Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation

March 2024

Version 3

This Guidance reflects the agreement reached by the National Contact Points and supersedes the chapter 11 of the Q&A on the application of the CTR (version 6.4).

Contents

1. Legal background [NEW]

From 31 January 2025 onwards only the Clinical Trials Regulation (EU) 536/2014 (CTR) and its Delegated Acts will apply, as laid down in Article 98 thereof.

Sponsors are, therefore, requested to transition to the legal framework of the CTR the ongoing clinical trials that are currently under the regime of the Clinical Trials Directive (CTD) and expected to be ongoing after 30 January 2025. This must be done by using the Clinical Trials Information System (CTIS).

Sponsors with clinical trials expected to continue beyond that date must consider the time required for Member States to complete the authorisation procedure, which can take up to three months.

If the clinical trials have not transitioned to the CTR by the end of the transitional period contemplated in Article 98 of the CTR, these trials are to be considered as non-compliant with the CTR and sponsors may be subject to corrective measures by Member States pursuant to Article 77 of the CTR.

The views expressed in the questions and answers reported below are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law.

2. General principles

The transition of clinical trials from the Clinical Trials Directive (CTD) to the CTR is an administrative process. Sponsors have to submit a "**transitioning application**".

The assessment by Member States is reduced to the minimum to ensure compliance with the CTR rules (i.e. transparency, trial category). To facilitate that process, **sponsors are encouraged to register their clinical trials under CTIS at their earliest convenience taking into account the time needed for the approval of the transitioning application**.

As a matter of principle,

- Only documents already assessed under the CTD must be submitted to CTIS. Consequently, these documents will not be reassessed[1];
- no need to update templates;
- no need to create retrospectively a site suitability form[2].

The following questions and answers provide information (i) on the timeline, (ii) on the type of clinical trials that sponsors must transfer to CTIS, and (iii) on the content of the application for mono- and multinational trials.

Clinical trials will be considered regulated by CTR when they will be approved under the CTR on the basis of the transitioning application.

Resources and guidance from the European Medicines Regulatory Network are available on the CTIS website, under the section "Transitioning Trials".

3. Timelines

Article 98 of the CTR outlines the **duration of the transitional period** (i.e., 3 years, **from 31 January 2022 to 31 January 2025).**

Sponsor could start transiting their clinical trials from the CTD to the CTR from the day of the entry into application of the CTR, on 31 January 2022.

Sponsor shall make use of the of the 3-year transitional period without the need to discontinue a clinical trial or put a trial on hold.

The maximum timeline for the expedited transition procedure of minimum dossiers for multinational trials restricted to documents already approved under the CTD is estimated to be maximum 22 days provided that no Requests For Information have to be sent: 10 days (validation phase without Request For Information) + 7 days (assessment phase provided no Request For Information is needed) + 5 days (decision).

Each Member State decides on the assessment of Part II documents. This could delay the notification of whether the transition application is accepted or not by a few days. Timelines in CTIS timetable are maximum timelines considering due dates according to the CTIS

[1] Additional Part I and II documents in Annex I of the CTR already approved by an MSC under CTD will be accepted. Additional Part II documents approved under CTD can also be requested by a MSC in a validation consideration.

[2] Part II documents on site suitability statements are only applicable for new trial sites added via Substantial Modifications for part II after initial transition approval.

implementation of the Regulation (EC/Euratom) No1182/1971 EU. Sponsors should take into account the time necessary for completion of the authorisation procedure, which can take up to 3 months.

Sponsors are strongly advised to submit the transition application early enough before 30 January 2025.

4. What are the clinical trials that must be transitioned from the CTD to the CTR?

Only clinical trials authorised under the CTD with at least one active site in the EU on 30 January 2025 need to transit.

'Active site' in the context of transition trials means that the last visit of the last subject, or other trial-specific interventions with the subject specified in the protocol, will take place after 30 January 2025. Hence, clinical trials with no active sites on and after 31 January 2025 do not need to be transitioned.

Trials that have ended locally in all EU/EEA Member States, in line with the CTD, will not need to be transitioned, even in the case where the global end of trial has not been reached yet[3].

5. What do sponsors need to do to transit a clinical trial?

The transitioning application shall reflect the application that was already approved by an ethics committee and authorised by an NCA under the CTD.

The transitioning application will not be reassessed. The documentation on the basis of which the trial was authorised is already available to the Member State(s).

This excludes the categorisation of the transition trial as a low-intervention clinical trial since this concept was not implemented under the CTD.

After transition to CTR, the sponsor may request via a Substantial Modification Part I application to categorise the clinical trial as low-intervention clinical trial if it fulfills the conditions of Article 2(2)(3) of the CTR.

Sponsors do not need to end or temporarily halt the trials that need to be transitioned.

6. What are the conditions to transition a trial to the Regulation?

Transitioning applications should be in line with the principles of the CTR[4] and the documentary requirements specified in question 7 (mononational trial) and question 8 (multinational trial) below.

It is the sponsor's responsibility to declare in the cover letter that the clinical trial is in line with the requirements for transitioning from CTD to CTR as referred to in this Guidance and in the CTCG Guidance[5].

Member States will check the compliance of the documents during the validation phase and,

[3] For CTD trials that do not need to transition to the CTR, the obligations for result reporting in EudraCT remain in place and, accordingly, EudraCT will remain open for the submission of trial result summaries even after 30/01/2025. This also applies until further notice for non-EU paediatric trials.

[4] Preamble (1) of CTR:" In a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interests of the subjects should always take priority over all other interests."

[5] The CTCG guidance on transition trials can be found on the following website (under "Key documents list", "Transitional trials"): Heads of Medicines Agencies: Clinical Trials Coordination Group (hma.eu)

pursuant to Article 77 of the CTR, may take corrective measure**s** after authorisation if they identify that a trial, does not comply with the Regulation.

Sequential application following Article 11 of the CTR are not allowed when transitioning clinical trials.

Only active clinical trials without any ongoing assessment of documents in any of the EU/EEA countries are eligible for the transition: clinical trials for which a request for a substantial amendment is under assessment are not eligible to the transition until the procedure is completed.

Clinical trials temporarily halted for safety or other reasons can be transitioned when foreseen to continue beyond the end of the transition period. These trials should immediately be notified by the sponsor as halted after transition.

For **multinational** clinical trials**, prior transition:**

- **all documents common to all MSCs** which are covered by the Part I assessment report e.g. protocol, Investigator's Brochure, Investigational Medicinal Product Dossier) will have to be either consolidated or harmonised, as explained in the CTCG best practice for sponsors on transition[5];
- such harmonisation is performed by a request for **substantial amendment under the CTD** before submitting a transitioning application. That request shall specify the intention of the sponsor to transition that clinical trial to the CTR.

7. How shall a sponsor proceed in case of mono-national clinical trials?

The sponsor shall submit an initial application in line with Article 5 of the CTR, which relies on the existing dossier already assessed and authorised by the Member States under the CTD.

The process will require:

- a new cover letter;
- GDPR statement; and
- all application structured data (including translations for Part I such as full and public title, description medical condition, primary and secondary objectives, inclusion and exclusion criteria and primary and secondary endpoints and II) to be completed in CTIS.

For Part I, the latest authorised versions of the following documents need to be provided as a minimum in the transitioning clinical trial application:

- protocol.
- investigator's brochure (IB);
- good manufacturing practice (GMP) relevant documents;
- investigational medicinal product dossier (IMPD); and
- documents related to non-investigational medicinal products (i.e. auxiliary medicinal products under the CTR), (if applicable)[5].

For Part II, the latest authorised versions of the subjects' information sheet(s) and the informed consent form(s) are those documents that are required as a minimum.

The sponsor may submit additional documentation in addition to what is required above for the transitioning application, if these documents were assessed and authorised under the CTD. No other documents should be submitted.

An MSC may raise a validation consideration requiring the sponsor to submit additional, earlier approved Part II documents (limited to those described in CTR Annex I).

Redacted versions of the documents are expected when necessary in compliance with transparency requirements[6].

Besides the minimum set of required documents for Part I and for Part II, it is acceptable that the sponsor:

- uploads a document in the corresponding document slots in CTIS clarifying that this aspect was assessed by NCA and/or ethics committee who has given a positive opinion on the clinical trial under the CTD (and therefore is covered by the conclusion of the assessment under the CTD)
- provides the document as part of the first substantial modification request at its best convenience after the authorisation of the transitioning application (see Question 10). For Part II, there is no need to retrospectively create a site suitability form.

Only the clinical trial sites which are active (See question 4) need to be included in the transition application.

In the cover letter, the name of the ethics committee which has given a positive opinion on the clinical trial under the CTD and the EudraCT number shall be included. It is expected that the ethics committee that carried out the initial assessment has remained responsible for the assessment of substantial amendments in the same trial under the CTD. Where relevant, the sponsor shall submit the name(s) of the ethics committee(s) that approved the latest versions of the documents.

As part of the cover letter for the transitioning application, the sponsor has to declare that the clinical trial is in line with the requirements for transition trials as set out in this Q&A and that the clinical trial is still in line with the authorisation given under the CTD.

The sponsor needs to declare in the cover letter that all documents which need approval and are transitioned have been approved by the MSC prior transition.

8. How should a sponsor proceed in case of multinational clinical trials?

A multinational clinical trial approved under the CTD is a trial conducted in different Member States under the same EudraCT number.

A transitioning application for a multinational trial should only be submitted to those MSCs where the trial has at least one active site (see question 4).

If clinical trials conducted under the same EudraCT number in different Member States are not sufficiently harmonised, a sponsor can chose to harmonise them via substantial amendments under the CTD in order to be able to transition them as one trial under the Clinical Trials Regulation (See CTCG guidance[5)].

Alternatively, [Part I of the application] for trials where full harmonisation of (i) protocol, (ii) Investigator's brochure (IB), or (iii) investigational medicinal product dossier (IMPD) cannot be achieved, a sponsor needs to prepare a consolidated protocol, IB or IMPD reflecting the common core provisions and capturing the differences as regards the nationally authorised trials as explained in the CTCG best practice for sponsors on transition[5]. The consolidated documents must correspond to what is authorised in each of the MSCs.

[6] Note on transparency requirements: revision of the rules is ongoing – consult regularly EMA website to be informed of the adoption of the new rules. Revised CTIS Transparency Rules,

A consolidated protocol, IB, or IMPD does not require a substantial amendment under CTD if it properly reflects the scope and conditions of the authorisations of the clinical trial in each of the MSCs and complies with the CTR. It is the sponsor's responsibility to ensure that the consolidated documents reflect what was authorised in each of the Member States Concerned.

For clinical trials in the Voluntary Harmonisation Procedure (VHP), it is strongly recommended to indicate the Reference NCA (Ref-NCA) as the Reporting Member State (RMS). This applies also to trials that are partly in the VHP. For multinational clinical trials that are outside the VHP, the RMS will be proposed by the sponsor and selected by the MSCs in accordance with the rules established under the Regulation.

In the specific case where the trial would not be active in the Ref-NCA of a VHP- procedure, the sponsor should indicate this clearly in the cover letter of the transitioning application.

The sponsor shall submit an initial application in line with Article 5 of the CTR, which relies on the existing dossier already assessed and authorised by the Member States under the CTD.

The process will require a new cover letter, a GDPR statement and all application structured data (including translations for Part I such as full and public title, description medical condition, primary and secondary objectives, inclusion and exclusion criteria and primary and secondary endpoints and II) to be completed in CTIS. For more information please read the CTCG Best practice guide.

For Part I, the latest authorised versions of the following documents need to be provided as a minimum in the transitioning application:

- protocol (harmonised or consolidated);
- investigator’s brochure (harmonised or consolidated);
- GMP relevant documents;
- IMPD (harmonised or consolidated);
- documents related to non-investigational medicinal products (i.e. auxiliary medicinal products under the CTR, if applicable)[5].

For Part II, the latest approved versions of the subjects' information sheet(s) and the informed consent form(s) are those documents that are required as a minimum in the transitioning clinical trial application.

The sponsor may submit additional documentation in addition to what is required above for the transitioning application, if these documents were assessed and authorised under the CTD. No other documents should be submitted.

An MSC may raise a validation consideration requiring the sponsor to submit additional, earlier approved Part II documents (limited to those described in CTR Annex I).

Redacted versions of the documents are expected when necessary in compliance with the transparency requirements[6].

Except for the minimum set of required documents for Part I and for Part II, it is acceptable that the sponsor:

- uploads a document in the corresponding document slots in CTIS clarifying that this aspect was assessed by the NCA and/or ethics committee who has given a positive opinion on the clinical trial under the CTD (and therefore is covered by the conclusion of the assessment under the CTD);

- provides the document as part of the first substantial modification at its best convenience after the authorisation of the transitioning application (see question 10). For Part II, there is no need to retrospectively create a site suitability form.

Only active clinical trial sites need to be included in the transition application (see question 4).

In the cover letter, the name of the ethics committee which has given a positive opinion on the clinical trial under CTD and the EudraCT number shall be included. It is expected that the ethics committee which carried out the initial assessment has remained responsible for the assessment of substantial amendments in the same trial.

Where relevant, the sponsor shall submit the name(s) of the ethics committee(s) of each of the MS(s) that approved the latest versions of the documents. As part of the cover letter for the transitioning application, the sponsor has to declare that the clinical trial is in line with the requirements for transition trials as set out in this guidance and the CTCG Sponsor Guidance[5] and that the clinical trial is still in line with the authorisation given under the CTD.

The sponsor also needs to declare in the cover letter that all documents which need approval and are transitioned, have been approved by all the MSCs prior transition (see Cover Letter template of the CTCG Best Practice Guidance on transitioning multinational clinical trials[5]).

9. What are the consequences of the transition for a clinical trial?

Clinical trials that were started under the CTD and subject to transition to the CTR will have to comply with the obligations of the Regulation, such as:

- obligations of notification via CTIS;
- safety reporting rules;
- archiving requirement;
- transparency requirements (including deferrals);
- rules for requesting substantial modification and addition of a MS, see Question 11); and
- rules for submitting the summary of results and the clinical study report (CSR).

After authorization of a transitioning application

After authorisation of the transitioned trial in CTIS, the sponsor should notify the day of start of the trial. Sponsors should enter the CTD date not a new one. As for GMP requirements, with the exception of labelling, the Commission Delegated Regulation (EU) 2017/1569 and the Implementing Regulation (EU) 2017/556 on the good clinical practice inspection procedures will become applicable once the trial is approved under the CTR[7].

10. When is a sponsor expected to update trial documents and labels?

The sponsor should bring documents related to the clinical trial in line with the CTR requirements at the first Substantial Modification (Part I and/or Part II).

Documents that have been replaced by a document as referred to in Questions 7 and 8 will need to be submitted as part of the first substantial modification application after the authorisation of the transition application.

[7] For trials authorised under the CTD, Annex 13 remains applicable until 30/1/2025.

For the first substantial modification to the application Part I, the sponsor should complete all elements related to Part I of the dossier.

For the first substantial modification to the application Part II, the sponsor should complete all elements related to Part II of the dossier, with the exception of the site suitability statement which does not need to be retrospectively created.

The sponsor is not requested to upload a new template for documents for procedures in the trial that were already completed, e.g. if recruitment of trial participants has ended.

For the labelling of IMP and AxMP, it is expected that the sponsor updates the label for those batches that are (re)labelled after the authorisation under the CTR. There is no need to pro-actively relabel released IMPs. Old label can still be used after transition for IMP batches manufactured after transition if the new label is not yet approved in an SM Part I application.

11. Can MSCs be added to an ongoing trial after it has been transitioned?

Yes, the sponsor can add a new MSC in line with Article 14 of the CTR once (1) the minimum dossier transitioning application has been submitted and (2) all documentation on Part I has first been completed in CTIS via a Substantial Modification (see Question 7 (mononational) and Question 8 (multinational) above and question 10)[5].

12. What should a sponsor do in case an urgent substantial modification is required after the submission of the transitioning application?

A sponsor should take necessary measures and inform the RMS and other MSCs.

The RMS may decide to speed up the transitioning procedure to allow the sponsor to introduce an application for a substantial modification.

The RMS may also advise the sponsor to withdraw the request for transitioning the trial and submit the request for substantial amendment under the Clinical Trials Directive.

The sponsor can then resubmit the request for transitioning the trial once the decision on the substantial amendment by all MSC under the CTD is issued.

13. What are the applicable transparency requirements?

Documents submitted by the sponsor in the transitioning application fall under the transparency requirements of the CTR and have to be made publicly available.

When transitioning a minimum dossier, the sponsor must prepare redacted versions of the protocol, subject information sheet(s) and informed consent form(s) in addition to submission of the non-redacted documents already approved by the MSCs. This is valid for all trials' categories, except for category one trials, where it sufficient to provide a redacted version of the protocol only, in line with the revised CTIS transparency rules[6]. In place of redacted versions for other parts of the application dossier, the sponsor can upload in CTIS a document mentioning the fact that the document was assessed by the NCA and/or ethics committee and the CTD clinical trial application had received from them a positive opinion.

At the time of the next substantial modification application, redacted versions for publication of those documents that are in scope of the revised CTIS transparency rules (as per Annex I of the said rules) must replace these minimum dossier documents.

Notifications and reports issued under the CTD for an ongoing trial do not fall retroactively under the transparency requirements (e.g., inspection reports, notifications) and do not need to be submitted through CTIS.

Once transitioned, a trial will fully fall under the applicable transparency rules[6] for any new information or document submitted to the system.

14. What are the requirements to refer to clinical trial data collected in clinical trials authorised under the CTD?

Data from a clinical trial under the CTR can only be submitted in a clinical trial application dossier if that clinical trial has been registered prior to its start in a public register which is a primary or partner registry of, or a data provider to, the WHO International Clinical Trials Registry Platform (ICTRP).

For data from clinical trials that started before applicability of the CTR, i.e., under the CTD can only be submitted in a clinical trial application if the clinical trial is registered in a public register which is a primary or partner registry of, or a data provider to, the WHO ICTRP or if the results of the clinical trial have been published in an independent peer- reviewed scientific publication.

These new provisions in the CTR impact data of trials in clinical trial applications that have been submitted under the rules from the Directive, but were not made public (e.g., phase I non-paediatric trials). Depending on the time of authorisation of the trial, Article 25(6) first or second paragraph will apply.

For trials submitted under the CTR that refer to clinical data generated under the CTD, the registration obligation is met for trials that have been registered in EudraCT, even when the data and information are not made public in the EU clinical trials register (e.g., phase I non-paediatric trials)[8].

The CTR accepts trial data submission as part of a clinical trial application only if the referenced

[8] This covers the use of data from phase I trials that ended before the end of the transitional period conducted solely in adults and UK was the only Member State in the trial (before Brexit). A waiver of Art 25(6) for non-phase I trials authorised under the CTD and being transitioned to CTR is not possible.

trial was registered publicly, including in the EU Clinical Trials Register (or, for trials that started before the CTR started to apply, the results have been published in a peer- reviewed journal. If a referenced trial is not registered in an ICTRP database or the results are not published, the data cannot be used to support a clinical trial application in the EU under the CTR, irrespective of whether it is a phase 1 trial in adults or not.

The main characteristics of trials including WHO International Clinical Trials Registry Platform data fields, will be published at the time of decision on the trial application, independent of the phase of the trial.

Annex I. Overview of requirements dossier part II for a transitioning CT application in the first administrative transition step [NEW]

Transition trials do not have to be re-assessed because the clinical trials are already authorised under CTD and ongoing.
An expedited administrative procedure without re-assessment is set up. The procedure for transition is limited to a validation procedure checking the minimum set of documents required for transition.

For all EU/EEA countries, the latest authorised version(s) of the subject information sheet and informed consent form have to be submitted for Part II of the Transitional Application.
MS can request additional Part II documents in the validation step.

The table below provides an overview of the documents that Member States request for Part II of the Transitional Application when clinical trials have to transition from CTD to CTR. No additional part II documents should be submitted. The documents outlined in the table below are only the **latest version(s)** of documents that were **already assessed** when the clinical trial was **authorized** under the CTD.
The table has to be considered as a living document as work is still ongoing to complete the rows for the missing countries.

	• Subjects' information sheet(s) • Informed consent form(s).	• Documentation on the damage compensation trial participants (insurance reference/certificate/other arrangements)	For all other part II documents, sponsors can upload on CTIS placeholder documents with a statement clarifying that this aspect was already assessed and approved under CTD.
AT	Yes	No	Yes
BE	Yes	No	Yes
BG			
CY	Yes	No	Yes
CZ			
DE	Yes	No	Yes
DK	Yes	No	Yes
EE			
EL			
ES	Yes	No	Yes
FI	Yes	No	Yes
FR	Yes	No	Yes
HR			
HU	Yes	No	Yes
IE	Yes	No	Yes
IS			
IT	Yes	No	Yes
LI	Na*	Na*	Na*
LT	Yes	No	Yes

LU	Yes	No	Yes
LV	Yes	No	Yes
MT			
NL	Yes	No	Yes
NO	Yes	No	Yes
PL	Yes	Yes	Yes
PT	Yes	No	Yes
RO			
SE	Yes	No	Yes
SI			
SK	Yes	No	Yes

**NA: not applicable (no CTD trials is ongoing in the MS)*

The table was endorsed by the National Contact Points (CTAG).