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

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 European Commission Questions and Answers Document - Regulation (EU) 536/2014 under the chapter 11 (European Commission Q&A).

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 (see 11.7 of the European Commission Q&A on transition of multinational clinical trials). Unless an assessment RFI is raised with considerations questioning the trial category and 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 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 (e.g. Investigator's Brochure, Investigational Medicinal Product Dossier). 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 CTIS (Clinical Trials Information System)**.**

• For the purposes of this guidance, a harmonised protocol is one where an identical protocol that includes the same trial procedures in all countries has been approved across all EU Member States under the CTD.

• A consolidated protocol is one in which there are some substantial differences in procedures in different Member States, but the protocol document itself is identical, i.e. Member State-specific issues are outlined within the protocol or in an appendix to the protocol. The consolidated protocol does not need prior approval under CTD before the transition.

It is expected that most clinical trials will have a harmonised protocol approved in all Member States where the trial is ongoing. However, where there are only a few differences in 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.

Scope

The CTCG was 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.

Guidance

In accordance with chapter 11 of the European Commission Q&A, the sponsor is responsible for ensuring that a transitioned protocol for a multinational clinical trial does not contain any substantial differences across MSCs compared to the authorised protocol in all Member States where the trial is ongoing. The transitioned protocol will not be subject to assessment by the Reporting Member State (RMS) or any MSC 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 does not include any substantial changes compared to the version(s) approved in each Member State concerned (in line with Annex IV of the European Commission Q&A, non-substantial changes are acceptable provided they are listed in the cover letter), 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 the substantial amendment under the CTD, harmonising the protocol in advance of the CTR, is to have a smooth transition into CTIS.

To transition a multinational clinical trial protocol, 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 a harmonised protocol is 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 Q&A) and sponsors must declare in the cover letter that this version of the protocol has been approved in all MSCs under CTD.

• If there are only a few substantial (e.g. 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 protocol, 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 (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 outlined in the bullets above, 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 protocol across MSCs. This should be done prior to transition of the trial to the CTR.

The sponsor should confirm the content of the harmonised /consolidated protocol including Member State-specific differences and the versions of the IB and IMPD (or SmPC) which have been approved under the CTD in all MSCs when transitioning. The approved 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.

Before the sponsor adds any additional MSC to a transitioned trial with a minimum dossier, a substantial modification application must be submitted and authorised upgrading the application dossier Part I to be in full compliance with the CTR. The intention to subsequently include additional Member States in the trial should always be announced in the cover letter for the substantial modification application.

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 described in Section 11 of the European Commission Q&A, point 497. 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.

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