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

Version history and publication

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Description of changes in vs. 4 compared to earlier version

Sponsor should propose trial category but not apply for low-intervention clinical at time of transition from CTD to CTR. Details on CTIS submission for specific situations: i) sponsor is not product owner of an IMP, ii) recommendations for IMPs and AxMPs, iii) when, under CTD, a study was regarded as an interventional clinical trial in some Member States and as a non-interventional clinical study in other Member States. Archiving rules and end of trial for CTD trials when some but not all Member States included in transition.

Description of changes in vs. 3 compared to earlier version

Concept of consolidated protocols clarified highlighting sponsor´s responsibility to decide on transition as a single clinical trial. **Example illustrating consolidated protocol version shown in figure. Clarification on background treatment - status of non–Investigational Medicinal Products under CTD regarded as IMP or AxMP under CTR.**

Description of changes in vs. 2 compared to earlier version

Consolidated Investigator's brochure (IB) and/or Investigational Medicinal Product Dossier (IMPD) not previously harmonised under CTD acceptable when submitting a transition application

If the first substantial modification application Part I after transitioning is a 'Multi-SM' submission, where the sponsor submits an IMP-related document in a single request for a substantial modification to several trials (CTR Annex II A.1, functionality restricted to IB, IMPD and GMP documents), the Application dossier should be updated to be in line with CTR in the following SM Part I application

Introduction

As provided for in Article 98 of Reg. 536/2014, clinical trials will be allowed to transition from the Directive 2001/20/EC (CTD) to the Regulation 536/2014 (CTR) before the end of the 3 years following the date when the CTR applies, in accordance with the Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation (European Commission Guidance).

For multinational transition trial applications, CTCG has agreed on an *expedited, harmonised* Member State evaluation procedure open until 16th of October 2024 focussing on the validation of minimum application dossiers restricted to documents already authorised under the CTD. After this date, an expedited procedure might not be feasible depending on the workload. Unless an assessment RFI is

raised with considerations questioning the trial category/deferral proposed by the sponsor, the assessment phase is shortened to one week for these minimum dossier transition applications.

Sponsors will be required to have a **harmonised** *or* **consolidated** protocol, Investigator's brochure (IB) and/or Investigational Medicinal Product Dossier (IMPD) for the transitioning. Transition of multiple versions of a protocol or other Part I documents within one application under a single EU CT number will not be possible. Sponsors should only upload **one version of the respective consolidated document for each trial** in the Clinical Trials Information System (CTIS)**.**

• For the purposes of this guidance, a harmonised protocol, IB and/or IMPD means that the respective document(s) is (are) identical and includes the same trial procedures in all countries approved across all EU Member States under the CTD.

• A consolidated protocol, IB and/or IMPD means that there are substantial differences in the respective document(s) in different Member States, but the document itself is identical, i.e. Member State-specific issues are outlined within the document text or in an appendix to the respective document. The consolidated protocol, IB and/or IMPD do not need prior approval under CTD before the transition.

Scope

The CTCG was initially asked to define the limits of what is acceptable within the same consolidated protocol for transitioning multinational trials with protocols that are not harmonised across Member States and for developing guidance on the best practice to be followed by sponsors when the protocol is not fully harmonised. This concept was then extended to the IB and/or the IMPD.

Guidance

In accordance with Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation, the sponsor is responsible for ensuring that a transitioned protocol, IB and/or IMPD for a multinational clinical trial do not contain any substantial differences across Member States Concerned (MSCs) compared to the authorised documents in all Member States where the trial is ongoing. The transitioned protocol, IB and/or IMPD will not be subject to assessment by the Reporting Member State (RMS) or MSCs following submission to CTIS.

For all clinical trial applications transitioning to the CTR, the sponsor should include in the cover letter a declaration that the protocol, IB and/or IMPD do not include any substantial changes compared to the version(s) approved in each Member State concerned, and the dates of authorisation in each Member State concerned should be provided (see Annex: CTCG cover letter template declaration). The sponsor should also declare that all other Part I and Part II documents are identical to the ones authorised under CTD, still allowing non-substantial changes (in line with Annex IV of the European Commission Q&A), see template tables in cover letter. See Figure illustrating a consolidated protocol based on different authorised versions in different Member States under the CTD.

As an example of acceptable consolidation, the following **aspects of the protocol** are the same across all MSCs:

• EudraCT number
• Trial Title
• Protocol version number (for a consolidated protocol a new version number is acceptable, when the cover letter clearly indicates the authorised version number per MSC used as a basis for the new consolidated version)

• Primary objective
• Primary endpoint
• Definition of end of trial

In addition, the main inclusion and exclusion criteria should be the same, while accepting national restrictions in e.g. trial population age group for a particular Member State.

It is the sponsor's responsibility to decide if the clinical trial can be submitted as a single trial transition application with consolidated Part I documents.

Sub-protocols can either be submitted as stand-alone documents or added as Annexes to the main protocol. In case of MS-specific sub-protocols submitted individually, the name of the MSC should be reflected in the file name and document title.

The following scenarios are foreseen:

• If harmonised documents, e.g. protocol, IB and/or IMPD, are already approved in all MSCs under the CTD, transition to the CTR can proceed by submission of the CT application to CTIS and sponsors should declare in the cover letter that the respective version of the protocol, IB and/or IMPD have been approved in all MSCs under CTD.

• Even if there are substantial differences in these documents, (e.g. for the protocol subject population age groups) and/or non-substantial differences across Member States concerned in the authorised versions of the documents, a consolidated version may be transitioned as a single new version without prior submission under the CTD. Sponsors must declare in the cover letter that there are no substantial differences in content beyond the described discrepancies across Member States compared to the latest versions approved in the respective MSCs under the CTD.

The sponsor should confirm that the content of the harmonised /consolidated protocol, IB and/or IMPD, including Member State-specific differences, is not deviating from what was approved under the CTD in all MSCs. When it comes to differences between MSCs based on earlier authorisation of different versions of a document (see Figure), it should be emphasised that what was approved under CTD still applies after the transition. Harmonisation should be reached when the first Part I substantial modification application is authorised, unless justified e.g. for local IMP sourcing specified in the IMPD.

The following recommendations for the sponsor uploading trial application documents into the Clinical Trials Information System (CTIS) apply:

- The transitioned IMPD could be uploaded in the CTIS slot for IMPD-Q, providing a reference to this document or to the IB/SmPC in the CTIS slot for IMPD S&E.
- The transition application must include proposed trial category/deferral[1], since this cannot be changed in subsequent Part I substantial modification applications.
- Transition trials cannot be categorised as low-intervention clinical trials.
- If the sponsor is not the product owner of an IMP used in the trial and the IMPD-Q is already submitted in another trial application to CTIS, a reference to this trial number should be provided in the cover letter. If the IMPD has only been submitted under the CTD, a reference to this EudraCT trial should be made. For subsequent substantial modification applications, the sponsor should follow the procedure on IMPD-Q only submission in the European Commission Questions and Answers Eudralex vol 10.

[1] See updated CTIS Transparency Rules, *Q&A on the protection of Commercially Confidential Information and Personal Data while using CTIS*

- If under CTD national laws the clinical trial is regarded as a trial in some, but not all Member States, the trial should be transitioned in those Member States where it was approved as a clinical trial.
- After transition of a clinical trial, CTR rules apply also in Member States not included in the transition application from CTD to CTR, i.e. where the trial approved under CTD will not have any active sites after Jan 30 2025. This means that the end of trial notifications will not be submitted in line with CTD to EudraCT, but only to CTIS. In the same way, after transition of a trial in at least one Member State, CTR archiving rules i.e. 25 years, for the Trial Master File are applicable in all Member States where the trial has been conducted.

The sponsor may wish to confirm the same for Part II documents. In this case the sponsor needs to declare which version of the respective documents were approved per MSC (see Annex: CTCG cover letter template declaration).

Before the sponsor adds any additional MSC (Article 14) to a transitioned trial with the agreed simplified minimum dossier of already approved documents, a substantial modification application must be submitted and authorised upgrading the application dossier documents Part I to be in line with the CTR. Information if any additional MSC(s) will be added in line with Article 14 of the regulation, should be announced in the cover letter to the SM Part I application to allow the RMS to make a meaningful summary of the assessment of the trial for the additional MSC.

The only exception to this rule aligning the content of the transitioned Part I dossier when submitting the first substantial modification Part I application is a 'multi-SM submission'[2] where the sponsor submits a single request for authorisation of the same substantial modification for Part I IMP documents (restricted to IB, IMPD and/or GMP documents) involving multiple trials of the same sponsor and the same investigational medicinal product (Annex II of Regulation (EU) No 536/2014). In such situations, the content of the Part I application dossier should be in line with CTR requirements at the next substantial modification application and always before any additional MSC is added to the trial. The intention to subsequently include additional Member States in the trial should always be announced in the cover letter for the substantial modification application. Also, use of the multi-SM submission functionality in CTIS must be clearly described in the cover letter, where the sponsor should also declare that the Part I dossier will be in line with CTR at the next SM Part I submission.

Additional information on Part I and Part II documents

In the Part I application dossier, a sponsor may choose to include additional documents as outlined in the CTR Annex I, provided that these have been approved under CTD in some, but not all, MSCs. This must be clearly explained in the cover letter. (e.g. the DSMB Charter for Part I or layperson protocol synopsis). Similarly, the sponsor may choose to submit Part II documents beyond the minimum acceptable dossier. Submission of such documents is acceptable if these are approved under the CTD. This should be stated in the cover letter. Also, an MSC may raise a validation consideration requiring the sponsor to submit additional, earlier approved Part II documents (limited to those described in the CTR Annex I) beyond the informed consent and the subject information leaflet.

[2] Functionality for a multi-SM (CTR Annex II A,1) CTIS submission by a sponsor is restricted to the following: IB, IMPD and GMP documents

Non-IMPs, IMPs and Auxiliary Medicinal Products

Under the CTR, the concept of non-IMPs has been changed into a new group of medicinal products "Auxiliary Medicinal Products (AxMPs)" [CTR, article 2.2 (8)]. For most clinical trials AxMPs are equal to non-IMPs and an easy transition is foreseen. However, in clinical trials where all trial participants are using standard of care (SoC) as a basic treatment for their condition, the classification of SoC as non-IMP or IMP could differ between MSs because of the different interpretation what is considered background treatment. To harmonise this for clinical trials under the CTR, the paper on recommendation for AxMPs in clinical trials[3] has been updated with the following classification rule:

- **Current standard of care, or parts of it, will be considered as IMP and not as background treatment if it is part of the trial hypothesis.**
- **This is the case if the primary or secondary trial objectives include investigation of interactions with the test product for complimentary effects or possible adverse interactions or if the standard of care treatment is being used as a reference[4] to compare the effect of the test product.**

In these situations, the standard of care is considered an IMP and not an AxMP. If a non-IMP under the CTD will be classified as an IMP under the CTR, the transition can take place without a prior substantial amendment under CTD harmonising the classification among the MSs concerned and the clinical trial can continue under the CTR as previously approved. However, all IMPs should be registered in CTIS (including IMPs which were classified as non-IMP under CTD for which the structured data of the product section should be completed already at the time of transition, see[3]). If an IMP is classified as AxMP under the CTR, registration in CTIS is only mandatory for not authorised AxMPs, for AxMPs only authorised in some, but not all, of the MSCs and for authorised AxMPs which are modified[5] when such modification is not covered by the marketing authorisation.

Other authorised AxMPs can be listed in the cover letter.

After transition, with the next Part I substantial modification application, the clinical trial application should be completed with the correct information because of the switch applying the CTR classification as IMP and/or AxMP.

[3] https://health.ec.europa.eu/document/download/47ad006a-6ad4-488d-bb51-ab91d11e2871_en?filename=2017_06_28_recommendation_on_axmps.pdf

[4] 'Investigational medicinal product' means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial

[5] Modifications which affect the product quality and/or GMP requirements.

Figure

An example illustrating transition of a CTD trial to CTR with different protocol versions approved in the Member States Concerned – for some MSCs including additional non-substantial changes.