# **Making the leap:** Transparency requirements for clinical trials moving from one regulatory framework to another

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**doi:** 10.56012/ghkj9468

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## Abstract
This article discusses the fast-approaching deadline for sponsors to transition ongoing clinical trials in the EU/European Economic Area from the Clinical Trials Directive 2001/20/EC to the Clinical Trials Regulation 536/2014. In particular, the authors discuss the medical writer's crucial role in ensuring that documentation meets the regulation harmonisation and transparency requirements; they also highlight challenges seen when redacting commercially confidential information in the preparation of transition applications.

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## Transitional trials and the imminent deadline

From January 31, 2025, onwards, only the Clinical Trials Regulation (CTR: Regulation [EU] 536/2014)[1] and its delegated acts will apply to clinical trials in the EU. This deadline will mark the end of a 3-year transition period that started when the CTR became applicable in the EU on January 31, 2022. All ongoing clinical trials currently governed by the Clinical Trials Directive 2001/20/EC[2] and expected to continue in the EU/European Economic Area (EEA) after January 2025 must transition to the CTR regulatory framework, per the European Commission guidance for the transition of clinical trials.[3] If such clinical trials have not transitioned to the CTR by that date, they will be considered non-compliant and in breach of the CTR. Sponsors could, therefore, be subject to corrective measures and penalties by member states (MSs) and civil and criminal liability pursuant to Article 77 of the CTR.

Sponsors of those clinical trials expected to continue after this deadline must submit a transition application. It is strongly advised to submit the transition application promptly to ensure sufficient time is given for approval. To help streamline the process for multinational transition applications, MSs will implement, where possible, an expedited, harmonised evaluation procedure as agreed by the Clinical Trial Coordination Group (CTCG)[4] for transitioning trials to the CTR. This expedited procedure is open until October 16, 2024.

### Transitional application preparation

Prior to proceeding with a transition application, the first step is to evaluate if the clinical trial is in line with the principles of the CTR. Early consideration must be given to any document harmonisation requirements for multinational clinical trials. Documents common to all MSs that are covered by the CTR Part I assessment report (e.g., protocol, investigator brochure and investigational medicinal product dossier) are to be either consolidated or harmonised. As per the CTCG guidance,[4] harmonisation means that the respective document(s) are identical and include the same trial procedures across all MSs. Consolidation is when there are substantial differences in the respective document(s) in different MSs but the document itself is identical, i.e., MS-specific issues are outlined within the document text or in an appendix to the respective document. If harmonisation is required, this must be first submitted as a substantial amendment under the Clinical Trials Directive prior to a transition application. The role of the medical writer is of importance here to support the regulatory submission team to ensure that documents meet these requirements prior to transition.

### Transition of a minimum dossier

The transition application is an administrative process. The assessment by MSs is reduced to the minimum to ensure compliance with the CTR rules, including transparency requirements. When transitioning a minimum dossier, teams must prepare redacted versions of the protocol, subject information sheets and informed consent forms in addition to submission of the non-redacted documents already approved by the MS. Box 1 shows the minimum dossier documentation. This is applicable for all trial categories, except category 1 trials, where it is sufficient to provide a redacted version of the protocol only, in line with the revised Clinical Trial Information System (CTIS) transparency rules.[5]

After approval of a transition application, teams must ensure that at the time of the next substantial modification, redacted versions for publication of those documents that are within the scope of the revised CTIS transparency rules (as per Annex I) must replace these minimum dossier documents. Resources must, therefore, be considered not only for the transition application but also the next substantial modification.

## What are the consequences of transitioning a study?

Clinical trials that transition have to comply with the obligations of the CTR. Documents submitted as part of a transition application fall under the transparency requirements and will be made publicly available. The public website[6] has a searchable function that can be used to find detailed information on clinical trials from January 31, 2022, based on the information contained within CTIS.

### Practical consequences of CTIS on transitional studies

This transition has resulted in an increased burden of documentation for sponsors. Effectively managing this documentation presents several challenges. Clear communication and a well-defined understanding of responsibilities are crucial, particularly in strategising redactions and adhering to strict timelines. This is especially important when responding to requests for information, given the limited 12-day maximum response window. A rapid response team, including medical writers, should be available to update documentation to ensure timely translations and appropriate redaction within this strict timeline.

> The transparency rules introduced with CTIS have heightened awareness of the importance of appropriate timing in the disclosure of any full or segmented information related to an active clinical trial.

Although the regulations for the redaction of personally protected data are clear and anchored in the widely recognised General Data Protection Regulation[7] and CTR standards, the scope of commercially confidential information (CCI) redaction poses a significant challenge in the preparation of dossiers for CTIS publication. A collaborative approach involving teams from medical writing, regulatory, transparency, and often legal, is essential, as CCI is unique to each company and often to each product or study. A clear definition of CCI, provided early, enables the medical writing team to draft documents that minimise CCI content. However, protocols and subject information sheets or informed consent forms for active trials transitioning from EudraCT to CTIS are rarely composed proactively with CCI considerations. The most significant hurdle in transitional trials is balancing the risk of over-publication, which could reveal excessive CCI, against over-redaction, which frequently stems from a sponsor's limited comprehension of what constitutes CCI in their documents.

### Short vs. long-term CCI

According to EMA guidance[8] the concept of CCI is time-dependent, with a particular focus on the development phase of the medicinal product used in a clinical trial. The revised CTIS transparency rules[5] have removed the deferral mechanism that allowed sponsors to delay the publication of key clinical trial documents for up to 7 years from the end of the trial in the EU/EEA. In the context of this change, for transitional trials, it is important to differentiate between CCI that is applicable in an earlier development phase at the time of submission of a clinical trial application and CCI during the trial life cycle.

### Publicly available information

Information that is already in the public domain cannot be considered CCI. For this reason, conducting a literature search for publicly available information is a standard part of the redaction process. With transitional trials underway, there is an increased likelihood that data may be prematurely published, particularly on sponsor websites, through conference presentations, and in scientific articles they have published. If the information sponsors wish to redact is even partially available in the public

### Box 1. Minimum dossier documentation

**General documents: form section**

- Cover letter
- Statement of compliance with regulation (EU) 2016/679
- Proof of payment (if applicable)
- EU application form (to be completed in the Clinical Trial Information System portal)

**Part 1 documents**

- Clinical trial protocol (latest harmonised or consolidated version)[a]
- Investigator brochure (latest harmonised or consolidated version)[a]
- Good manufacturing practice relevant documents, e.g., manufacturer's importation authorisation
- Investigational medicinal product dossier (latest harmonised or consolidated version)[a]
- Latest approved version of documents related to non-investigational medicinal products, if applicable

**Part 2 documents**

- Latest approved versions of the subject information sheet(s) and informed consent form(s)[a]

[a] Clinical documents written by medical writing teams that are affected.
Please refer to guidance for the transition of clinical trials, annex 1, for country-specific requirements.[3]

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domain, it can impact the planned redaction strategy for information-dense documents such as the protocol. For example, a dose escalation scheme for one cohort that was presented at a scientific conference and made publicly available as a PowerPoint presentation could compromise the sponsor's intention to protect the overall dose escalation plan as CCI. The transparency rules introduced with CTIS have heightened awareness of the importance of appropriate timing in the disclosure of any full or segmented information related to an active clinical trial.

#### Licence-protected material

The protection that should be applied to service providers (for example vendors for scales and questionnaires) does not fall under CCI, but it is a highly sensitive matter for transitional trials. The EMA recognised the issue[9] and introduced the option for sponsors to upload a placeholder for licence-protected material where the sponsor and the third-party service provider have written agreements in place that expressly establish that patient-facing documents cannot be disclosed publicly. Standard contractual clauses between sponsors and vendor companies usually provide approval for using copies of the vendor's intellectual property for regulatory submissions. Some of the clinical trials transitioning to CTIS signed their contracts with vendor companies before they were aware that all patient-facing material related to study endpoints would become publicly available when the clinical trial was posted on CTIS; considering this, it is unlikely that this provision was included as a standard contractual clause. In essence, vendors agreed that their intellectual property would be reviewed by regulatory authorities, but they may not have been informed or consented to the same material being available to the public. Public disclosure could undermine their economic interest or competitive position; hence, reassessing the vendors standing under these new circumstances is necessary

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#### National requirements

The industry has noted that MSs continue to impose national requirements on submission documentation. This practice has not spared the CTIS transparency rules for transitional trials, even now when a minimum dossier requires a minimum number of documents. For instance, for reimbursement and insurance amounts provided in subject information sheets and informed consent forms, the majority of MSs approve the redaction of such details, while some states require the disclosure of these types of financial agreements. Applying different redaction strategies to the same document types that will all eventually be available on the public CTIS portal as part of the same package cannot be an example of good transparency practice.

#### Improvement

Before the revised CTIS transparency rules became effective, the greatest challenge in protecting personally protected data lay in managing site-level documents, primarily due to the sheer volume of such documentation. These included investigator curricula vitae and site suitability forms that were created using non-standardised templates, and which varied by country or site. The information in these documents often contained unnecessary personal details of investigators and third parties, such as nationality, family status, home addresses, names of mentors and supervisors, personal photographs, and names of site personnel, necessitating extensive redaction. Although a slight improve-

ment was made with the introduction of standardised Part II application document templates,[10] ensuring that sites actually used the EMA template was nearly impossible. With the revised CTIS transparency rules, site-level documents are no longer subject to publication, which has significantly decreased the workload for transparency teams.

## Conclusion

For clinical trials that are expected to continue in the EU/EEA after January 30, 2025, it is advisable that transition applications be submitted at the earliest date to ensure sufficient time for approval. Study teams, including medical writers and transparency specialists, must collaborate to assess the time required to prepare this package, ensure appropriate documentation consolidation and harmonisation, and apply the necessary redactions to comply with the CTR transparency requirements.

## Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employer or EMWA.

## Disclosures and conflicts of interest

The author declares no conflicts of interest.

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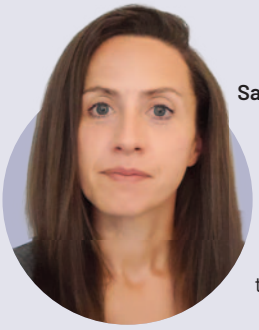

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