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Transitioning Trials to the EU Clinical Trials Regulation

September 2023

Introduction

Demystifying the Complex Transition from EU Clinical Trials Directive to Regulation: A Practical Roadmap and Checklists to Navigate Change and Achieve Compliance.

The transition from the EU Clinical Trials Directive (CTD) to the new Clinical Trials Regulation (CTR) represents a significant shift in how trials will be conducted across Europe. While this overhaul aims to streamline processes, navigating the new rules and systems is complex.

Sponsors and researchers have found dense guidance documents challenging to interpret. How do you update protocols and documents? What are the timelines and requirements? How do new submission processes work?

On July 19, 2023, the EU Clinical Trials Coordination and Advisory Group (CTAG) published guidance to clarify the path forward, adding to prior guidance for transitioning trials from the CTD to the CTR.

These documents are essential reading. But make no mistake — careful planning and coordination will be required. Documents, systems, contracts, and teams will need alignment across countries and institutions.

We have distilled the recommendations into actionable checklists to aid in planning, and our proposed workflow highlights steps to help sponsors navigate the transition process.

Now, let's examine the path forward. The checklists below summarize the process, while the later sections provide additional details and resources.

Transition Checklist

Yes	No	Criteria
☐	☐	Is the clinical trial authorized under the CTD through the EudraCT system?
☐	☐	Does the clinical trial have one or more sites in any EU/European Economic Area (EEA) member state (MS) that will be active *after* **Jan. 30, 2025?** OR Is this an ongoing trial under CTD that requires approval of a substantial amendment, such as adding sites in a new member state? *This assessment considers a site "active" until the Last Patient Out (LPO).*
☐	☐	Does the clinical trial have an expected end date after **Jan. 30, 2025?**
☐	☐	Is the trial NOT a third-country trial?[1] *If the trial is **not** a third-country trial, answer "**Yes**"; if it **is** a third-country trial, answer "**No**."*

If the answer is "Yes" to all four questions, the clinical trial must be transitioned from the CTD to the EU CTR and the clinical trial information system (CTIS).

If the answer is "No" to *any* of the above questions, the clinical trial does NOT need to be transitioned.

Documents Required for Submission

☐ A **cover letter** stating compliance with transition requirements	• The EudraCT Number
	• For mono-national trials:
	  - The name of the ethics committee (EC) that gave the initial CTD opinion
	• For multinational trials:
	  - The name of the ECs that approved the trial in each member state
	  - A table indicating the protocol version approved per member state if a consolidated protocol is used, along with any member state-specific aspects
	  - A list of any non-substantial changes made compared to the approved CTD documents, in line with Annex IV of the Q&A document
	• Dates of protocol approval for each member state
	• Listing of any additional CTD-approved documents submitted beyond the minimum requirements
	• Declarations that:
	  - The documents are approved and aligned across member states, and whether the protocol is fully harmonized or consolidated
	  - The trial remains in line with the original CTD authorization and the requirements for transition trials as set out in the Guidance for the Transition of Clinical Trials from the Clinical Trials Directive to the Clinical Trials Regulation and the CTCG Sponsor Guidance
	
	NOTE: *For further details, see the CTCG cover letter template for applications to transition a clinical trial from CTG to CTR.*

☐ The documents and data required for the **Part I Assessment**	• CTIS structure data required for Part I • Protocol (consolidated or harmonized version) • Investigator's brochure (latest harmonized version) • Full IMPD (latest harmonized version) • Scientific advice • Patient-facing materials related to outcomes • Clinical label proofs • Qualified person good manufacturing practice (QP GMP) certification • Documents related to non-investigational medicinal products (i.e., auxiliary medicinal products under the CTR, if applicable) • Any other documents approved under CTD (e.g., Data and Safety Monitoring Board (DSMB) charter)
☐ The documents and data required for the **Part II Assessment**	• CTIS structure data required for Part II • Informed consent form • Subject information sheet ***NOTE:*** *You may submit additional documentation for the transitioning application provided those documents are assessed and authorized under the CTD. Other documents should not be submitted.*
☐ A **GDPR statement** on compliance with personal data protection laws	

NOTE: Other than the cover letter, GDPR statement, and the CTIS structure data required for Parts I & II, only documents previously approved under the CTD are submitted as part of the transition. Additional documents required by CTR are initially submitted as placeholder documents. Following a successful transition, these placeholder documents are replaced with the completed versions as part of a major amendment.

Documents That Might Not Be Required

Document	Notes
Site Suitability Forms	Do not resubmit these forms for sites approved under CTD in the transition package; afterward, submit for new sites added after the transition.
Annotated eCRF	The annotated electronic case report forms (eCRFs) are not required for the CTA submission. The eCRF is part of the final "full" Clinical Study Report (CSR) that must be uploaded if used in a marketing application.
Investigator CVs	Do not resubmit CVs for investigators previously approved under the CTD in the transition package; afterward, provide CVs using the harmonized template only for investigators added after the transition.
Documents for completed phases	Do not resubmit documents for completed trial phases. (e.g., the recruitment arrangements if recruitment has been completed)
Translations	Only resubmit translations previously approved under CTD.
Product labels for the investigational product	Do not resubmit these labels approved under CTD in the transition package; afterward, submit only for batches that are (re)labeled after the transition.
Insurance/indemnification documents	Do not submit updates. Rely on existing documents approved under CTD unless policies have expired and renewal resulted in substantive changes to coverage.

NOTE: Refrain from submitting documents that are not required since submitted documents may trigger a request for information (RFI).

Workflow Steps

STEP 1 Prepare transition application in CTIS.*

STEP 2 Ensure all pending amendments submitted under the CTD are approved before initiating the transition.

STEP 3 Submit Parts I and II documents previously approved under CTD. For those documents that will be publicly available, submit two versions, one that is not for publication and one for publication where personal data has been anonymized, and company confidential information (CCI) has been redacted.

STEP 4 Include the required cover letter, accuracy statement, GDPR compliance statement, and placeholders for those documents required under CTR but not previously approved under CTD.

STEP 5 Validate and review comments within targeted timelines.

STEP 6 Upon authorization, comply with CTR requirements.

***NOTE:** For multinational trials where one or more documents require(s) harmonization, first submit an amendment to harmonize the documents for approval under CTD and proceed with Step 1 after approval.

Other Considerations

- Plan for documenting remaining items at first substantial modification.
- Plan for a timeline that will allow ample time for validation, assessment, and authorization no later than **Jan. 30, 2025**.[2]
- Track the transition application status for each MS in CTIS.
- Document CTD trial start dates for each MS after CTR authorization and plan to start providing other trial status updates within 15 days.
- Comply with CTR safety reporting, notifications, archiving, etc., after approval of the transition, including providing intermediate study reports and a layperson's summary of the trial results when those are due.
- Develop a process for identifying, redacting, and uploading applicable third-country inspection reports into CTIS for trials started new or transitioned under CTR. Although there is no current deadline for providing these reports, identifying which ones are in scope and defining the review process can be time-consuming.
- Prepare to update the investigational labels for those batches that are (re)labeled after the authorization under the CTR *(if applicable)*.
- Draft withdrawal letter in case urgent amendment is needed before the transition completes (if applicable).
- Submit substantial amendments for any remaining changes needed for full CTR compliance after the initial transition *(if applicable)*.
- Before transition, prepare a list of any urgent safety amendments needed *(if applicable)*.

Please note that it is advised to consult with legal counsel when determining what documents and processes are required to transition trials from the directive to the regulation. While this article is based on guidance, it is not legal advice. This is a summary and does not replace reading and understanding the European Commission/Clinical Trials Coordination and Advisory Group (CTAG) guidance for the transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation from July 19, 2023.

References

- Clinical trials - Regulation EU No 536/2014, April 16, 2014
- Guidance for the transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, European Commission/Clinical Trials Coordination and Advisory Group (CTAG), July 19, 2023
- CTCG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under the Directive 2001/20/EC that will transition to the Regulation (EU) No. 536/2014, Heads of Medicines Agencies (HMA)/Clinical Trials Coordination Group (CTCG), June 27, 2023
- CTCG cover letter template to transition a clinical trial from CTG to CTR, Heads of Medicines Agencies (HMA)/Clinical Trials Coordination Group (CTCG), June 27, 2023

1. A “third-country trial” is a trial that supports an EU pediatric investigation plan (PIP) or an EU marketing authorization application for a pediatric indication and has no trial sites in an EU or EEA member state.
2. The typical maximum timeline for the expedited transition procedure of trials approved under the CTD is expected to be 22 days. However, assessment Part II is decided by member states and may lead to additional days. Allow for the limited resources available at your organization and the health authorities between late December 2024 and mid-January 2025 and the backlog of transition trial submissions in January 2025.

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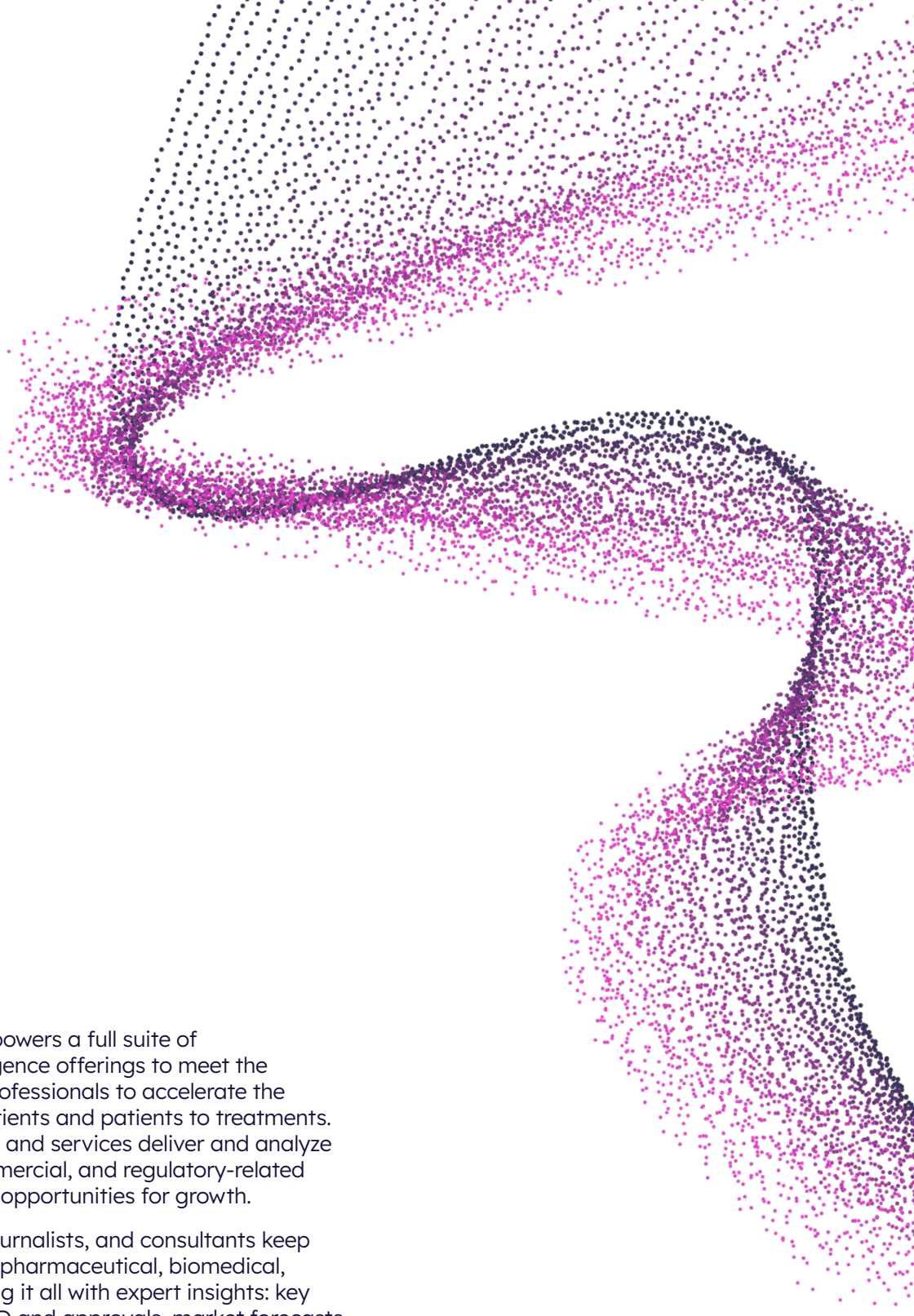

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