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SOP: Transition of Ongoing Clinical Trials from the EU Clinical Trial Directive to the EU Clinical Trial Regulation

March 2024

Purpose

To describe the process for assessing ongoing clinical trials and submitting regulatory applications to transition trials from the EU Clinical Trials Directive 2001/20/EC (CTD) to the EU Clinical Trials Regulation 536/2014 (CTR) using the Clinical Trials Information System (CTIS).

The CTD established the principles for conducting clinical trials of medicinal products in member states of the European Union (EU)/European Economic Area (EEA). The CTD has been replaced by the Clinical Trials Regulation that became applicable on Jan. 31, 2022, though certain legacy trials may remain under the Directive until Jan. 30, 2025.

Scope

This standard operating procedure (SOP) applies to all ongoing interventional clinical trials authorized under the CTD with at least one active site in the EU/EEA as of Jan. 30, 2025, as well as those trials on EudraCT requiring an amendment subject to approval by the member states (e.g., adding sites in a new member state) before Jan. 30, 2025.

Responsibilities

- The Clinical Operations department assesses trials and determines which needs to be transitioned.
- The Regulatory Affairs department is responsible for preparing and submitting the applications to transition trials to the CTR.

See your organization's EMA CTA Submission SOP for additional roles and responsibilities.

Procedure

Assess trials for transition:

1

Assess your organization's ongoing trials on EudraCT. Trials must be transitioned if:

- The trial will have at least one active site in an EU/EEA member state on or after Jan. 30, 2025, where a site is considered active until the Last Patient Last Visit (LPLV) or if trial-specific interventions are ongoing.
  NOTE: Trials that have ended locally in all EU/EEA member states in line with the CTD do not need to be transitioned, even if the global end of the trial has yet to be reached.
- The trial requires an amendment subject to approval by the member states before Jan. 30, 2025, such as adding sites in a new member state.

2

For trials meeting initial criteria, determine if all Part I and II documents have been harmonized across member states or consolidated into a single version reflecting country-specific differences.

3

Categorize trials into two groups:

- Expedited: Single-country or multinational trials where all documents are harmonized, and the protocol is either harmonized or consolidated across member states. The transition of trials eligible for the expedited procedure is expected to be completed within 22 days.
- Not expedited: Multinational trials where the documents are not yet harmonized or consolidated across member states. Based on guidance, unless there are substantial differences (e.g., the trial objectives), it is recommended to consolidate documents such as the protocol, Investigational Medicinal Product Dossier (IMPD), and Investigator Brochure (IB) across member states instead of submitting an amendment to harmonize these.

  However, the appropriate approach should be discussed with the member state's regulatory authorities. While a consolidated version may be acceptable in cases of alignment, sufficient time should be allowed to address any concerns or requests for modifications during the assessment process. If it is not possible to submit consolidated documents, a recent survey suggests planning for at least 100 days to harmonize the documents of a multinational trial to be conservative.

Procedure

Prepare expedited transition applications:

4

For expedited transitions:

- Author, review, and approve a cover letter for the transition application per your organization's EMA CTA Submission SOP
- Prepare a statement on compliance with GDPR on compliance with personal data protection laws in line with the EMA template Statement of Compliance with Regulation (EU) 2016/679 (GDPR)
- In CTIS, enter the required structured data for Parts I and II
- Upload previously approved CTD documents
  - Part I: Protocol, IB, IMPD, Good Manufacturing Process (GMP) docs, non-Investigational Medicinal Product (IMP) info
  - Part II: Informed Consent Forms (ICFs), subject info sheets
- Provide additional previously approved CTD documents if applicable
- Create placeholder documents for those not yet approved under CTD
- Generate the transition application

5

Complete a quality review per your organization's EMA CTA Submission SOP.

6

Submit an expedited transition application by **Oct. 16, 2024**, per EMA guidelines.

7

If the Oct. 16 deadline to submit the transition application is missed, the processes may take longer than 22 days. Additionally, the EMA has an end-of-year "clock stop" for the holidays, expected to last 17 days from Dec. 20, 2024, to Jan. 6, 2025, which will further slow the transition process, though these dates have not yet been confirmed.

Procedure

Prepare non-expedited transition applications:

8

For transitions with non-harmonized documents:

- Follow your organization's EMA CTA Submission SOP to consolidate or harmonize documents across member states
- Once harmonized or consolidated, follow the same steps as expedited transitions

9

If it is required to harmonize instead of consolidating the documents, plan to submit amendments to harmonize trial documents by early **June 2024** to allow up to 120+ days to complete the harmonization process in time to submit the transition application by Oct. 16, 2024, for an expedited review
NOTE: This June due date is not an official deadline; it is simply a recommendation based on the possible duration for approving the harmonized documents. Transitions should be initiated as early as possible to avoid a potential backlog of applications towards the end of 2024.

Monitor and closeout

10

Monitor the transition application status in CTIS to closure

11

Address any validation comments or requests for information (RFI) per your organization's EMA CTA Submission SOP

12

Follow the process in your organization's SOPs to manage updates and amendments, submit additional documents, report results, redact or anonymize data, etc., per the CTR requirements

13

Document closure per your SOPs.

References

The sponsor's EMA CTA Submission SOP

EMA Q&A on the protection of Commercially Confidential Information and Personal Data while using CTIS

EMA Template Statement of Compliance with Regulation (EU) 2016/679 (GDPR)

Clinical trials - Regulation EU No 536/2014, Apr. 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), Dec. 21, 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), Nov. 13, 2023

Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, Heads of Medicines Agencies (HMA)/Clinical Trials Coordination Group (CTCG), March 2024

CTCG cover letter template to transition a clinical trial from CTG to CTR, Heads of Medicines Agencies (HMA)/Clinical Trials Coordination Group (CTCG), Jun. 27, 2023

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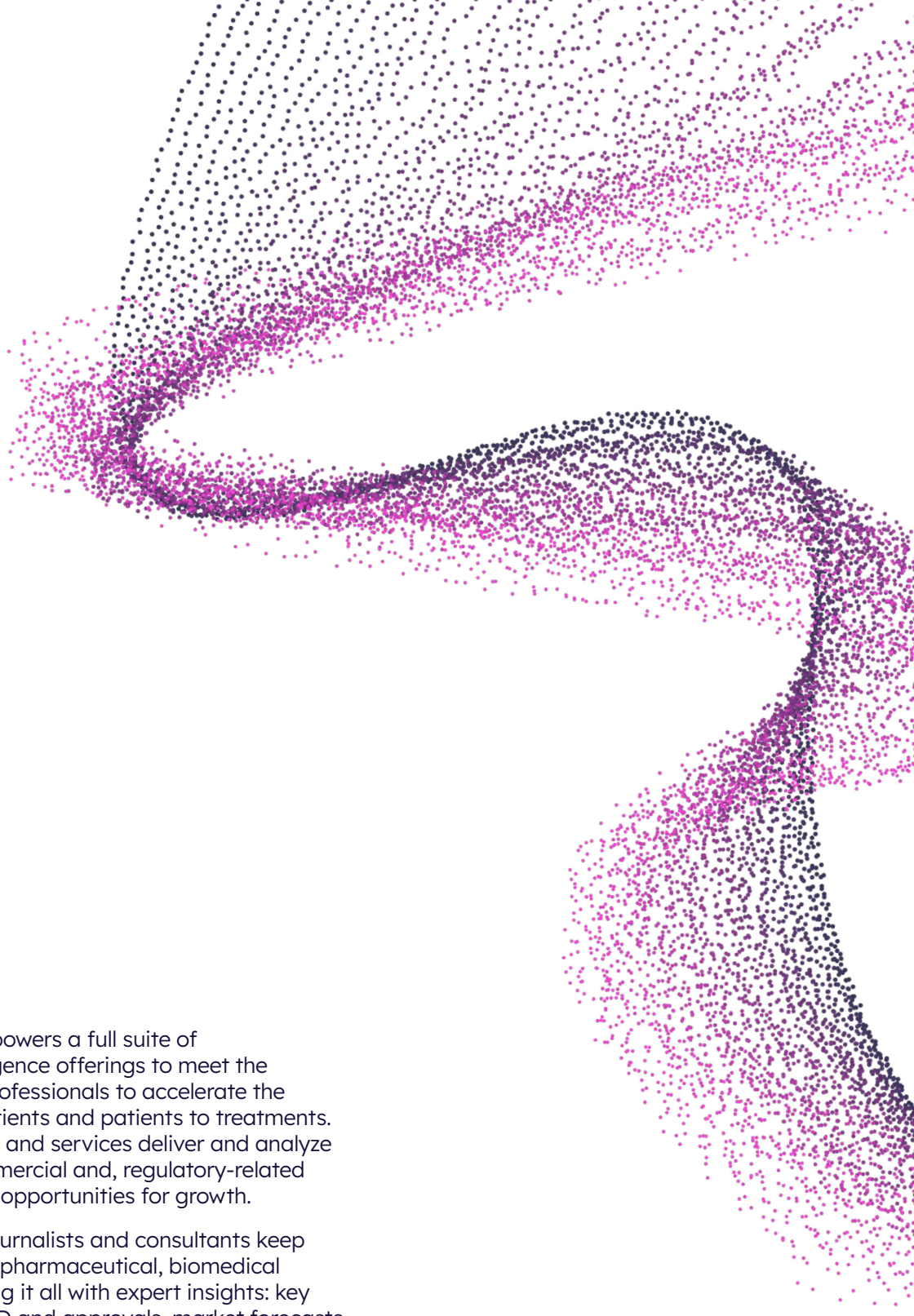

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