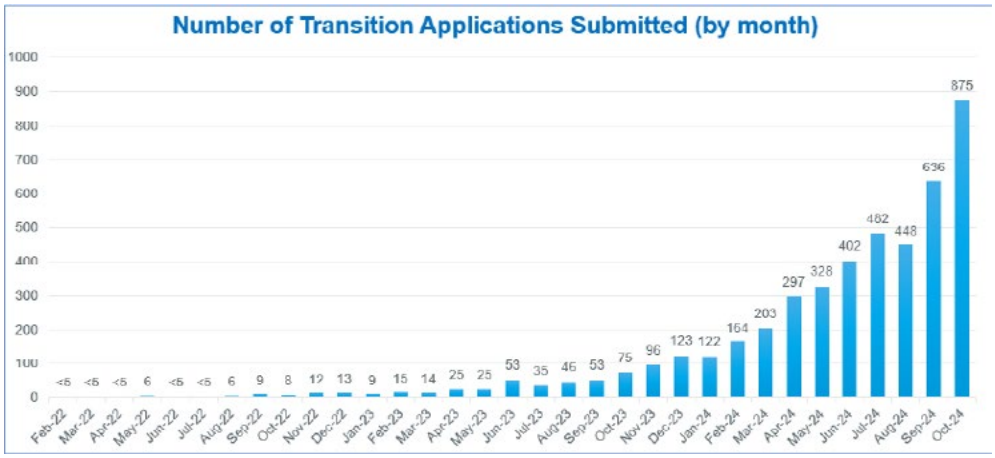
Adapting from a country-specific approach to a centralised system, the CTR and CTIS portal submission process has required relevant team members' roles to evolve. For example, from the time of transition, there must be tight alignment between roles responsible for regulatory assessment and ethics committee assessment, which was not as important previously. And as guidance routinely evolved, our experiences with the CTR transition period have emphasised the critical role of engaging with the EMA and other EU agencies to gauge the agency's likely perspective on all remaining unknowns.

In open discussion forums, webinars, talk sessions, sponsor surveys, step-by-step guides on the CTR and CTIS, and more, the EMA has welcomed engagement with sponsors and CROs to address questions and ensure compliance. Those who took advantage of every resource provided by the EMA in the last several years were able to stay informed about minor or major guidance updates to implement more quickly into plans.

Also, in some cases, the EMA loosened regulation components after some dialogue. For example, in regard to sponsor concerns around publicly available trial documents, the EMA held an open consultation on the CTR Transparency Rules in May 2023, inviting industry stakeholders and the general public to discuss best practices for information transparency that upholds confidentiality requirements. In early October 2023, the EMA released revised rules, which significantly reduced the range of documents and information published, and removed the deferral mechanism that had been in place since 2022 to simplify the process and potentially reduce redaction while continuing to provide the information most valuable for patients and investigators.

Tremendous value in long-term preparation while staying realistic

Over more than eight years of monitoring, getting familiar with the EU CTR, conducting trial submissions activities, etc., clinical trial stakeholders invested in timely transitions have been on the frontlines of significant change, gaining key lessons from specific experiences that can be applied to other trials and future regulatory changes.



Since the EU CTR was implemented in January 2022, the EMA has provided regular metrics for trial transitions. The EMA has also noted it will take up to 106 days from an active trial transition submission to potentially receive authorisation to continue. As such, we are seeing an influx of sponsors submitting transition documentation for review within the last six months. According to EMA metrics, 875 transitions were submitted in October 2024 alone (a nearly 12-fold increase from October 2023).

Being realistic about what any regulatory authority can manage in an allotted timeframe, especially when reviewing with a careful eye to nuanced details per trial, it is possible that transition applications submitted close to the deadline may not receive approval to continue in time. Also, what if sponsors receive a RFI within this time that further delays the review? Submission after 16th October 2024 carries increased risk of missing the transition deadline.

To avoid being part of a massive compression of review, it was of tremendous value to map out transition timelines, roles, and responsibilities and action items as early as possible upon learning of the transitional provisions within the EU CTR.

A work in progress

Over three years, the EU CTR has changed and will continue to change.

Looking forward, whether a sponsor has successfully transitioned to CTR, is awaiting authorisation, or has not yet applied, continuously monitoring updates to the regulation and related information will persist to ensure compliance. For instance, improvements might be made to the CTIS portal to make it more user-friendly, or additional insights into the trial document transparency rules may be provided. Regardless, being up-to-date, maintaining open communication with regulators, and disseminating pertinent information to guide trial direction will always be integral to an effective plan to meet requirements.

About the authors

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