WHITE PAPER
July 2022

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

1. Introduction

The European Union (EU) Clinical Trial Regulation 536/2014 (EU CTR) became applicable on 31 January 2022, 8 years since it was first published. EU CTR harmonises the management and regulation of clinical trials in the EU and it should make the EU a more attractive place to conduct clinical trials. Benefits 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

EU CTR is, however, considerably different from previous regulations and it will require significant effort from sponsors to transition effectively to the new ways of working.

2. Key differences from the old directive

Differences between EU CTR and the former EU Directive 2001/20/EC (EU Directive) must be carefully considered by sponsors as they adapt their processes to the new regulation (see Table 1)

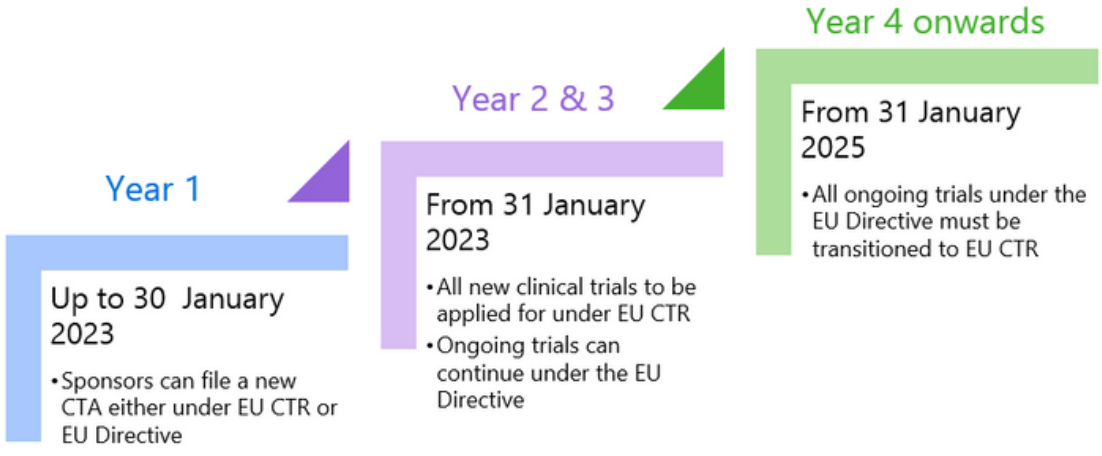
Table 1. Key differences between EU Directive and EU CTR

EU Directive 2001/20/EC	EU CTR 536/2014
Separate Clinical Trial Application (CTA) required for each member state	A streamlined harmonised process for CTAs for all member states
Separate Ethics Committee (EC) review process for each member state	Harmonised process includes EC review
Variable timelines to respond to requests for information (RFIs)	RFI response timeline is fixed to 12 calendar days
Substantial modifications, including the addition of new countries, can be managed in parallel during the review process	No substantial modifications can be made while the review is ongoing
Limited information is made public (includes the main characteristics of the trial and summary of scientific results)	The majority of clinical documents are made public

3. Transition plan

While EU CTR became applicable on 31 January 2022, transition to the new regulation is occurring in phases through January 2025. Sponsors were given 6 months to prepare before the regulation came into effect. Additionally, until 30 January 2023, sponsors can continue to submit CTAs under the EU Directive. Further details of the transition plan are presented in Figure 1.

Figure 1. Transition plan



4. EU CTR requirements: a comprehensive overview

The new regulation supports coordinated assessment and monitoring of clinical trials by member states, including ethics committee (EC) review. Enabling this is the new clinical trial information system (CTIS). This platform is used for CTA submission and review and for sponsors to provide regular updates on the status of clinical trials. Information on CTIS that is made available to the public is accessible through the clinical trials website.

4.1. Trial initiation

Under EU CTR, CTAs comprise 2 parts (Parts I and II) which may be submitted in parallel or sequentially. If the sponsor initially submits Part I, they have up to 2 years from the date of the decision on Part I to submit Part II. If Part II is not submitted within that 2-year period, the CTA will expire and the sponsor will be required to restart the CTA for that clinical trial.

Table 2. Documentation included in Parts I and II of the CTA

Part I	**Part II** (submitted for each member state concerned [MSC] with sites that are intended to recruit patients)
• Cover letter • EU application form • Protocol • Protocol synopsis • Investigator's brochure • Documentation relating to compliance with Good Manufacturing Practice (GMP) for the Investigational Medicinal Product (IMP) • IMP dossier (IMPD) • Auxiliary medicinal product dossier • Scientific advice and Paediatric Investigation Plan (PIP) • IMP labelling content	• Recruitment arrangements • Subject information, informed consent form, and informed consent procedure • Suitability of investigators • Suitability of facilities • Proof of insurance cover or indemnification • Financial and other arrangements • Proof of fee payment • Proof that data will be processed in compliance with EU Data Protection laws

4.2. Trial conduct

Information on specific clinical trial events in each MSC must be updated in CTIS within 15 days of the event occurring. This means that sponsors must develop an effective and efficient process for managing the updating information within CTIS.

Events include:

- Start of trial
- Start of recruitment
- End of recruitment
- End of trial in each MSC, global end of trial
- Temporary halt
- Restart of trial
- Restart of recruitment

Depending on their seriousness, the following safety events must be reported through CTIS within 7 to 15 days of the sponsor becoming aware of the event.

- Unexpected event
- Serious breach
- Urgent safety measure

4.3. Trial documentation subject to publication

More clinical documents are required to be published under EU CTR than any previous regulation. To protect commercially sensitive information, sponsors have the option of deferring the publication of certain clinical documents. Deferral depends on the category of the trial and is subject to approval by the reporting member state (RMS) or MSCs. See Table 3 for the maximum allowable publication deferral for trial categories.

Table 3. Maximum allowable publication deferral for trial categories

	Category 1 trials	Category 2 trials	Category 3 trials
Definition	Phase I, Phase 0, bioequivalence, bioavailability, similarity, and equivalence trials	Phase II Phase III trials	Phase IV Low intervention trials
Maximum deferral option	Up to the time of marketing authorisation or up to 7 years after the end of the trial	Up to the time of marketing authorisation or up to 5 years after the end of the trial	Until the publication of the summary results

Appendix I provides details of publication timelines and deferral options for each applicable document.

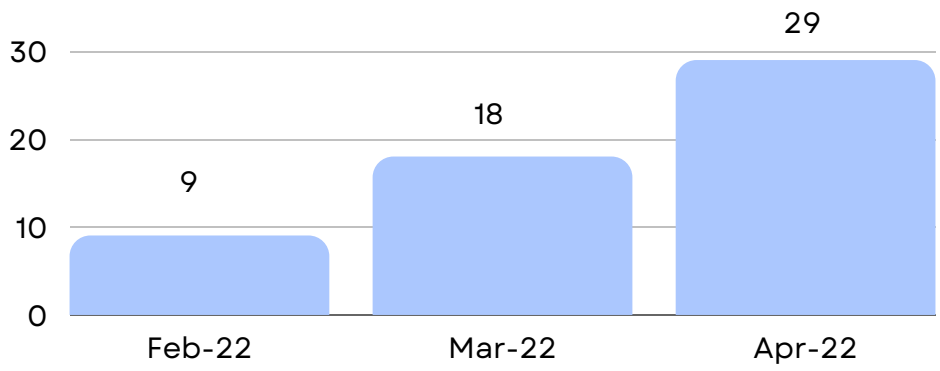
It is important to note that even if a publication deferral is granted, sponsors are still required to submit all documents to CTIS within the specified timelines.

Sponsors can redact personal protected data (PPD) and commercially confidential information (CCI) from documents before they are published. However, this process requires time and resources and may be difficult to achieve under the stringent EU CTR timelines. Sponsors should, therefore, aim to write “disclosure-ready” documents from the start to reduce the effort needed for redaction and anonymisation of sensitive information prior to publishing.

5. Information on EU CTIS utilisation

According to the report 'Key Performance Indicators (KPIs) to monitor the European clinical trials environment' released on 18 May 2022, a total of 56 CTAs were submitted through CTIS between 31 January and 30 April 2022.

Figure 2. Number of CTAs submitted through CTIS

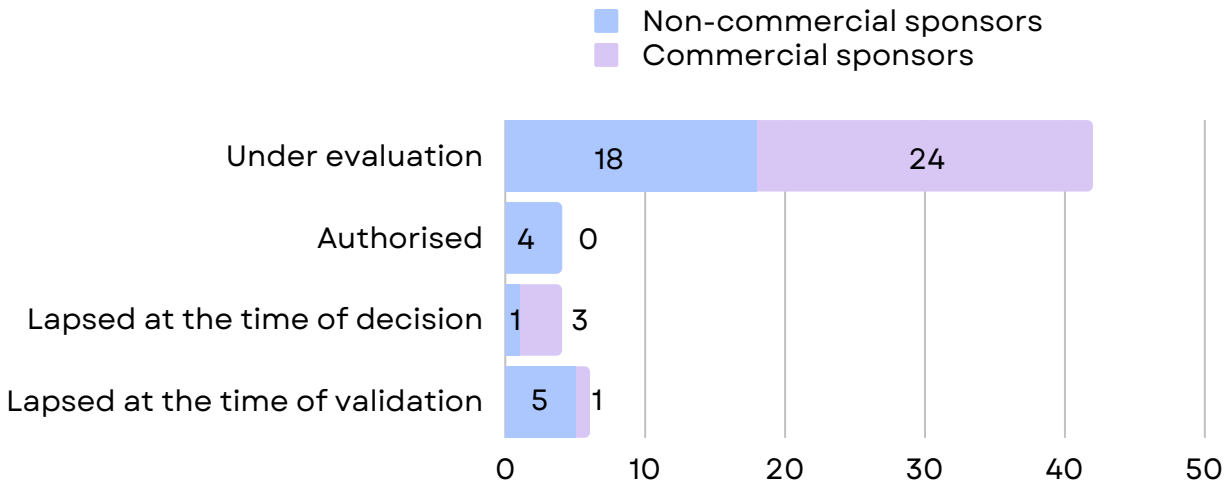


A decision had been made on 4 CTAs:

- All of these were submitted by non-commercial sponsors
- Three were single country trials
- One trial was a Phase II, 2 were Phase III, and 1 was Phase IV
- One trial each was for viral diseases and neoplasms and 2 were for cardiovascular diseases.

As of 30 Apr 2022, the majority of the 56 CTAs submitted remained under evaluation in CTIS. The proportion of CTAs that had lapsed (or had been withdrawn) at the time of validation is high (18%). This perhaps highlights the need for better planning and preparedness for EU CTR by sponsors.

Figure 3. CTA status in CTIS



6. Recommendations for implementation

Fully implementing EU CTR will be a huge undertaking for any sponsor. Initial KPIs indicate that there are gaps in the preparedness of both commercial and non-commercial sponsors. From 31 January 2023, CTAs can no longer be be submitted under the CT Directive. They must follow EU CTR and use CTIS. Sponsors should utilise the remaining time to develop a strong understanding of the new requirements and update internal processes to achieve compliance.

Krystelis recommends that sponsors take a structured approach to implementation. See our white paper "EU CTR 536/2014: A guide to support implementation" for pragmatic advice on how to achieve this in your organisation.

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

Making clinical research crystal clear

Appendix I

Timelines for publication and possible deferral options for clinical documents

Documentation to be made public for each trial under EU CTR	When will it be published?	Possible deferral options
Important dates (e.g., start, end, temporary halt, and termination of the trial)	When each date is submitted (dates must be submitted to CTIS within 15 days of the milestone)	None
Main trial characteristics including WHO ICTRP data fields, cover letter and details of clinical investigators and sites	At the time of decision on the trial	• Category 1 trials: Publication can be deferred for certain fields until the publication of the first summary results* • Category 2 & 3 trials: None
Subject information sheet, including each version and modification that has occurred.	At the time of decision on the trial	• Category 1 trials: Up to the time of marketing authorisation or up to 7 years after the end of the trial • Category 2 trials: Up to the time of marketing authorisation or up to 5 years after the end of the trial • Category 3 trials: None
Protocol and all subsequent amendments	At the time of decision on the trial or submission of an updated document	• Category 1 trials: Up to the time of marketing authorisation or up to 7 years after the end of the trial • Category 2 trials: Up to the time of marketing authorisation or up to 5 years after the end of the trial • Category 3 trials: Until the publication of the summary results
Product specific documents – IMPD S and E sections and investigator brochure	At the time of decision on the substantial modification	• Category 1 trials: Up to the time of marketing authorisation or up to 7 years after the end of the trial • Category 2 trials: Up to the time of marketing authorisation or up to 5 years after the end of the trial • Category 3 trials: Until the publication of the summary results

Documentation that would be made public for each trial under EU CTR	When will it be published?	Possible deferral options
Substantial modifications	At the time of decision on the substantial modification	• Category 1 trials: Until the publication of the summary results • Category 2 & 3 trials: None
• Requests to sponsor on any aspect of the trial • Assessment reports in relation to any aspect of the trial • Conditions for the conclusion on part I or II or decision on the trial.	At the time of decision on the trial or decision on substantial modification, or conclusion on other assessments	RMS to decide whether to defer the publication of the assessment report.
Responses from sponsor in relation to any aspect of the trial	At the time of decision on the trial or substantial modification	• Category 1 trials: Up to the time of marketing authorisation or up to 7 years after the end of the trial • Category 2 trials: Up to the time of marketing authorisation or up to 5 years after the end of the trial • Category 3 trials: Until the publication of the summary results
• Conclusion on Part I, including disagreement on the conclusion of the assessment of Part I by an MSC • Conclusion on Part II • Decision on the trial, or a substantial modification	At the time of decision on the trial	None
Product specific documents	Investigational Medicinal Product Dossier – Quality (IMPD-Q) will not be made public. Instead, the reference to Summary of Product Characteristics (SmPC) will be published	None

Documentation that would be made public for each trial under EU CTR	When will it be published?	Possible deferral options
Clinical trial results summary for an intermediate data analysis**	12 months after the intermediate data analysis date	• Category 1 trials: Up to the time of marketing authorisation or up to 30 months after the end of the trial • Category 2 & 3 trials: None
Clinical trial results summary and lay person summary (plain language summary) at the end of trial**	12 months after the end of the trial in the EU	• Category 1 trials: Up to the time of marketing authorisation or up to 30 months after the end of the trial • Category 2 & 3 trials: None
Clinical study report	30 days after the marketing authorisation decision or application withdrawal	None
Supervisory measures: Serious breaches, inspections (EU and third country), Union Controls, Corrective Measures.	At the time of conclusion on the procedure by the MSC	• Category 1 trials: Until the publication of the summary results unless the trial had to be terminated due to safety reasons. • Category 2 & 3 trials: None
Important notifications related to unexpected events or urgent safety measures during the trial	Once the assessment and/or supervision by the MSC has been completed	• Category 1 trials: Until the publication of the summary results • Category 2 & 3 trials: None

*First summary results are usually published within 12 months of the end of the trial.
**Deferral does not apply to paediatric trials or trials that are part of a paediatric investigation plan (PIP). Sponsors can either partially or fully defer summary results at the interim analysis and at the end of the trial, and the layperson summary at the end of the remaining Category 1 trials. In partial deferral, a redacted version of the summary is made public at its due date and the full summary is posted at the end of the deferral period.