WHITE PAPER
July 2022

EU CTR 536/2014: A guide to support implementation

1. EU CTR 536/2014: A harmonised approach to regulating clinical trials

The European Union (EU) Clinical Trial Regulation 536/2014 (EU CTR) became applicable on 31 January 2022. EU CTR harmonises the management and regulation of clinical trials in the EU. Benefits expected from EU CTR include:

- a streamlined and collaborative process for submission and assessment of clinical trials and associated documentation
- less duplication of effort for sponsors
- more clinical trial transparency
- enhanced safety reporting

The regulation is also intended to make the EU a more attractive place to conduct clinical trials.

An early report on the use of the regulation (Key Performance Indicators (KPIs) to Monitor the European Clinical Trials Environment (18 May 2022)) shows that 18% of Clinical Trial Applications (CTAs) submitted under EU CTR were either withdrawn by the sponsor or had lapsed at the time of validation. This suggests that sponsors are experiencing challenges with the implementation of EU CTR.

The relevant legacy regulation (EU Directive 2001/20/EC (EU Directive)) will remain in force through a period of transition to EU CTR. However, it is now imperative that sponsors determine how they will transition their operating models and clinical trials to comply with the new regulation.

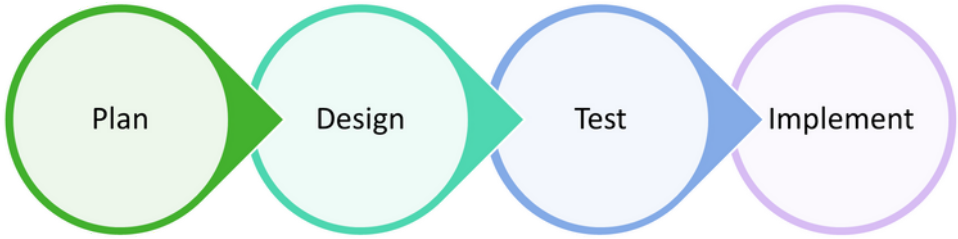
For more details on the regulation, read our white paper on EU CTR 536/2014: A harmonised approach for regulating clinical trials.

We have identified the following important points that sponsors must consider when implementing EU CTR:

- EU CTR impacts the whole lifecycle of a clinical trial, from planning through to close out. Changes to processes, roles and responsibilities will be needed to meet the new regulation.
- During the transition period, sponsors are likely to introduce the EU CTR gradually to their portfolio. This will allow new approaches to be piloted. This will add complexity to operations as sponsors will also have trials running under the legacy regulation. Managing this will require clear communication with stakeholders along with strong quality assurance oversight to ensure compliance.
- Under the legacy EU Directive, CTAs were submitted by local affiliates. Submissions under EU CTR will be through the centrally managed CTIS. The flow of information will be reversed as local affiliates will need to submit required documents to central groups. This change in the relationship between central teams and affiliates will need to be handled sensitively.
- Under EU CTR, sponsors are required to make public more clinical trial documents than ever before. They will need to redact and/or anonymise any personal protected data (PPD) and company confidential information (CCI) prior to document publication. This should motivate sponsors to create lean, disclosure-ready documents at the authoring stage. It is unlikely though that the need to redact can be completely eliminated. Therefore, sponsors will require additional resources, expertise, and time to manage redaction and anonymisation, both centrally and in affiliates.
- During CTA validation and assessment, the Member States Concerned (MSCs) may issue requests for information (RFIs) to which sponsors are required to respond within 12 calendar days. Failure to do so could lead to withdrawal of the CTA. Sponsors will need to develop processes to manage timely responses to these requests.
- Once the trial is underway, sponsors must also provide updates following specific trial events through CTIS within set timelines. This requires trial management processes to be as efficient as possible.

2. Strategy for success

To successfully implement EU CTR 536/2014 a sponsor will need to plan carefully and design, test and implement new ways of working. Based on our experience, we present a structured approach to help sponsors achieve this.

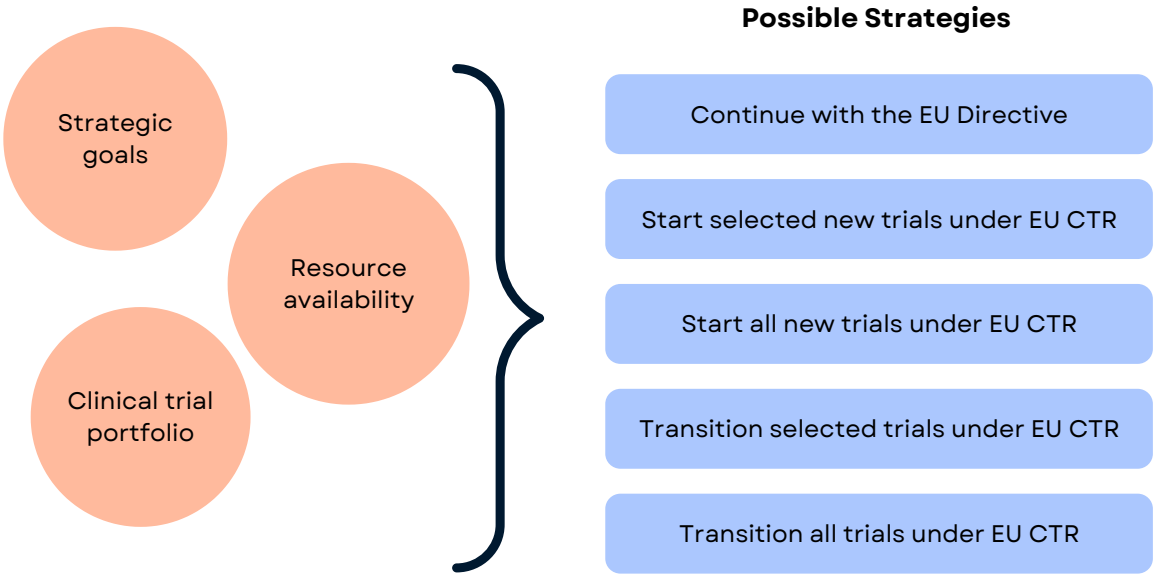


2.1. Plan the project

2.1.1. Determine the implementation strategy

A clear strategy for the implementation of the change must be developed based on the sponsor's overall strategic goals, clinical study portfolio, and availability of resources to affect the change.

Figure 1. Possible implementation strategies



2.1.2. Identify a core team

A core team should be identified who will be responsible for planning and managing the transition. This team should have representation from all relevant functions (e.g., clinical operations, regulatory, safety, medical writing, IT, quality assurance and clinical trial transparency). Local affiliates should also be represented.

The team should include the following mix of skills and experience:

- Knowledge of the current process
- Knowledge of the new regulation
- Good project management skills
- Process design expertise
- Change management skills
- Information technology skills

If these capabilities are not available in-house, the sponsor could supplement these with expertise from a third-party consultancy.

It is important for the team to have a proactive and engaged senior sponsor who can help them get access to the resources they need and who can help navigate through any organisational challenges that are encountered.

2.1.3. Build a project plan

The team should develop a comprehensive plan to deliver the strategy that has been set. The plan should be tailored to the sponsor's operating model and circumstances. The plan should consider:

- The availability of key members of the team
- Planned trials that would follow the new regulation
- The expected timelines for implementation
- The amount of change management that will be needed

The plan will need to be adapted and revised as the team better understands the changes that are needed, implementation challenges are encountered and/or business priorities change.

2.2. Design the new process

2.2.1. Understand the impact of regulation on existing processes

To determine the impact of EU-CTR on existing processes, the implementation team must have a good understanding of the regulation. EMA has made available several resources to help sponsors prepare (CTIS training and support).

Despite these resources, the regulatory language can still be difficult to decipher. To address this, the team can tap into the shared knowledge and experience of the network of professionals involved in EU CTR implementation (e.g., at relevant conferences and industry forums as well as external consultants). This can help avoid common pitfalls and support implementation of the changes. Where queries cannot be resolved within the network, questions or comments can be sent to EMA through organisations like EFPIA.

Once the regulation is understood, the team should create an inventory documenting its impact on:

- Stakeholders (internal and external)
- Controlled documents (e.g., SOPs)
- Work processes
- IT systems

2.2.2. Design the changes

The team should work through the inventory of impacted processes, system, stakeholders, and documents and agree on the required changes. This should include:

- Draft revisions to SOPs (or draft new SOPs)
- Draft role revisions (or consider any new roles required)
- Systems requirements (including changes to access)
- Considerations on the interactions with existing partners or the introduction of new partners (e.g., CROs and other vendors)
- Paying particular attention to changes in the interaction between central teams and affiliates

Table 1. Process design - Key considerations

Key considerations for process design
Timely access to and training on CTIS and connected systems (e.g. CTMS)
Careful planning & site selection for clinical trials to avoid delays in the process
Preparation of clinical trial applications in line with the updated regulatory requirements
Preparing lean disclosure-ready clinical documents
Timely preparation of redacted documents for publication
Ensuring efficient trial management so that status and milestones are updated in CTIS on time

Key considerations for process design (cont.)
Timely submission of safety documents – annual safety reports (ASRs) via EU CTIS and suspected unexpected serious adverse reaction (SUSARs) via EudraVigilance database (EV CTM)
Preparation of scientific summary at interim (new requirement) and final analysis
Preparation following final analysis of plain language summaries in the local languages of the country where the trial was conducted
Timely posting of clinical documents following the end of the trial

2.3. Test the new process

2.3.1. Design a pilot

The initial process changes will be designed "on paper", however these should be fully tested in a real life setting before proceeding to full implementation. This can be achieved by selecting an upcoming new study on which to pilot the new processes. Significant effort will be required from the implementation team to support a pilot. Therefore, it is recommended that the initial pilot is conducted on a single study. Sponsors that will need to transition on-going trials that were started under the legacy EU Directive should also consider running a pilot for that scenario.

Selecting an appropriate study for the pilot is important. Consideration should be given to:

- Timing of the study (study timelines should align with the overall implementation plan)
- Study priority (it is prudent to select a lower priority study, not on the critical path)
- Willingness of the study team to participate (select a study team that would be more likely to embrace the change)
- Interaction with CROs and other vendors
- Consultation with the internal Quality Assurance group to minimise compliance risks (ensuring appropriate waivers for standard processes are in place)
- Parts of the process to be included in the pilot

The implementation team must work very closely with the pilot study team, providing them with all necessary support as they work through the new process.

Regular feedback from the pilot study and a detailed lessons learned exercise on completion of the pilot is crucial to help the implementation team revise the process. If significant changes are required to the process following the pilot it may be necessary to repeat the pilot on another study.

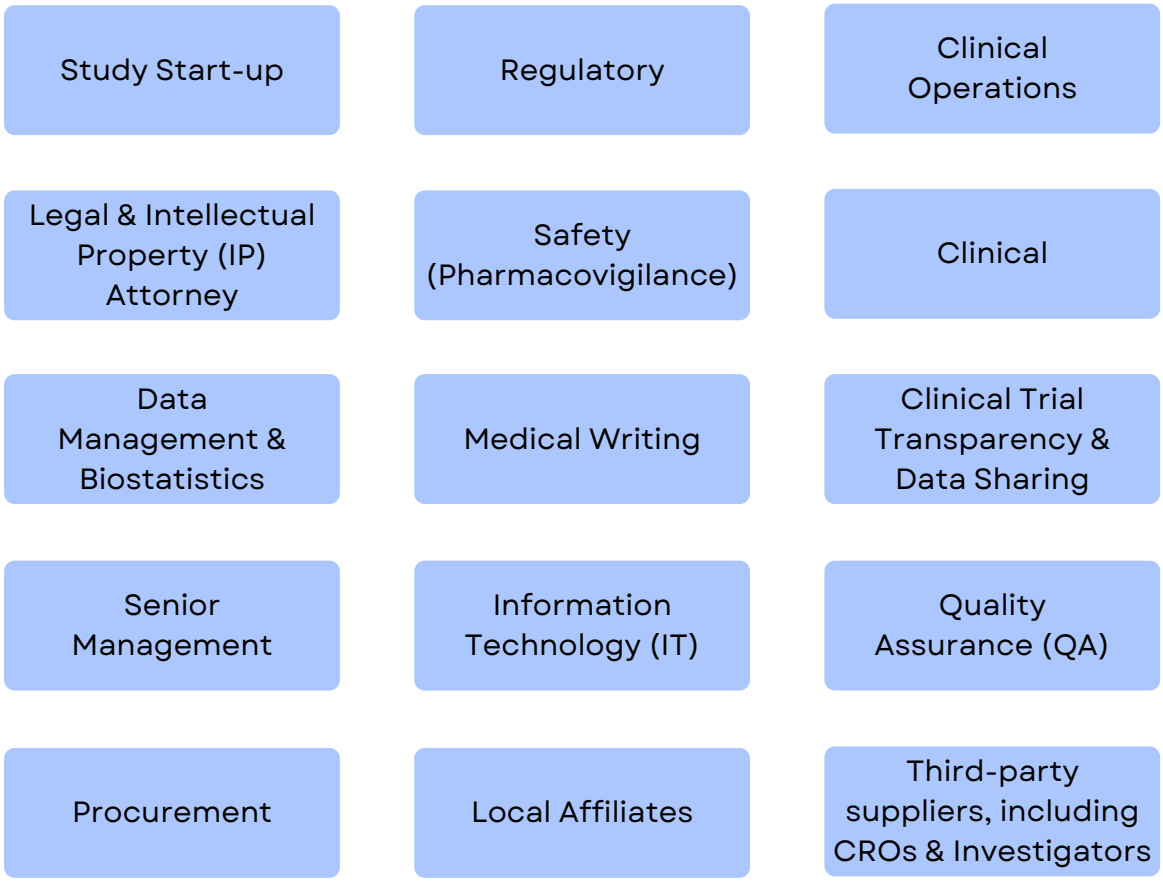
2.4. Implementation

2.4.1. Develop the implementation plan

Once the implementation team is satisfied that the process has been optimised, they should move to full implementation. Key aspects of implementation include:

- Securing necessary approvals and buy in from senior stakeholders
- Updates to Controlled Documents (e.g., SOPs)
- Updates to any contracts or operating practices with vendors (e.g., CROs)
- Developing training material for all impacted stakeholders (see Figure 2 below)
- Developing a comprehensive change management plan
- Aligning with the overall implementation strategy (phased or “big bang”)

Figure 2. Impacted stakeholders



The change management plan is vital for successful implementation. This aspect of the change requires more support and effort than the planning, design, and testing phases. Nevertheless, this aspect of implementation is invariably neglected. The consequences of this are significant, causing quality issues, study delays and frustration within study teams.

2.4.2. Gather feedback and refine the process

The implementation team should remain in place until the new processes have been extensively tested and they have become “business as usual”. Regular feedback should be sought from study teams and process owners. This should inform process “tweaks” or revisions to training materials.

3. The time to act is now

Transitioning to EU CTR 536/2014 can be a daunting task. Now that the regulation has been applied, the countdown to the completion of the transition has begun. Utilising this transition period effectively will be critical for sponsors to achieve compliance by January 2025. This will require sponsors to take a focussed and organised approach. Following the blueprint outlined above to plan, design, test, and implement the change can improve trial sponsors chances of success and bring all impacted stakeholders along the journey.

Reach out to us at info@krystelis.com to discuss your needs related to EU CTR 536/2014 implementation.

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