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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

Vs. 1 adopted at the CTCG plenary June 27 2023

Vs. 2 adopted at the CTCG plenary September 12 2023

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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 focusing on the validation of minimum application dossiers restricted to documents already authorised under the CTD. 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. It is required that all other documents common to all Member States Concerned (MSCs), i.e. those documents covered by the Part I assessment report, will be harmonised. 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 protocol 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 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 some 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.

It is expected that most clinical trials will have harmonised documents approved in all Member States where the trial is ongoing. However, where there are only a few differences, e.g. for a protocol regarding trial procedures or subject population between the versions of the protocol approved across the EU Member States, transition of a consolidated version of the protocol, to the CTR will be acceptable. The same principles apply for a consolidated IB or IMPD.

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 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.

If there are significant differences across Member States, authorisation of a harmonised protocol under the CTD is required prior to transition, as detailed below. The purpose of a substantial amendment under the CTD, harmonising the protocol or other documents in advance of the CTR, is to have a smooth transition into CTIS.

As an example of acceptable consolidation, the following **aspects of the protocol** must be 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 limited national restrictions in e.g. trial population age group restriction for a particular Member State.

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 without a CTD substantial amendment (as per the European Commission Guidance) and sponsors must declare in the cover letter that the respective version of the protocol, IB and/or IMPD have been approved in all MSCs under CTD.

• If there are only a few substantial differences in these documents, (e.g. for the protocol subject population age groups) and/or non-substantial differences (e.g. administrative differences, in line with Annex IV of the European Commission Q&A) 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 few substantial discrepancies across Member States (protocol example above) compared to the latest versions approved in the respective MSCs under the CTD.

• If there are extensive substantial differences between MSCs in the aspects of the protocol, IB and/or IMPD, a substantial amendment (under the CTD) should be submitted to National Competent Authorities (NCAs) and ethics committees in Member States where the trial is ongoing, in order to harmonise these aspects of the respective document across MSCs. This should be done prior to transition of the trial to the CTR.

The sponsor should confirm that the content of the harmonised /consolidated protocol, IB and/or IMPD including Member State-specific differences have been approved under the CTD in all MSCs when transitioning. The transitioned IMPD could be uploaded in the Clinical Trials Information System (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 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 that were approved per MSC (see Annex: CTCG cover letter template declaration).

Before the sponsor adds any additional MSC to a transitioned trial with an initial minimum dossier, a substantial modification application must be submitted and authorised upgrading the application dossier Part I to be in line with the CTR.

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'[1] 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.

[1] 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

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.