EORTC
European Organisation for Research and Treatment of Cancer

Feedback on progress on CTIS and CTCG/CTAG guidance: Non-commercial Sponsor perspective

Clinical Trials Information System (CTIS): Information day

Presented by Xiao Mang Zhou (EORTC) on 22 May 2025

Our experience is based on…

- 22 CTR trials:
  - 10 initial applications
  - 12 transitioned trials

Cover letter template

- A high-quality cover letter will facilitate validation and assessment
- Earlier validation conclusion → shorten evaluation timelines
- 8 validation RFIs regarding cover letter

Cover letter template for initial applications

- 1 RFI stating that information is missing in the cover letter
  - Specific study population
  - First administration in humans
  - Scientific advice
  - Paediatric Investigation Plan
  - etc.

Please tick items below which are applicable. Where necessary, complete the specific sections or delete the sections not applicable to your clinical trial

☐ This is a complex clinical trial (CCT). See CTCG website for more information.

☐ This clinical trial contains one or more decentralized elements that are identified as a critical-to-quality factor.

☐ This clinical trial is linked to the IMPD-Q-only application with trial number [xxxx].

☐ This is a partial application (without Part II, CTR article 11) for the following Member States: [mention Member States]

☐ This clinical trial is identical to the CTA with EU CT number [insert trial number]. There are [no/the following] overlapping MS in both trials: [names of the overlapping MS]. If there are overlapping Member States, please choose one of these MS as the proposed RMS for both trials. Please also provide any additional information about these two identical studies in the cover letter if considered relevant for the RMS and MSCs. If possible, please submit both applications on the same day.

☐ This clinical trial is related to a public health emergency. [provide description]

☐ The study population consists of [subjects not able to give informed consent] / [emergency situation subjects (CTR Article 35)] / [minors] / [pregnant women] / [breastfeeding women].

☐ The clinical trial involves the first administration of a new active substance to humans (first-in-human trial). If the IMP is a biosimilar or bioequivalent, indicate this here.

☐ Scientific advice relating to the clinical trial or the investigational medicinal product has been given by EMA, a Member State or a third country. This can be found in [insert name of document].

☐ The clinical trial [is part] / [is intended to be part] of a Pediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3, of Regulation (EC) No 1901/2006. The Agency [has issued] / [has not yet issued] a decision on the PIP: [enter here the link to the decision of the Agency on its website].

☐ The investigational medicinal product (IMP) or auxiliary medicinal product (AxMP) is a [narcotic] / [psychotropic] / [radiopharmaceutical].

☐ The investigational medicinal product consists of or contains a genetically modified organism.

☐ The investigational medicinal product is considered a prophylactic vaccine.

☐ An orphan designation for the IMP for an orphan condition has been obtained.

☐ This trial investigates a new indication for an authorised medicinal product.

☐ The trial is a low-intervention clinical trial (as defined in CTR article 2). [Please provide a justification here why this is considered to be a low-intervention clinical trial, and explain if the (proposed) RMS is one of the MS where the use of IMP is evidence-based].

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Cover letter template for initial applications

- 3 RFIs regarding medical devices
  - Whether any medical device is used in the trial
  - Whether they are investigated in the trial
  - Whether they are CE marked for their intended use

Combined studies (interplay CTR with MDR and/or IVDR)

☐ The following **medical devices** in this clinical trial are also part of a clinical investigation application submitted under the Medical Device Regulation (EU MDR 2017/745): Only mention devices that are investigated or in development in this trial, not devices that are used but not investigated. Please provide a list of the national MDR applications, with (expected) submission dates and national dossier numbers, if applicable and available.

Name of device	Not CE-marked	CE-marked but used outside intended use	In-house device
	☐	☐	☐
	☐	☐	☐

☐ The following **in vitro diagnostics** (IVD) in this clinical trial are also part of a performance study submitted under the In Vitro Diagnostics Regulation (EU IVDR 2017/746): Only mention IVD that are investigated or in development in this trial, not IVD that are used but not investigated. Please provide a list of the national IVDR applications, with (expected) submission dates and national dossier numbers, if applicable and available.

Name of IVD	Not CE-marked	CE-marked but used outside intended use	In-house assay
	☐	☐	☐
	☐	☐	☐

Cover letter template for initial applications

- 1 RFI asking for submission of summary of changes or tracked changes version of IB
- EORTC is not a product owner

→ RFIs are not necessarily specific to type of sponsor

Annex I – additional information (remove if not applicable)

IMPD-Q and IB history:
For unauthorised IMPs where the sponsor is the Product Owner: mention the most recently authorised version of the IMPD-Q and IB. Either attach a Summary of Changes (SoC) as an appendix to the cover letter or submit the IMPD-Q/IB with tracked changes in CTIS.

Most recently authorised version of the IMPD-Q and/or IB

Name of IMP	EU CT number	Document, version, date

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Cover letter template for initial applications

- No additional labelling is only applicable for use under authorized indication
- Waiver for labelling drugs not under authorized indication is also possible

Product labelling:

☐ No additional labeling is required in accordance with CTR Article 67, because the medicinal product is authorised and commercially available in the countries of use, locally sourced through local pharmacies or country vendors as an open label product in its original unmodified commercial packaging intended for use in authorized indication, similar to the use per SmPC.

☐ Additional labelling is proposed for authorised IMPs/AxMPs.

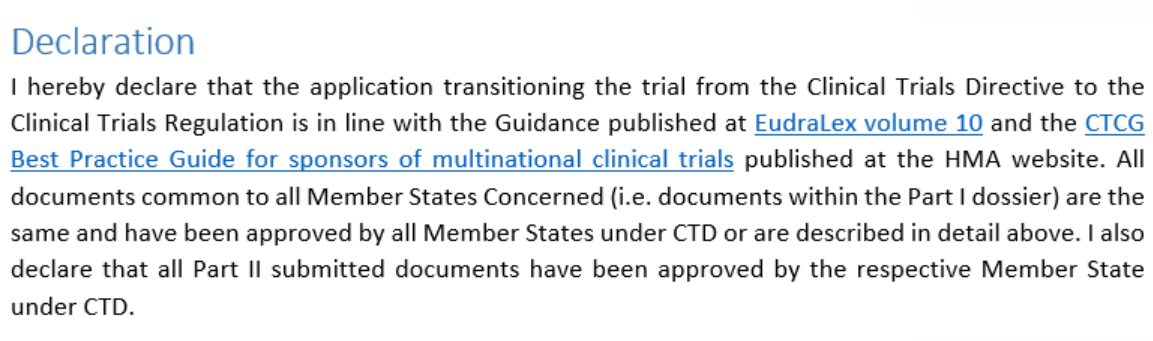
☐ The address and telephone number of the main contact are not included on the labels (CTR Annex VI), but the sponsor confirms that these details have been provided on a leaflet or card to the trial participants, who have been instructed to keep this in their possession at all times.

CTCG best practice guide naming of documents

- *"CTCG accepts that the CT numbers within the documents uploaded into the system do not include the last 2 digits, so that they do not need to be changed for re-submission. In case of a decision letter, the full number including the last 2 digits will be reflected.*
  If the full number is reflected in the documents and a re-submission takes place, there is no expectation that these numbers are immediately corrected within the documents during the ongoing procedure. This can be done at a later stage when the documentation is updated during a SM procedure."
- 1 resubmission: 2 out of 6 MSCs requested all Part II documents to be updated with full incremented EU trial number

Cover letter template for transition

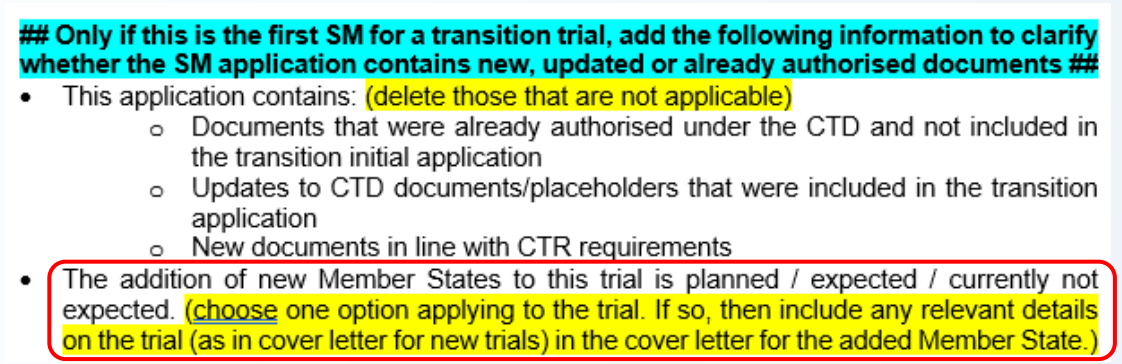
- End of transition period on 30 January 2025
- 4 RFIs regarding additional statements:
  - All Part I and Part II documents will be submitted with the next SM
  - In line with the requirements for transition trial and with the authorisation given under the CTD
  - Whether an additional member state procedure is planned



Declaration

I hereby declare that the application transitioning the trial from the Clinical Trials Directive to the Clinical Trials Regulation is in line with the Guidance published at EudraLex volume 10 and the CTCG Best Practice Guide for sponsors of multinational clinical trials published at the HMA website. All documents common to all Member States Concerned (i.e. documents within the Part I dossier) are the same and have been approved by all Member States under CTD or are described in detail above. I also declare that all Part II submitted documents have been approved by the respective Member State under CTD.

CTCG cover letter template for transition



Only if this is the first SM for a transition trial, add the following information to clarify whether the SM application contains new, updated or already authorised documents

- This application contains: (delete those that are not applicable)
  - Documents that were already authorised under the CTD and not included in the transition initial application
  - Updates to CTD documents/placeholders that were included in the transition application
  - New documents in line with CTR requirements
- The addition of new Member States to this trial is planned / expected / currently not expected. (choose one option applying to the trial. If so, then include any relevant details on the trial (as in cover letter for new trials) in the cover letter for the added Member State.)

CTCG cover letter template for first SM after transition

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IMPD-Q-only application

- EORTC is not a product owner
- IMPD-Q-only application is a good short-term solution
- Administrative burden of IMPD-Q-only application for product owners
- Addition of MSC(s) to sponsor trial requires a resubmission IMPD-Q-only application with all MSCs by product owners
- Download Part I application and send to product owner to avoid mistakes
- All IMPD-Q considerations were also included in Part I RFIs of sponsor trial

➔ Solution: With simplification of CTIS Sponsor Roles, CT Admin would not have access to IMPD-Q anymore

AxMPs

- *“Registration in CTIS is only mandatory for non-authorised AxMPs and for authorised AxMPs for which such modification is not covered by the marketing authorisation“*

- 1 RFI regarding addition of authorised AxMPs in product details section of CTIS

Auxiliary Medicinal Products in Clinical Trials dated March 2024

Registration in xEVMPD

- Products not authorised within the EEA must be registered in xEVMPD by the sponsor

- A unique EU medicinal product number is attributed to the sponsor

- Timelines: almost 4 weeks to obtain EU medicinal product number

➔ Solution: EU medicinal product numbers not specific to sponsor

Guidance on the electronic submission of information on investigational medicinal products for human use in the Extended EudraVigilance medicinal product dictionary (XEVMPD) version 1.4 dated 4 December 2024

Conclusion

- Use of CTCG templates and following CTCG guidance does not decrease number of RFIs

- Guidance and templates are mainly focused on product owners and not non-commercial sponsors

- Certain processes/work around solutions (e.g. registration in xEVMPD and IMPD-Q-only application) are an administrative burden

Take home messages

- Continuous updates in CTIS
- Continuous updates to CTR Questions & Answers
- Continuous updates to training material
- Continuous updates to CTCG/CTAG guidance and templates
- CTIS newsflash and communication e-mails
- EMA Service Desk (Helpdesk)
- RMS and CTR national contact points

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THANK YOU

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