Clinical Trial Facilitation Group
CTFG

Transition of Clinical Trials to Regulation (EU) No. 536/2014:

CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No. 536/2014

Introduction

As provided for in Article 98 of Reg. 536/2014, clinical trials will be allowed to transition from Directive 2001/20/EC to Regulation 536/2014 (CTR) during the 3 years following implementation of the Regulation, in accordance with the European Commission Question and Answer document regarding transition[1]. It is required that all documents common to all Member States concerned (i.e. those documents covered by the part I assessment report) other than the protocol will be harmonised across Members States (e.g. Investigator's Brochure, Investigational Medicinal Product Dossier). Transition of multiple versions of a protocol within one application under a single EU CT number will not be possible. The EU portal will allow sponsors of clinical trials to upload only **one protocol document for each trial.**

Thus, sponsors will be required to have a harmonised or consolidated protocol approved under Directive 2001/20/EC, prior to transitioning.

- *For the purposes of this guidance, a **harmonised protocol** is one where an identical protocol that includes identical trial procedures in all countries has been approved across all EU Member States.*
- *A **consolidated protocol** is one in which there are 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).*

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 slight differences in the versions of the protocol approved across the EU Member States, transition of a consolidated version of the protocol to the Regulation will be acceptable, if the changes made by consolidation are limited to the Member State-specific requirements.

Scope

The CTFG 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 practices to be followed by sponsors when the protocol is not fully harmonised*.

[1]The rules governing medicinal products in the European Union, VOLUME 10 - Chapter V Additional Information, **Question and Answer Document – Regulation (EU) 536/2014**

Guidance

In accordance with the Commission document regarding transition, the sponsor is responsible for ensuring that a transitioned protocol of a multinational clinical trial does not contain any substantial differences across Member States concerned (MSC) 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 the EU Portal.

For all clinical trial applications through the EU portal for trials that have been authorised under the Directive and are transitioning to the Regulation, the sponsor should include in the signed cover letter a declaration that the protocol does not include substantial differences to the version(s) approved in each Member State concerned, and should list the dates of authorisation in each Member State concerned (see Annex: CTFG template declaration). The sponsor should also declare that all other part I documents are identical to the ones authorised under Directive 2001/20/EC.

If there are significant differences across Member States, authorisation of a harmonised or consolidated protocol under the Directive is required prior to transition, as detailed below.

The purpose of the substantial amendment (to consolidate or harmonise the protocol in advance of the Regulation) is to have a smooth transition into the EU portal and database.

For transition of 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
- Primary objective
- Primary endpoint
- Definition of end of trial

In addition, the main inclusion and exclusion criteria should be the same.

The following scenarios are foreseen:

- If a harmonised protocol is already approved in all Member States concerned, transition to the Regulation can proceed by submission of the CT application to the EU Portal and Database without a substantial amendment (as per the European Commission Q&A[1]) and sponsors must declare in the cover letter that this version of the protocol has been approved in all MSCs under the Directive.

- If there are any non-substantial differences (e.g. administrative differences) across Member States concerned in the authorised versions of the protocol **a consolidated or harmonised version may be submitted / transitioned as a single new version**, and sponsors must declare in the cover letter that there are no substantial differences in content to the latest versions approved in the respective MSCs under the Directive .

- If there are **substantial differences** among MSCs in the aspects of the protocol outlined above, a substantial amendment (under Directive 2001/20/EC) 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 Regulation**.

- Sponsors may wish to harmonise the protocol so that all trial procedures are the same across all Member States concerned. If any harmonisation results in a substantial change, as per CT-1 with respect to the authorised protocol version in a MSC, a substantial amendment under the Directive is required in that MS.

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 Directive in all MSCs when transitioning.

It is possible that the sponsor may wish to confirm the same for part II documents. In this case the sponsor needs to declare which version of which documents were approved per Member State concerned.

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Annex

CTFG template declaration for transition of harmonised & consolidated protocols that have been approved under the Directive 2001/20/EC

The following declaration (with the table completed) should be included in the cover letter of the clinical trial dossier for multinational clinical trials that transition from Directive 2001/20/EC to Regulation 536/2014. The cover letter should be signed by the sponsor or legal representative of the sponsor.

The protocol for transition is ____fully harmonised /___ consolidated (tick) across all Member States concerned. I hereby declare that the content of this version of the protocol (version x. dated x) has been approved in the following Member States, and does not contain substantial differences.

	Date of approval	
Member State	National Competent Authority	Ethics Committee

(add rows as appropriate)

I hereby declare that all other documents common to all Member States concerned (i.e. documents within the part I dossier) are the same and have been submitted/approved by all MS concerned.

Investigator's Brochure / SmPC (version x, dated x)

	Date of approval	
Member State	National Competent Authority	Ethics Committee

(add rows as appropriate)

Investigational Medicinal Product Dossier (version x, dated x)

	Date of approval	
Member State	National Competent Authority	Ethics Committee

(add rows as appropriate)