Guide to sponsors on requirements for updating documents in line with the Clinical Trials Regulation at the time of the first SM Part I after a minimum trial dossier was transitioned from the Clinical Trials Directive to the Clinical Trials Regulation. See Annex III for Part II SM requirements.

Summary of changes compared to earlier version:

Vs. 2 In order to simplify submission requirements, a harmonised interpretation of which documents need to be updated at the time of the first SM has been agreed by CTCG Members. Requirements are summarised in a table and depend on i) if one or several additional MSC is/are planned to be added to the trial, ii) if recruitment and/or treatment is ongoing in at least one MSC and iii) if remaining procedures are restricted to trial-specific follow-up interventions without subject recruitment and/or treatment. Part I documents in line with the requirements in the table should be updated when there is a need for changing the content of the Part I dossier in a substantial modification application. Recommendations for updating Part II documents are included in the guide as a new Annex III.

The first substantial modification application Part I after transition should *update documents in line with the requirements of the Clinical Trials Regulation* EU No 536/2014 (CTR) at the time there is a need for the sponsor to update any of the documents in the Application Dossier Part I through a substantial modification (SM) application. The only exception to this rule, that the documents in line with the requirements in the table below should *all* be updated when there is a need for changing the content of any document in the Part I dossier, is, when the sponsor submits *a single request for authorisation of a multi-trial substantial modification application* restricted to modification of IMP documents (IB, IMPD and/or GMP documents) used in multiple trials with the same sponsor and with the same investigational medicinal product (see CTR Annex II of and Questions and Answers on CTR published at EudraLex Volume 10[1], Question 3.8). In such situations, the content of the *Part I application dossier should be in line with CTR* requirements (*see table below)* at the next substantial modification application Part I. For Part II document requirements, see list Annex III.

If the sponsor wants to add an additional Member State Concerned (CTR Article 14) after a trial has been transitioned to CTIS, the Part I documents should first be updated in line with the requirements of the CTR before an additional Member State Concerned (addMSC) is added[2,3]. This update should be done through an SM part I application in line with the table below.

With the aim to harmonise simplified requirements for transitioned ongoing trials in EU/EEA, the table below lists three different trial stages after transition (horizontal) and the harmonised agreement between Member States in CTCG on differential requirements depending on the stage of the trial regarding which documents/structured data (vertical) need to be updated to be considered “in line with CTR requirements” (vertical). Where the term ‘update’ of a document is

[1] See Questions and Answers on CTR (QnA), vs 6.8 published at EudraLex Volume 10
[2] See Guidance for Transition of Trials from CTD to CTR, vs. 3 published at EudraLex Volume 10
[3] See CTCG naming of documents published at the CTCG HMA website, under CTCG, Key documents

used, this means uploading the document as a new version in CTIS. Sponsors are recommended to adhere to the CTCG 'Best Practice guide naming of documents in CTIS'[4]

In addition to the list below of documents that should be updated and uploaded in CTIS, sponsors should also consider the need to prepare redacted documents in CTIS for Category 2 and 3 trials for the public in line with the revised transparency rules (see Questions and Answers document on future CTIS transparency rules[5])

Trial stage (horizontal)/ Part I documents (vertical)	a) **Planned inclusion of additional Member State concerned** (CTR Article 14)	b) **Recruitment and/or treatment/IMP administration ongoing in at least one MSC**	c) **Declared closed treatment/IMP administration in all MSCs**, i.e. remaining procedures restricted to **trial-specific follow-up interventions**
Cover letter	See Annex I Cover Letter Template for First SM after transition (as well as Annex II Substantial Modification Description template)	See Annex I Cover Letter Template for First SM after transition (as well as Annex II Substantial Modification Description template)	See Annex I Cover Letter Template for First SM after transition (as well as Annex II Substantial Modification Description template)
Protocol	• EU trial number [CTR Annex I 15 (a)] • Statement that clinical trial is conducted in compliance with (EU) No 536/2014 [CTR Annex I 17 (a)] • Details on emergency situation trial requirements in line with protocol requirements, if applicable [CTR Annex I 17 (d)] • Trial result reporting [CTR Annex I 17 (ai)] • DSMB Charter, if applicable [CTR Annex I 23]	• EU trial number [CTR Annex I 15 (a)] • Statement that clinical trial is conducted in compliance with (EU) No 536/2014 [CTR Annex I 17 (a)] • Details on emergency situation trial requirements in line with protocol requirements, if applicable [CTR Annex I 17 (d)] • Trial result reporting [CTR Annex I 17 (ai)] • DSMB Charter, if applicable [CTR Annex I 23] • Other changes when need to adapt earlier approved CTD protocol text, e.g.	Update protocol in line with column b) only if substantial modification application concerns the content of *this document*

[4] See CTCG 'Best Practice guide naming of documents in CTIS', published at the CTCG HMA website, under CTCG, Key document list
[5] See ACT EU Questions and Answers on protection of Commercially Confidential Information and Personal Data while using CTIS

	• Other changes when need to adapt earlier approved CTD protocol text, e.g. regarding details on notifications not required under CTD, [CTR Articles 52-54] and changes in archiving of Trial Master File (25 years) [CTR Articles 58]	regarding details on notifications not required under CTD, [CTR Articles 52-54] and changes in archiving of Trial Master File (25 years) [CTR Articles 58]	
Protocol synopsis (for laypersons, as applicable[6])	Update protocol synopsis (and upload in CTIS) in **English or national language[6]**, so that later translations could be provided for an addMSC	Update protocol synopsis (and upload in CTIS) in **English** or national language[7]	Update protocol synopsis in line with column b) only if substantial modification application concerns the content of *this document*
Patient-facing documents[8]	Update in **English or national language[8]** so that later translations could be provided for an addMSC	Update in **English** or national language [8]	Update patient-facing docments in line with column b) only if substantial modification application concerns the content of *this document*
GMP compliance/QP declaration	Update in CTIS when need for new IMP batches foreseen, see [1,2]	Update and upload in CTIS when need for new IMP batches foreseen, see [1,2]	-
IB, Scientific advice and PIP	Update IB, Scientific advice or PIP only if substantial modification application concerns the content of *this document*	Update IB, Scientific advice or PIP only if substantial modification application concerns the content of *this document*	-
IMPD, AxMPD	There is no need to split the IMPD approved in the initial application into separate documents IMPD-Q and IMPD-SE	There is no need to split the IMPD approved in the initial application into separate documents IMPD-Q and IMPD-SE	-

[6] See Questions and Answers on CTR (QnA), vs 6.8 at EudraLex Volume 10, Question 5.8. Note i) the CTIS upload slot for a redacted version of this mandatory CTIS document, which will be public for Category 2 and 3 trials in line with ACT EU Questions and Answers on protection of Commercially Confidential Information and Personal Data while using CTIS ii) for already included MSCs without need for change in this documents, agreed to be acceptable in English. For later additional Member States concerned or if substantial modification concerns this document, the document should be provided in languages as shown in See Questions and Answers on CTR (QnA), vs 6.8 Annex II Language requirements for Part I documents published at EudraLex Volume 10

[7] English version not required for e.g. mononational clinical trials (national language accepted in line with CTR Article 26 – see language requirements for Part I in each Member State, Annex II of the QnA, vs 6.8 publishe at EudraLex Volume 10, https://health.ec.europa.eu/document/download/bd165522-8acf-433a-9ab1-d7dceae58112_en?filename=regulation5362014_qa_en_0.pdf

[8] Restricted to those related to the endpoints of the clinical trial (note for already included Member States without changes agreed to be acceptable in English, for later additional Member States concerned or if substantial modification concerns these documents in languages as shown in Annex II Language requirements for Part I documents, Questions and Answers document - Regulation (EU) 536/2014 published at EudraLex Volume 10

	Update IMPD only if the substantial modification application concerns the content of this document. In line with the revised Recommendations on AxMP/IMP at EudraLex Volume 10[9] , in situations when a previous Non Investigation Medicinal Product (NIMP under CTD is now regarded as IMP, the relevant product information should be provided[3]	Update IMPD only if the substantial modification application concerns the content of this document. In line with the revised Recommendations on AxMP/IMP at EudraLex Volume 10[9] , in situations when a previous Non Investigation Medicinal Product (NIMP under CTD is now regarded as IMP, the relevant product information should be provided[3]	
Labelling[2]	When need for new IMP batches is foreseen, sponsor should prepare updates well in advance in line with i) Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation[2] and ii) CTR QnA Annex II Language requirements for part I documents[1]	When need for new IMP batches is foreseen, sponsor should prepare updates well in advance in line with i) Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation[2] and ii) CTR QnA Annex II Language requirements for part I documents[1],	-
Structured data fields in CTIS (EU application form)	Add if sponsor considers trial to be a low-intervention clinical trial. Also add justification document	Add if sponsor considers trial to be a low-intervention clinical trial. Also add justification document	-

[9] See Revised Recommendations on AxMP/IMP published at EudraLex Volume 10