krystelis

November 2023

Riding the CTIS rollercoaster: What is the impact of the new transparency rules?

Contact us at:
info@krystelis.com

Introduction

Over the last two decades, the pharmaceutical industry has experienced a significant tightening of data transparency regulations and policies. As a result, clinical trial sponsors and marketing authorisation holders must make an increasing amount of clinical trial data and documents accessible to the public, while protecting their proprietary information.

The European Medicines Agency (EMA) has driven multiple clinical data transparency initiatives. EMA Policy 0043 caters to the requests for access to any document originated, received, or held by EMA (i.e. reactive disclosure). EMA Policy 0070 requires the publishing of clinical trial data and information for medicines approved for marketing following a centralised marketing authorisation application (MAA). More recently, EMA has introduced the EU Clinical Trial Regulation 536/2014 (EU CTR). This requires sponsors to submit clinical trial application (CTA) documents through an online portal, known as the Clinical Trial Information System (CTIS). Many of the documents submitted to CTIS are made available to the public.

While the EMA promotes transparency, it also recognises the importance of balancing this with the protection of personal data (PPD) and commercially confidential information (CCI). EMA regulations establish processes and expectations for identifying and redacting sensitive information while maximising the data utility of the information within documents. Following a public consultation, EMA has recently revised the EU CTR transparency rules. This paper sheds light on these revisions.

Contact us at:
info@krystelis.com

Background of the Revision

EU CTR became effective in January 2022 and has been implemented for both ongoing and new trials through a phased approach. In May and June 2023, EMA conducted a consultation to gather feedback on EU CTR transparency from CTIS users and the general public. As a result, on 5th Oct 2023, EMA released its revised transparency rules for EU CTR.

Transparency Rules at the Lauch of CTIS

Sponsors currently submit 'For Publication' versions of documents to CTIS which have PPD and CCI redacted. 'Not for Publication' versions of the same documents are submitted for assessment by Member States. In addition to redaction, to further protect CCI, sponsors have been able to request a deferral of the publication of documents (Table 1 below). This deferral delays the publishing of certain clinical trial documents, including the protocol, for up to 7 years after the end of the trial in the EU/EEA.

Table 1: Deferral Options in CTIS

Group	Category 1 (FIH, PK/PD, BA/BE, Biosimilarity)	Category II (Phase II and III)	Category III (Phase IV)
Main Characteristics*	Publication of final summary of results	Not applicable	Not applicable
Notifications*	Publication of final summary of results	Not applicable	Not applicable
Subject Information Sheet	Up to 7 years after the end of the trial in EU/EEA	Up to 5 years after the end of the trial in EU/EEA	Not applicable
Protocol and Scientific Advice	Up to 7 years after the end of the trial in EU/EEA	Up to 5 years after the end of the trial in EU/EEA	Publication of final summary of results
IMPD (S & E) and IB	Up to 7 years after the end of the trial in EU/EEA	Up to 5 years after the end of the trial in EU/EEA	Publication of final summary of results
Responses to RFI	Up to 7 years after the end of the trial in EU/EEA	Up to 5 years after the end of the trial in EU/EEA	Publication of final summary of results
Result Summary for Intermediate Data Analysis*	1.12 months after interim result date 2.Up to 30 months after the end of the trial in EU/ EEA	Not applicable	Not applicable
Result Summary and Lay Person Summary*	1.12 months after interim result date 2.Up to 30 months after the end of the trial in EU/ EEA	Not applicable	Not applicable

*Not applicable if the trial includes pediatric population or is a part of a Pediatric Investigation Plan (PIP)

Adapted from EMA's presentation (CTIS publication rules: How CTIS supports access to clinical trial data) available at https://health.ec.europa.eu/system/files/2021-03/ev_20210309_co23_en_0.pdf

Reasons for the CTIS Transparency Rule Revision

The public consultation revealed some challenges with the current process. These included the complexity of the deferral functionality from information management and data security perspectives and lack of clarity on the applicability of the publication requirements. Feedback also included concerns that sponsors were required to create "for publication" versions of documents that had not been authored with EU CTR in mind and so contained extensive CCI and PPD. The feedback received reflected an Accelerating Clinical Trials in the EU report (ACT EU survey report), which mentioned common issues experienced with CTIS, *"...Numerous technical problems are reported, such as notification to entities that are not participating in the trial, issues when answering to the request for information (RFI), no access to uploaded documents, deferral request disappearing after submission, incorrect timetable calculation, inability to update application..."*

Concerns were also raised by advocates of transparency about the delay of up to 7 years in the publication of key clinical documents and the over-redaction of documents that are published. These may limit the utility of clinical documents for potential consumers of the information – including researchers, patients, healthcare professionals and NGOs.

Revised Transparency Rules

Based on the feedback, EMA has revised the EU CTR transparency rules to be simpler, more efficient, and easier to navigate. EMA will also update CTIS to reflect these rule changes. The new approach will allow more timely access to the information that is most relevant to the public.

What remains the same:

- Categorisation of clinical trials
- The earliest possible timelines for publication of data and documents (when the CTA decision is issued by the Member States Concerned)
- Overriding public interests can be applied to publish information in exceptional circumstances
- Information on applications that did not reach the decision phase (i.e. lapsed or withdrawn or not valid applications), will continue to be exempt from publication
- CTIS acting as provider of data to the WHO International Clinical Trials Registry Platform (ICTRP)

- The information contained in EudraCT for trials that have been authorised under Directive 2001/20/EC (CTD), and published via the EU Clinical Trial Register continues to remain in place
- Transitional arrangements of clinical trials from EU CTD to EU CTR
- EMA can edit the published information on justified grounds (e.g. in the event of accidental CCI disclosure)
- Publication of structured data fields in the CTA remains largely unchanged, except for dose and strength details for some trials, which will no longer be published

What has changed:

- Publication of fewer (redacted) documents of interest (see table below).
- Deferral functionality removed, applicable documents in each clinical trial application (CTA) will be published at the time of CTA decision. Sponsors must therefore rely on redaction to protect PPD and CCI. Protocol and synopsis for Category 1 trials will be published with a final summary of results (see next bullet point for results summary, and Table 2 for publication timings)
- Results summary publication: under the current rules, sponsors can request a deferral to the publication of results of Category 1 trials for up to 30 months after the end of the trial, unless the trial was part of a PIP or involved a pediatric population. Under the new rules, this 30-month period will automatically apply (for paediatric trials this is 6 months). Rules for publishing results summaries of Category 2 and 3 trials remain the same (6 months and 12 months after the end of a trial involving a paediatric or adult population, respectively).

Table 2 lists the changes to the documents that will be published. This is based on the information provided by EMA in Revised CTIS Transarency Rules, published on 05 Oct 2023.

Table 2: Documents Submitted to CTIS and Timing of Publication*

Documents required to be published at CTIS launch (January 2022)

Part I Documents

- Cover letter for the CTA
- Study protocol and synopsis
- Investigator brochure (IB)
- GMP-related documents
- Investigational medicinal product dossier (IMPD) – efficacy and safety
- Drug labels
- Scientific advice
- Summary of product characteristics (SmPC)
- Paediatric investigation plan (PIP) decision

Part II Documents

- Informed consent form and subject information leaflet
- Suitability of investigators and facilities
- Investigators CVs
- Data protection rules
- Proof of insurance or indemnification
- Details on recruitment arrangement
- Compliance with the use of biological samples
- Inspection reports

Documents required to be published based on the revised rules (October 2023)

- Protocol, including synopsis
- Patients facing documents
- Summary of medicinal product characteristics (SMPC)

- Informed consent form and patient information sheet
- Recruitment arrangements, including procedures for inclusion, and advertising material

Timing of Document Publication (October 2023)

- For Category 2 and 3 trials, the protocol will now be published when the first MSC issues the decision. Whereas, previously:
  - For Category 2 trials, sponsors were able to defer the protocol for up to 5 years after the end of the trial
  - For Category 3 trials, the protocol used to be published with the final summary of results
- Final summary of results and a layperson summary will be published when submitted to CTIS - 6 months after the end of the trial (for paediatric trials) and 12 months after the end of the trial (for adult population trials)
- For Category 1 trials, the protocol and summary of results, and a layperson summary will be published simultaneously: 6 months after end of trial (for paediatric trials) and 30 months after the end of trial (for adult population

Documents that will no longer be published (October 2023) after the new rule implementation

- Requests for information (RFI) and RFI responses
- IB in part I of the CTA dossier
- MSs final assessment reports part I and part II
- Decision letters for the CTA
- GCP inspection reports

- Any documents attached to RFI, RFI responses, notifications
- Documents provided with an ad hoc assessment
- Union Control plans and corresponding reports
- Dose and strength details for certain types of trials

What's Next?

EMA has indicated that implementing these changes will take a few months and therefore the launch of the revamped CTIS public portal and application of new transparency rules will most likely apply at the earliest from Q2 2024.

There remain several questions for EMA and sponsors about the changes:

- What happens to clinical documents submitted prior to the revised rules becoming effective? Will documents still be released at the end of the deferral period, or will sponsors have an opportunity to submit updated documents for earlier release to protect their CCI?
- To compensate for the removal of the option to defer publication sponsors may decide to redact documents more extensively. How will EMA control this? Will it require justifications for CCI redaction to be submitted (as it does with EMA Policy 0070)?
- Is there any impact on transitional trials? What would be more efficient: continue to prepare the CTAs in the same manner until the implementation of the revised rules in CTIS, including requesting deferrals, or wait for the implementation of the revised rules?
- The list of documents to be published under the revised rules includes protocol synopsis. Does this refer to the lay synopsis of the protocol, or the scientific synopsis (generally ICH format)? Presently, creating a lay synopsis is recommended, not mandatory. Clarity on this from EMA is needed.
- The list of documents provided by EMA specifies certain documents that will be published under the revised transparency rules. Can sponsors assume that the other documents that are currently required to be published are now exempt from publication (e.g., Investigators' CVs, GMP documents, insurance documents, PIP, scientific advice)?

The goalposts for EU CTR clinical trial transparency are shifting. Stakeholders will need to prepare for this change and adapt their processes accordingly. At this point, many questions remain unanswered, and more concrete guidance from EMA on the new transparency rules is needed. In the meantime, EMA is encouraging sponsors to continue to submit to CTIS under the current guidelines for new and transitional trials. Those of us involved in clinical trial transparency eagerly await the next developments.

krystelis

Making clinical research crystal clear...

Contact us

Reach out to us at info@krystelis.com to discuss your needs related to EU CTR 536/2014 implementation, training, and document/data redaction and anonymisation, EMA Policy 0070 and Health Canada PRCI.

For details of our other services, visit our website, **www.krystelis.com**, or get in touch with:

Pooja Phogat
Co-founder & Co-CEO
+91-9810 889208

Stuart Donald
Co-founder & Co-CEO
+44-7806 565974

info@krystelis.com
www.krystelis.com