

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

19 July 2023

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

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The transition of clinical trials from the CTD is an administrative process following which the assessment by MS is reduced to the minimum required 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 applications¹.

As a matter of principle,

- what was already assessed will not be reassessed²;
- no update of templates is needed; and
- no need to retrospectively create a site suitability form³.

The following questions and answer provide information on the type of clinical trials that sponsors have to transfer to CTIS, on the timeline and on the content of the application for mono- and multinational trials.

Clinical trials will be considered regulated by CTR when they will be authorised under the CTR by a first MS on the basis of a transition application.

1 WHAT ARE THE CLINICAL TRIALS THAT HAVE TO 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 be transitioned. 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. This means that clinical trials with no active sites do not need to be transitioned. Trials that have ended locally in all EU/EEA MSs, 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 yet⁴.

2 WHEN DO CLINICAL TRIALS HAVE TO BE TRANSITIONED?

The transition of clinical trials from the CTD to the CTR is open to sponsors:

¹The 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: 10 days (validation phase without RFI) + 7 days (assessment phase provided no RFI is needed) + 5 days (decision).

Note: Assessment Part II is decided per MS, which could lead to additional days before transition is accepted (notification/decision). Timelines in CTIS timetable are max timelines taking into account due dates according to the CTIS implementation of the Regulation (EC/Euratom) No1182/1971 EU.

² 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.

³ Part II documents on site suitability statements are only applicable for new trial sites added via SM part II after initial transition approval.

⁴ 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. An application to transition a CTD trial only needs to be submitted to those MSCs where the trial is ongoing (i.e., has active sites in that MS on 30/1/2025).

- from the day of the entry into application of the Regulation, on **31 January 2022**
- until the end of the 3-year transitional period, on **30 January 2025**, without the need to discontinue a clinical trial or put a trial on hold.

Sponsors should however take into account the time necessary for completion of the authorisation procedure under Chapter 2 of the CTR and this guidance. Therefore, the sponsor is strongly advised to submit the application early enough before 30 January 2025.

3 WHAT DO SPONSORS NEED TO DO TO TRANSIT A CLINICAL TRIAL?

Clinical trials will transit to the CTR upon submission of a “**transitioning application**”.

The transitioning application shall reflect the application that was already approved by an ethics committee and authorised by an NCA under the CTD⁵.

4 WHAT ARE THE CONDITIONS TO TRANSITION A TRIAL TO THE REGULATION?

Transitioning applications should be in line with the principles of the CTR⁶ and the documentary requirements specified in question 5 (mononational trial) and question 6 (multinational trial) below.

It is the sponsor's responsibility to assess this compliance and 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 Guidance⁷.

MSs will check the compliance of the documents during the validation phase and may take **corrective measures**⁸ 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 (see Question 1) **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**:

⁵ The transitioning application will not be reassessed - the documentation on the basis of which the trial was authorised is already available within the MS(s).

⁶ 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.”

⁷ The CTCG guidance can be found on the following website (under “Key documents list”, “Transitional trials”): [Heads of Medicines Agencies: Clinical Trials Coordination Group \(hma.eu\)](https://hma.europa.eu/hma/heads-of-medical-agencies-clinical-trials-coordination-group)

⁸ Article 77 of the CTR

- **all documents common to all MSCs** which are covered by the Part I assessment report) **other than the protocol have to be harmonised.** (e.g., Investigator's Brochure, Investigational Medicinal Product Dossier);
- 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.
- regarding the protocol, a **harmonised protocol approved under the CTD or a consolidated protocol**⁹ is needed.

5 HOW SHALL A SPONSOR PROCEED IN CASE OF MONO-NATIONAL CLINICAL TRIALS?

The sponsor shall submit an initial application¹⁰, which relies on the existing dossier already assessed and authorised by the MS under the CTD. The process will require a new cover letter, GDPR statement and all application structured data (Part I 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).

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).

⁹ A harmonised protocol is one that includes identical trial procedures in all MSs approved across EU/EEA, whereas a consolidated protocol is one in which there are differences in procedures across MSs, but the protocol document itself is identical

A consolidated protocol is feasible where the following aspects are the same across MSC: EudraCT number, trial title, protocol version number, primary objective, primary endpoint, and definition of end of trial. Also, the main inclusion and exclusion criteria should be the same. Non substantial MS-specific issues are outlined within the protocol or in an appendix to the protocol. See updated guidance for sponsors on transition of multinational trials at [HMA website](https://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Best_Practice_Guide_for_sponsors.pdf) under CTCG key documents, guidance https://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Best_Practice_Guide_for_sponsors.pdf and template cover letter https://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Cover_letter_template_Best_Practice_Guide_for_sponsors.pdf

¹⁰ Article 5 of the CTR

Redacted versions of the documents are expected when necessary in compliance with transparency requirements (See also question 11 below)¹¹

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 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 8). For Part II, there is no need to retrospectively create a site suitability form.

Only the clinical trial sites which are active (see Question 1) 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.

6 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 MSs 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 1).

If clinical trials conducted under the same EudraCT number in different MSs are not sufficiently harmonised, a sponsor needs to harmonise them via substantial amendments under the CTD in order to be able to transition them as one trial under the Clinical Trials Regulation¹².

¹¹ Note on transparency requirements: revision of the rules is ongoing – consult regularly EMA website to be informed of the adoption of the new rules.

¹² See guidance for sponsors on transition of multinational trials at [HMA website](https://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Best_Practice_Guide_for_sponsors.pdf) under CTCTG key documents, guidance https://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Best_Practice_Guide_for_sponsors.pdf and https://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Cover_letter_template_Best_Practice_Guide_for_sponsors.pdf

Alternatively, for trials where full harmonisation of the protocol to be submitted in the Part I of the application cannot be achieved due to different national requirements, a sponsor needs to prepare a consolidated protocol (reflecting the common core provisions and capturing the minor differences as regards the nationally authorised trials¹⁰). The consolidated protocol must correspond to what is authorised in each of the MSCs.

A consolidated protocol does not require a substantial amendment 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 a consolidated protocol reflects what is authorised in each of the MSs.

For clinical trials in the Voluntary Harmonisation Procedure (VHP), it is strongly recommended to indicate the Reference NCA (Ref-NCA) as the 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 application¹³ which relies on the existing dossier already assessed and authorised by the MSs. The process will require a new cover letter, a GDPR statement and all application structured data (Part I 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 application:

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

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).

¹³ Article 5 of the CTR

Redacted versions of the documents are expected when necessary in compliance with the transparency requirements (See also Question 11 below)¹⁴

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 8). For Part II, there is no need to retrospectively create a site suitability form.

Only active clinical trial sites (see Question 1) 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 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 Guidance¹⁵ 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 trials¹⁶.

7 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 even if these are not included in the protocol, such as:

- obligations of notification via CTIS;
- safety reporting rules;
- archiving requirement;
- transparency requirements (including deferrals);

¹⁴ Note on transparency requirements: revision of the rules is ongoing – consult regularly EMA website to be informed of the adoption of the new rules.

¹⁵ https://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Best_Practice_Guide_for_sponsors.pdf

¹⁶ https://www.hma.eu/fileadmin/dateien/HMA_joint/00-About_HMA/03-Working_Groups/CTCG/2023_07_CTCG_Cover_letter_template_Best_Practice_Guide_for_sponsors.pdf

- rules for requesting substantial modification and addition of a MS, see Question 9); and
- rules for submitting the summary of results and the clinical study report (CSR).

Decision on a transition application can technically be **tacit**. However, such a tacit Part II conclusion is not in line with the expedited CTD procedure for the transition of minimum dossiers restricted to documents approved under the CTD, since this would contradict the shortened timelines for approval of the transition trial.

After authorisation of the transitioned trial in CTIS, the sponsor should notify the day of start of the trial under the Directive (CTD start date before the CTR authorisation date is technically possible in CTIS), indicating the date of start for every MSC in CTIS.

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 CTR¹⁷.

8 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 5 and 6 will need to be submitted as part of the first substantial modification application after the authorisation of the transition application. 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 upload of new template documents for procedures in the trial already completed, e.g. if recruitment of trial participants has ended, is not required.

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.

9 CAN MSCs BE ADDED TO AN ONGOING TRIAL AFTER IT HAS BEEN TRANSITIONED?

Yes, the sponsor can add a new MSC¹⁸ once all documentation on Part I has first been completed in CTIS, via a Substantial Modification after the minimum dossier transition application (see question 5 (mononational) and question 6 (multinational) above and question 8)¹⁹.

¹⁷ For trials authorised under the CTD, Annex 13 remains applicable until 30/1/2025.

¹⁸ Article 14 of the CTR

10 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 under the Regulation.

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.

11 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 (see Questions 5 and 6), 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. In place of redacted versions for other parts of the application dossier, a document referring to the NCA and/or ethics committee who assessed and gave a positive opinion on the clinical trial under the CTD can be uploaded in CTIS²⁰.

At the time of the next substantial modification application redacted versions for publication must replace these minimum dossier documents.

Notifications and reports issued under the CTD for an ongoing trial do not fall retroactively under the transparency requirements²¹ (e.g., inspection reports, notifications) and do not need to be introduced into CTIS.

Any new notification as of the moment of the transition of a trial will fully fall under the transparency rules of the CTR (including deferrals) for making certain documents publicly available.

¹⁹ [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](#)

²⁰ Proposed statement: "Assessed by  NCA and/or ethics committee  who gave a positive opinion on the clinical trial under the CTD, covered by the conclusion of the assessment under the CTD".

Note on transparency requirements: revision of the rules is ongoing – consult regularly EMA website to be informed of the adoption of the new rules.

²¹ Appendix on transparency rules to the Functional Specifications of the EU clinical trials portal and database (europa.eu) EMA/228383/2015

12 WHAT ARE THE REQUIREMENTS TO REFER TO CLINICAL TRIAL DATA COLLECTED IN CLINICAL TRIALS AUTHORISED UNDER THE CTD?

Data from a clinical trial can only be submitted in an 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, it is acceptable as well that 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 CTAs 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)²².

The CTR accepts trial data submission as part of a CTA only if the referenced 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 marketing authorisation 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 ICTRP data fields, will be published at the time of decision on the trial application, independent of the phase of the trial.

²²This 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 MS 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.