FAMHP webinar on transition of Clinical trials from CTD to CTR

June 13, 2024

Research and Development Division
Directorate General PRE authorisation

famhp
federal agency for medicines and health products

.be

Practicalities about the webinar

Bear-in-mind practicalities

- ❑ All participants are **muted** during presentations
- ❑ **Chat** option is **disactivated**
- ❑ During presentation part we will provide answers to the **questions on transition** raised in advance via **SLIDO**
- ❑ You will have the opportunity to raise additional questions/requests for clarification **orally** at the end of the session
- ❑ For this, **please raise your hand** => we will unmute you and give you the possibility to switch your camera on
- ❑ Webinar is recorded
- ❑ Slides and recording will be available on the FAMHP website after the event

Overview

- ❑ Introduction and state of the play in Belgium.
- ❑ Where can I find more information on how to transition trials to CTIS?
- ❑ Answers to the SLIDO questions.
- ❑ New important information.
- ❑ Questions and answers.
- ❑ Conclusion.

Introduction and state of the play in Belgium

- Starting from January 31, 2025, only the **Clinical Trials Regulation (EU) 536/2014 (CTR)** will apply as regular framework for clinical trials in EU.

- **Clinical trials (CTs)** authorised under the **Clinical Trials Directive (CTD)** that are expected to continue (with at least one active site in the EU) beyond January 30, 2025 need to be transitioned to the **Clinical Trials Regulation (CTR)**.

- A transition dossier must be submitted through the European Portal CTIS.

Introduction and state of the play in Belgium

- Transition is an administrative accelerated process.

- However, sponsors are encouraged to submit their transition application as soon as possible and not later than October 16, 2024.

- CTD trials still ongoing and not transitioned at the end of the transition period will be considered **non-compliant and in breach with CTR.**

Introduction and state of the play in Belgium

What if a still ongoing trial is not transitioned to the CTR after January 30, 2025?

- CTD trials still ongoing and not transitioned at the end of the transition period will be considered **non-compliant and in breach with CTR.**
- This could trigger a GCP **inspection** (CTR article 78).
- Member states can apply CTR article 77 related to **corrective measures** (revocation or suspension of the authorisation of a clinical trial).
- Member states could also apply articles 94 and 95 of CTR respectively on **penalties** and on investigators' and sponsors' **liability.**

Introduction and state of the play in Belgium

- Number of clinical trial applications submitted for transition since CTR entered into force.
  - 2022: 23.
  - 2023: 174.

- Contact persons of non-commercial trials for which no end of trial notification was received: contacted by FAMHP by e-mail on November 3, 2023 about the need to transition to CTR if their clinical trial is expected to be ongoing on January 31, 2025.

  → A considerable amount of delivery failure notifications received due to e-mail addresses no longer in use (please verify whether you have trials expected to be ongoing on January 31, 2025).

Introduction and state of the play in Belgium

- Excel list containing EudraCT number of all clinical trials under Directive expected to be ongoing on January 31, 2025 provided by EMA on February 1, 2024, based on following assumptions.
  - ❑ Authorisation date = Most recent date between NCA decision date and EC opinion date.
  - ❑ Assumed starting date = Six months after authorisation date or one year after CTA load date.
  - ❑ Estimated duration = Estimated duration in member state concerned according to information provided in clinical trial application or, in case not filled in, in all countries.
  - ❑ Estimated completion date = Assumed starting date + Estimated duration + Additional eighteen months as suggested by CTCG.

  → **912** clinical trials to be transitioned within one year before January 31, 2025 in Belgium.

Introduction and state of the play in Belgium

- 364 clinical trial applications for transition submitted in 2024 (until June 9, 2024).

- End of trial notifications received for Directive trials also have an impact on the number of clinical trials expected to be ongoing on January 31, 2025.

- Number of clinical trials expected to be submitted for transition to CTR before January 31, 2025 decreased from **912** on February 1, 2024 to **± 500 - 525** by June 9, 2024.

Where can I find more information on how to transition trials to CTIS?

FAMHP website

https://www.famhp.be/en/eu_regulation_5362014

Transition of clinical trials from CTD to CTR

Which clinical trials need to be transitioned to CTR/CTIS ?

From 31 January 2025, all trials will be running according to the Clinical Trials Regulation (CTR) 536/2014 rules.
Clinical trials authorised under the Clinical Trials Directive (CTD) that are expected to continue beyond 30 January 2025 need to be transitioned to the CTR.

What is the deadline for transitioning trials to CTIS ?

Trials that need to be transitioned should be submitted early enough in advance in CTIS to allow sufficient time for the administrative transition process.
Our advice is to submit transition trials at the latest by 16 October 2024 as stated in the communication from the European Medicines Agency (EMA) available here.
Additionally, if applicable, when submitting a final CTD substantial amendment to enable transition to CTR, sponsors are asked to clearly state this in the first section of the cover letter.

Where can I find more information on how to transition trials to CTIS ?

Please consult section related to transition trials on the Clinical Trials, Guidance and Q&As page on the EMA website.
A video recording of the EMA CTIS training event for non-commercial sponsors transitioning clinical trials to the Clinical Trials Regulation is available.

The video recording from the February 9, 2024 EMA event on transition for non-commercials provides some guidance, including a demo.

Additional videos on transition prepared by EMA available: video 1 and video 2.

Where can I find more information on how to transition trials to CTIS?

EMA website

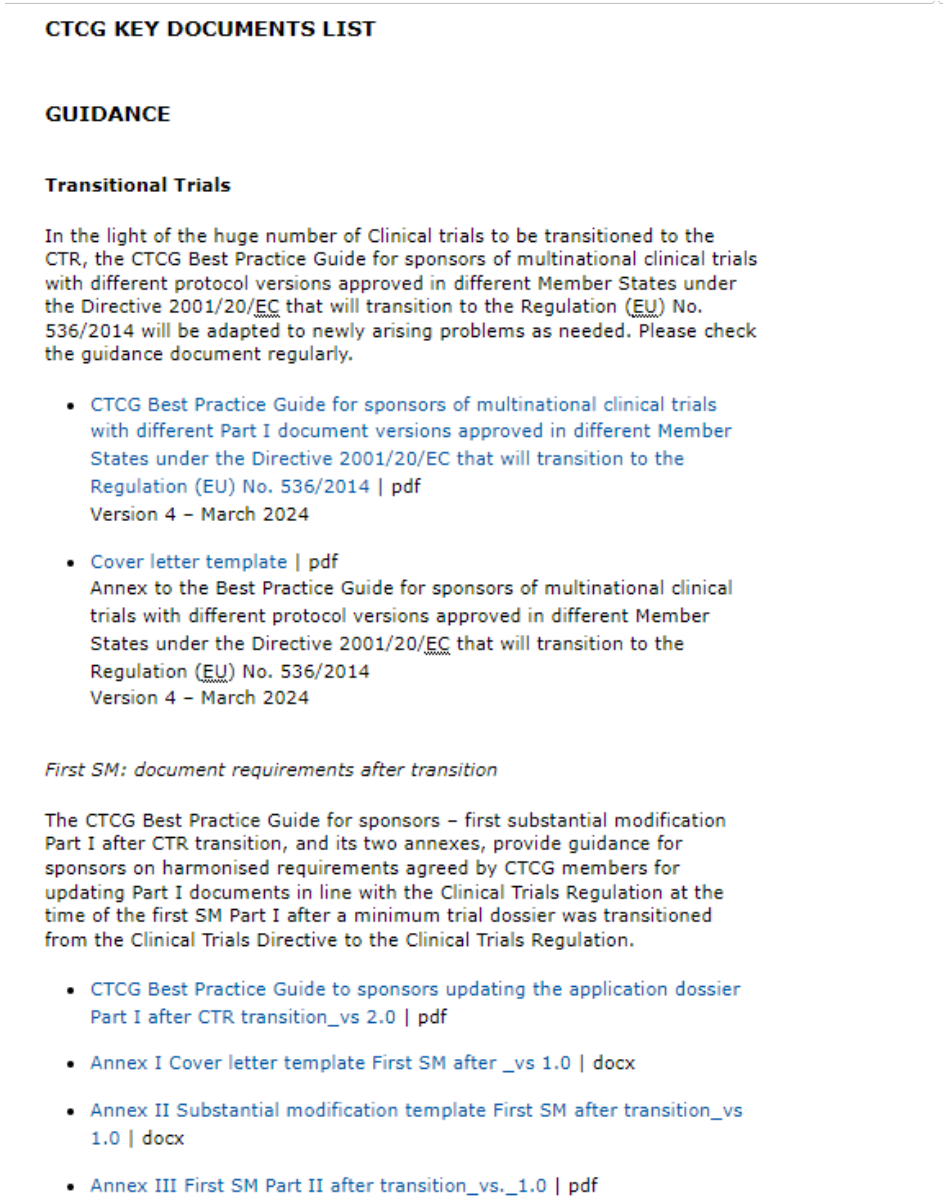
https://euclinicaltrials.eu/guidance-and-q-as/?lang=en#qas-transitioning

Transitioning trials

- **Which clinical trials need to be transitioned to CTR/CTIS?**
- **What is the deadline for transitioning trials to CTIS?**
- **How can I create and submit a transitional trial in CTIS?**
- **Where can I find more information on how to transition trials to CTIS?**

Where can I find more information on how to transition trials to CTIS?

CTCG website



CTCG KEY DOCUMENTS LIST

GUIDANCE

Transitional Trials

In the light of the huge number of Clinical trials to be transitioned to the CTR, the 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 will be adapted to newly arising problems as needed. Please check the guidance document regularly.

- CTCG Best Practice Guide for sponsors of multinational clinical trials with different Part I document versions approved in different Member States under the Directive 2001/20/EC that will transition to the Regulation (EU) No. 536/2014 | pdf
  Version 4 – March 2024
- Cover letter template | pdf
  Annex to the 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
  Version 4 – March 2024

First SM: document requirements after transition

The CTCG Best Practice Guide for sponsors – first substantial modification Part I after CTR transition, and its two annexes, provide guidance for sponsors on harmonised requirements agreed by CTCG members for updating Part I documents in line with the Clinical Trials Regulation at the time of the first SM Part I after a minimum trial dossier was transitioned from the Clinical Trials Directive to the Clinical Trials Regulation.

- CTCG Best Practice Guide to sponsors updating the application dossier Part I after CTR transition_vs 2.0 | pdf
- Annex I Cover letter template First SM after _vs 1.0 | docx
- Annex II Substantial modification template First SM after transition_vs 1.0 | docx
- Annex III First SM Part II after transition_vs._1.0 | pdf

Where can I find more information on how to transition trials to CTIS?

Upcoming EMA events

CTIS walk-in clinics (livestream events) for stakeholders on 10 July, 18 September, 20 November

[Clinical Trials Information System (CTIS): walk-in clinic – September 18, 2024]

[Clinical Trials Information System (CTIS): walk-in clinic – July 10, 2024]

Answers to the SLIDO questions

Question
Can IMPD-Q only trial(under CTD) be fully transitioned by the sponsor? MAH prefers no IMPD-Q only submission anymore, also not at the time of first SM in CTIS.

Answer
A transition dossier is always a CTD authorised clinical trial full dossier (part I + part II).

The IMPD-Q only application is a new concept introduced in CTIS. This workaround is proposed when sponsor is not the product owner as it is currently impossible to submit a part of a dossier in CTIS that would not be accessible to the CT sponsor.

The IMPD-Q only (part I only) application cannot be authorised in CTIS and must always be linked to a clinical trial application that can be authorised.

The IMPD-Q only submitted in parallel at the time of the first SM is currently necessary if no trial from the product owner with the same IMPD is already available in CTIS (in a new submitted trial or in a CTD transitioned trial).

Answers to the SLIDO questions

Question

What if the sIMPD makes reference to an IMPD of a Clinical Trial which will never transition to CTR? Can we transition as such? What needs to be done at first SM?

Answer

IMPDs that have not been transitioned or uploaded in CTIS officially 'do not exist' outside CTIS, therefore either include the original IMPD in the trial with the sIMPD or upload it separately as an IMPD-Q. This can be done during the first SM.

Answers to the SLIDO questions

Question

Transitioned CTs get many (blocking) Pt 2 questions, not aligned between CTs: ECs are not aligned. How will this improve? This impacts CT likelihood in Belgium.

Answer

No assessment RFI (neither on part I nor on part II) is raised during transition initial trial (IN) process.
However, considerations/requests for improvement on part II could be provided at the occasion of the first SM (e.g. on the ICF) as CTR EC is independent from the sites and different from the CTD EC.
But harmonisation is indeed very important and College and Barec are working on alignment of ECs in Belgium.
A new group is also working on part II harmonisation at EU level: MedEthics EU with two Belgian representatives involved.

Answers to the SLIDO questions

Question

In case of transitioning, will the dossier go to the same EC that initially reviewed the dossier under the directive?

-

Will there be a handover of the CTD approved documentation from the CEC (under CTD) to the independent evaluating EC (under EU CTR)?

-

Will the former CEC under CTD be informed about transition decision if this was assessed by another CEC?

Answer

No, a new EC will be selected by the College as according to CTR, the EC must be independent from the sites.

-

There will be no handover, therefore the submitted dossier must at least comply with the minimum requirements and be in line with the approved CTD dossier.

-

No, sponsor is responsible of informing the CEC under CTD of transition.

Answers to the SLIDO questions

Question

Will it be possible to submit DSUR during CTIS transition

Answer

If the trial is not yet approved in CTIS, the CTD/CTA safety rules must be applied.
As soon as the trial is approved in CTIS, the CTR safety reporting rules must be followed.

The condition to be able to submit the DSUR (ASR) in CTIS is that the trial must be authorised (in CTIS).
A demo is available in this video which is part of the CTIS Module 18 from the EMA (how to create and submit ASR ?).

Answers to the SLIDO questions

Question

What advice can be given if a PI change is taken place at the time of a planned transition?

Answer

If the trial is not yet submitted in CTIS, you can submit the PI change as a Pilot/CTA SM and send a separate mail asking for expedited review.

If the transition trial is already submitted in CTIS, our advice is to wait for approval of the trial and then immediately submit an SM (best practice within one week) for the PI change.

Answers to the SLIDO questions

Question

Can booklet labels referring to EudraCT number be used after the transition to the CTR? Assuming the study name/protocol number is also mentioned on the label.

Answer

Guidance on transition available on Eudralex volume 10 (point n°12):
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.

Answers to the SLIDO questions

Question

Trial dossier must be transitioned before January 31, 2025. SM to update documents in line with CTR must then be submitted. Should this SM be approved by January 31, 2025?

Answer

A SM must be submitted if needed; e.g. if a document (such as protocol, IB, ICF or IMPD) is substantially modified and must be approved via SM.

If no SM is needed **and if no subsequent addition of a member state is foreseen**, no need to submit one to complete the dossier according to CTR.

The deadline is for transition of the CTD trials.
Initial transition dossiers must all be approved in CTIS by January 30, 2025.
The deadline is not related to the subsequent SMs.

Answers to the SLIDO questions

Question

If no SM of the trial is foreseen after the transition and until the end of the study, when should the sponsor bring documents of CT in line with the CTR?

Answer

The first SM after transition should update documents in line with the requirements of the CTR at the time there is a need for the sponsor to update any of the documents in the application dossier through a SM application.

However, if the sponsor wants to add an additional Member State Concerned (CTR article 14) after a trial has been transitioned to CTIS, the part I documents should first be updated in line with the requirements of the CTR before an additional Member State Concerned is added.

Answers to the SLIDO questions

Question

In which part to upload patient facing documents linked to endpoints of protocol: part I (as per EU CTR Q&A) or part II (previously approved by EC under CTD)?

Answer

Upload under part I. The EC is involved in the consolidated review of part I documents.

Answers to the SLIDO questions

Question

If a site is just closed but the study is not closed in Belgium, does this site needs to be included within the transition package?

Answer

No, only active sites must be transitioned.
See point 6 of the guidance for sponsors available on Eudralex volume 10 for the definition of active site.

See also annex II (decision tree) of the guidance on transitional trials.

Answers to the SLIDO questions

Question

Is it necessary to add dummy documents for the Biological sample, data protection, and DOI sections in the CTIS for the transition part II binder preparation?

Answer

No, this is not necessary as those documents are not indicated with an asterisk in CTIS.

However, in case of subsequent SM on part II, mandatory documents according to annex I of the CTR (such as DOI of the investigator) should be provided to complete the dossier.

Answers to the SLIDO questions

Question

Should patient facing doc, approved under CTD but no longer required for submission under EU CTR/BAREC advice, still be submitted with SM1 after transition?

Answer

No, this is not necessary.
See also the CTR Q&A V6.8 question 1.24 section 77 - 81 related to patient facing documentation.

Answers to the SLIDO questions

Question

Per guidance you may submit additional docs if these docs were authorised under the CTD. What with recruitment materials in format not supported by CTIS like video?

Answer

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.

Video format I not supported by CTIS and videos are not part of the mandatory material to be submitted in the initial transition application.

EMA asks to provide **transcriptions** of audio or **screenshots** of video recordings in CTIS, which has already been evaluated under CTD, **only if specifically requested by the EC** to not unnecessarily overload the system. A simpler solution might be to submit a document containing a link that refers to visual or audio recordings.

Answers to the SLIDO questions

Question

1 CEC informed us the initial CEC is responsible after transition until 1SM and therefore NC also responsible until 1st SM. Is this correct?

Answer

As stated in the EU Commission guidance, point 3 general principles, clinical trials will be considered regulated by CTR when they will be approved under the CTR based on of the transitioning application.

As stated in the EU Commission guidance, point 11 ‘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.

This means for e.g. that sponsors will have to comply with CTR notifications and CTR safety reporting rules as soon as the transition trial is authorised in CTIS.

Answers to the SLIDO questions

Question

Transition trial with both authorised formulation and non-authorised formulation of a product > Need to register product twice in CTIS + in XEVMPD as DMP?

Answer

If both formulations are used in the trial, both need to be registered in CTIS in the Products section.

The non-authorised formulation, if not yet available in CTIS, must indeed first be registered in XEVMPD. This is important for safety follow up. The saMS should be able to identify the exact formulation in the reports/notifications.

More information on registration of products in XEVMPD can be found in chapter 6 of the CTIS sponsor handbook and module 10 of the CTIS training material catalogue.

Answers to the SLIDO questions

Question

For studies that have previous Country Specific Supplement submitted under CTD, will they still be allowed to submit CSS in CTR if needed? Or requested as RFI?

Answer

In case of Country Specific Supplement, a consolidated protocol should be submitted, clearly highlighting which part is only applicable to a specific country.

The consolidated protocol should be the consolidation of what has been authorised in each country under CTD.

Sponsors should only upload one version of the respective consolidated document for each trial in the Clinical Trials Information System (CTIS)

We refer you to the CTCG Best Practice for sponsors on transition V4 where the concept of consolidated protocol has been clarified.

Answers to the SLIDO questions

Question

If the draft contract was submitted with initial submission under CTD, do we need to submit draft contract with transition and signed contract during next SM?

Answer

This is not mandatory to submit the contract at the moment of the transition of the trial from CTD to CTR.

Therefore, the signed contract can be submitted at the time of the first SM on part II.

Answers to the SLIDO questions

Question

- If a study has transitioned to CTIS, should we still submit SUSARs from that study to all lead ECs with a study involving this product?
- If among several studies for a same product included in a DSUR, one of the studies has transitioned to CTIS, should we still submit the DSUR to all lead EC?

Answer

- Once the trial is transitioned, SUSARs should only be reported to the Eudravigilance Database (CTR Q&A V6.8 question 7.30)
  However, if trials with the same product are still ongoing under the CTD, CTD reporting rules still apply for these trials (CTR Q&A V6.8 question 7.52). For these trials, all leading ECs must indeed still be notified.

- Same principle for the submission of the DSUR (ASR) : once the trial is authorised in CTIS, ASR must be submitted in CTIS. However leading ECs of the still ongoing trials with the same product under the CTD must be notified as well (CTR Q&A V6.8 question 7.51).

New important information

New version of the EU Commission Guidance

A new version of the Guidance for the Transition of clinical trials from the CTD to the CTR dated May 2024 has been published on the Eudralex volume 10.

- Clarification on what is an **active site** (+ decision tree in annex II).
- Clarification of **consequences of non-compliance** with transition requirements.
- Clarification on the interface with medical devices and in vitro diagnostics.

New important information

IMPD-Q only process

When a clinical trial is transitioned from the CTD to the CTR which includes a reference to an IMPD not available in CTIS (and where the option described in Eudralex CTR Q&A under point 128 is not feasible), then an “IMPD-Q-only” submission should be done **together with the first substantial modification of part I after transition**.

Please consult the EU Commission guidance on transition on Eudralex volume 10 and the CTCG Best Practice on transition for sponsors (and associated documents) on the HMA website.

Still important information

Naming conventions

Please consult the best practice guide naming of documents in CTIS, not legally binding but important for a smooth validation and assessment
(e.g. instead of naming different languages of the ICF with 001, 002, 003, please indicate NL, DE, FR in the name of the document).

- A transition IN dossier is always a part I + part II dossier.

- Please do not forget to tick "transition" when drafting the dossier.

Questions and answers

Additional FAQ

Question

When updating the EU CT number, could we keep in parentheses the previous EudraCT number? This could help avoiding any confusion on the clinical trial "identity".

Answer

No, all references to the previous EudraCT number should be removed to avoid mix-up of the correct reference by investigators and/or patients.

Additional FAQ

Question

If CTD trials are complete and in line with the CTR at the time of transition, do we need to re-submit the 'additional documents' required under CTR (e.g. a protocol synopsis in three languages for Belgium) with the first SM?

Answer

No, if the clinical trial dossier has been brought in line with CTR requirements before transition, the documents do not have to be re-submitted during the first SM.

It is not allowed to submit these documents for the first time during the transition trial dossier, but either submit them before (with a SM under CTD) or afterwards (with the first CTR SM).

Additional FAQ

Question

For trials that will not be transitioned to CTR (e.g. because there are no more active sites) and so will have no dossier in CTIS, do we still need to report results after January 31, 2025? What about trials with no EU sites but that are still ongoing outside of the EU?

Answer

According to the guidance on transitional trials: "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 January 30, 2025.
This also applies until further notice for non-EU paediatric trials"

Trials with no active sites within EU/EEA Member States do not need to be transitioned to CTIS.

Conclusion

Thanks a lot for your attention!

Contact

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