Guide to sponsors on requirements for updating Part I 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

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 planned substantial modification (SM) submission.

The only exception to this rule 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 and the *table below* at the next substantial modification application Part I.

If the sponsor wants to add an additional Member State Concerned (CTR Article 14) to a transition trial, 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, unless the Part I dossier is already completed at the time of the initial transition or at a previous SM part I.

With the aim to harmonise requirements in EU/EEA, the table below lists different stages for clinical trials after transition (horizontal) and the agreement in CTCG on which documents/structured data (vertical) should be required to be updated to be in line with CTR.

Where the term ‘update’ of a document is used in this document, this means i) uploading a document in CTIS approved under CTD but not included in the initial application of the transition minimum dossier, ii) updating an already existing document/placeholder in CTIS as a new document version *or* iii) uploading a new document to the application dossier 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, 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 new transparency rules (see Questions and Answers document on future CTIS transparency rules[5])

---

[1] See Questions and Answers on CTR (QnA), vs 6.7 published at EudraLex Volume 10
[2] See Guidance for Transition of Trials from CTD to CTR published at EudraLex Volume 10
[3] See CTCG Best Practice Guide for Sponsor on transition of trials from CTD to CTR published at the CTCG HMA website, under CTCG News and Events
[4] See CTCG ’Best Practice guide naming of documents in CTIS’, published at the CTCG HMA website, under CTCG Key documents list
[5] See ACT EU Questions and Answers on protection of Commercially Confidential Information and Personal Data while using CTIS

	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] • Other changes of the protocol text *only* if the information in the version approved in the initial application (and under CTD) is in conflict with CTR, e.g. protocol text regarding details on notifications, [CTR Articles 52-54] or archiving of Trial Master File (25 years) [CTR Articles 58]	• 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 of the protocol text *only* if the information in the version approved in the initial application (and under CTD) is in conflict with CTR, e.g. protocol text regarding details on notifications, [CTR Articles 52-54] or archiving of Trial Master File (25 years) [CTR Articles 58]	Update protocol in line with column b) only if substantial modification concerns *this document*

Protocol synopsis (for laypersons, as applicable[6])	Update protocol synopsis in **English or national language[6]**, so that later translations could be provided for an addMSC	Update protocol synopsis in **English** or national language[7]	Update protocol synopsis in line with column b) only if substantial modification concerns *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 documents in line with column b) only if substantial modification concerns *this document*
GMP compliance/QP declaration	Update in CTIS when need for new IMP batches foreseen[1,2]	Update and upload in CTIS when need for new IMP batches foreseen[1,2]	-
IB, Scientific advice and PIP	Update IB, Scientific advice or PIP only if substantial modification concerns *this document*	Update IB, Scientific advice or PIP only if substantial modification concerns *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 Update IMPD only if the substantial modification concerns *this document.* In line with the revised Recommendations on AxMP/IMPat EudraLex Volume 10[9], in situations when a previous Non Investigational Medicinal Product (NIMP) under CTD is now regarded as an IMP, the	There is no need to split the IMPD approved in the initial application into separate documents IMPD-Q and IMPD-SE Update IMPD only if the substantial modification concerns *this document.* In line with revised the Recommendations at EudraLex Volume 10[9], in situations when a previous Non Investigational Medicinal Product (NIMP) under CTD is now regarded as an IMP, the	-

[6] See Questions and Answers on CTR (QnA), vs 6.7 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 6.7 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 Annex II of the QnA, vs 6.7 publishe at EudraLex Volume 10

[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

[9]See Revised Recommendations on AxMP/IMP published at EudraLex Volume 10, under Chapter III Quality

	relevant product information document should be provided[3]	relevant product information document 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, Questions and Answers document[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	-