Centrale Commissie Mensgebonden Onderzoek

CCMO: CTIS Submission Guide First Substantial Modification (SM) after Transition (page 2) + SM (page 21)

MOST IMPORTANT TIPS!

- A list of possible reasons for an SM can be found in Annex IV (Classification of changes to ongoing clinical trials) of the CTR Q&A of the European Commission.
- When uploading updated document(s) to CTIS, ensure the version and date inputted into CTIS match the version and date of the document itself.
- When uploading an updated document, click on the "Update" (paper) icon found next to the previous version of the document. Make sure that a redacted document is uploaded on top of the previous redacted document and that the non-redacted document is uploaded on top of the previous non-redacted document.
- **After submitting a trial in CTIS, your work is not done! The sponsor/delegate is responsible for checking CTIS daily for any Requests For Information (RFIs)/communication from the authority regarding the trial. Neither CTIS nor CCMO/MREC will inform you by email. If you receive a RFI in CTIS, make sure you respond to the RFI by the deadline. Otherwise the submission will lapse and you will have to submit again.**

*Please note this information is subject to change.

*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

Centrale Commissie Mensgebonden Onderzoek

FIRST SUBSTANTIAL MODIFICATION (SM) AFTER THE TRANSITION (if applicable*): Document List

*This type of SM is only applicable for studies previously submitted under the Clinical Trials Directive (CTD) and then transferred to the Clinical Trials Regulation (CTR) via CTIS. For the first SM after the transition, the dossier needs to be completed as if it were an initial submission and documents need to be made compliant with the CTR.

*The documents for this SM will include:

- New documents for the CTR (that need to be assessed),
- Updated CTD documents (that need to be assessed), and/or
- Already approved under the CTD documents (submitted unchanged in CTIS)

*For further guidance, please see the CTCG website – Key Document List – documents:

- *CTCG Best Practice Guide to sponsors updating the application dossier Part I after CTR transition*
- *Annex III First SM Part II after transition*

Legend
Blue text: text needs to be completed by sponsor.
Green text: Document subject to publication (depending on trial category). See the Guidance document and Annex 1 found under transparency.
Orange text: New document for CTR

Location in CTIS	Document & Naming Convention	Link	Additional Information

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FORMS Form MSCs Part I Part II Evaluation Timetable			
Form MSCs Part I * Part II Evaluation Form details Substantial modification details Cover letter *	B1_Cover letter SM# EU CT number	Clinical Trials Coordination Group website (hma.eu) Template under Key Documents List – First SM: document requirements after transition. Template name: *Annex I Cover letter template First SM after _vs 2.0*	-Mandatory European template- agreed to by all Member States -If the IB/SmPC is updated, the cover letter should clearly indicate if the Reference Safety Information (RSI) is modified and if so, where the RSI is located.

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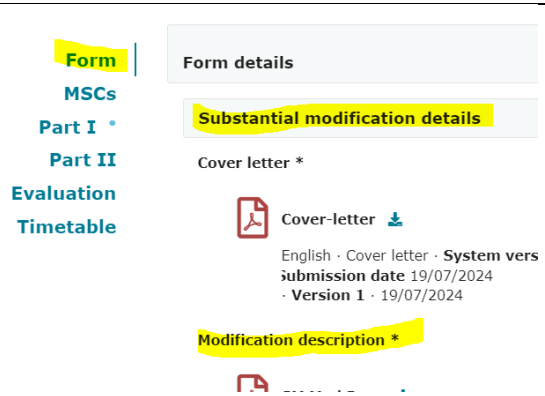
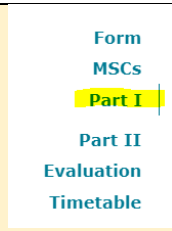
*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

	B1_Description of the modification	Clinical Trials Coordination Group website (hma.eu) Template under Key Documents List – First SM: document requirements after transition. Template name: *Annex II Substantial modification template First SM after transition_vs 2.0*	-Mandatory European template- agreed to by all Member States -Clearly indicate which documents are • New (and need to be assessed) • Updated (and need to be assessed) • Already approved under the CTD and submitted unchanged in CTIS
	B2_NL-NL_Proof of Payment (NL-NL= country code, language code)	CCMO Website - Proof of Payment NL EN	-Mandatory template -Complete all fields (except KvK if not applicable) -Ensure that a reference, purchase or order number is included in section Payment Characteristics (not the EU CT number)
PART I 			

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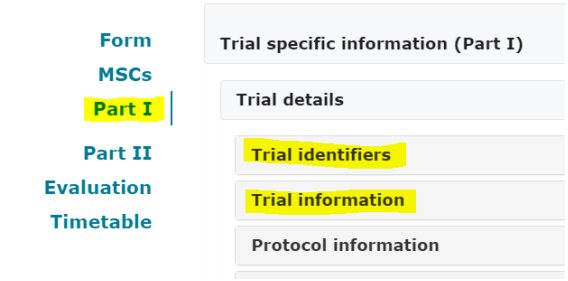
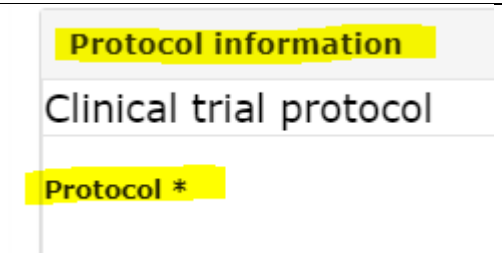
	NA	EudraLex - Volume 10 - European Commission (europa.eu) -See Annex II of the *Questions and Answers Document – Regulation (EU) 536/2014*	-If not yet done, enter all information in English and add the Dutch translations for the full and public study title (Part I, Trial Identifiers) and for the Medical condition, Objectives, Inclusion/Exclusion criteria, Endpoints (Part I, Trial Information)
	D1_Protocol EU CT number	CCMO Website - Protocol NL EN	**-If the protocol is not yet in line with the requirements of the CTR and does not yet list the EU CT number on the first page, submit an updated protocol** -PDF preferred. PDF needs to be searchable -To be published for all trial categories (different timelines apply). Therefore a "For Publication" version (with redactions) and a "Not for Publication" version (without redactions) can be submitted. If no redactions are needed, submit a "For Publication" version only

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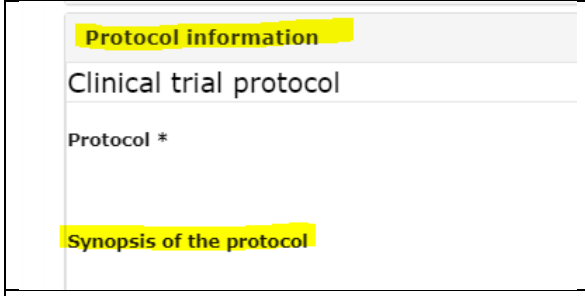
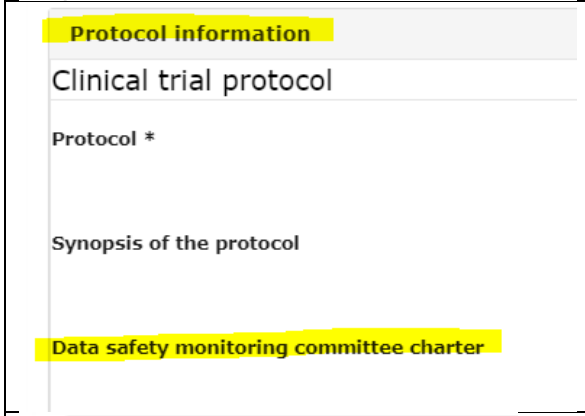
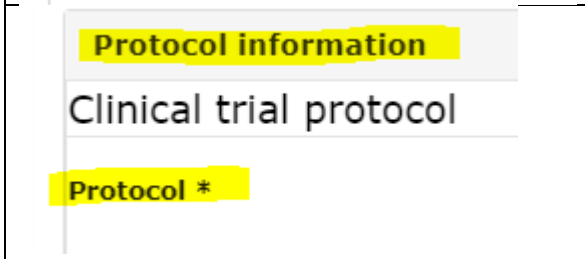
	D1_ NL-NL_Protocol synopsis EU CT number (NL-NL= country code, language code)	CCMO Website - Protocol NL EN	**NEW DOCUMENT FOR CTR!** -Template available, should be 2-3 pages long -Recommended to write this in layman terms -Submit a synopsis in English and Dutch --To be published for all trial categories (different timelines apply).
	D3_DSMB Charter EU CT number	CCMO Website - Protocol NL EN	-If a DSMB Charter was submitted and authorized under the CTD, provide this document, unchanged, in CTIS. If updates have been made for this submission, make this clear in the modification description document and submit clean and track changes versions.
	D4_NL-NL_Patient facing document xxx (NL-NL= country code, language code)	CCMO Website - Protocol NL EN	-If patient facing documents were submitted and authorized under the CTD, provide the documents, unchanged, in CTIS. If updates have been made for this submission, make this clear in the modification description document and submit clean and track changes versions.

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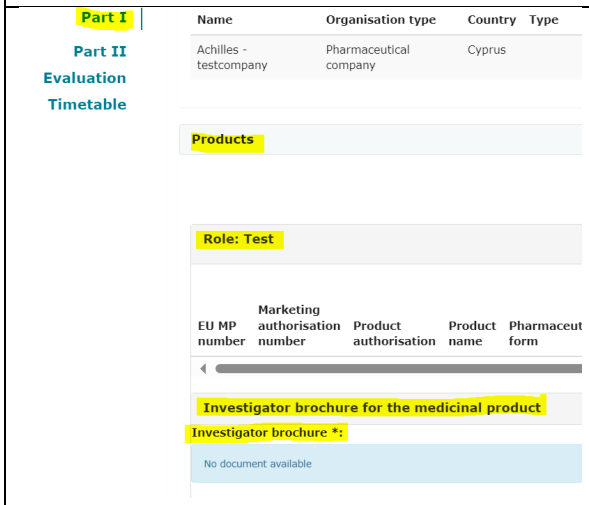
*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

			-Patient-facing documents are documents, other than recruitment material or subject information sheets, presented to clinical trial participants after they have signed the ICF. These documents should not be submitted, unless they are **used to measure study endpoints as described in the protocol, such as questionnaires and diaries,** which then should be submitted in the Protocol section in Part I. -To be published for all trial categories (different timelines apply).
	E1_IB Product name	CCMO Website - IB NL EN	-If applicable -Should not be older than 1 year. Needs to be updated annually. Alternatively the sponsor can submit a sponsor statement in the IB section in CTIS stating that the yearly evaluation did not lead to any substantial changes including changes of the trial benefit/risk. -Needs to contain a clearly identifiable section called “Reference Safety Information” (RSI) -PDF needs to be searchable

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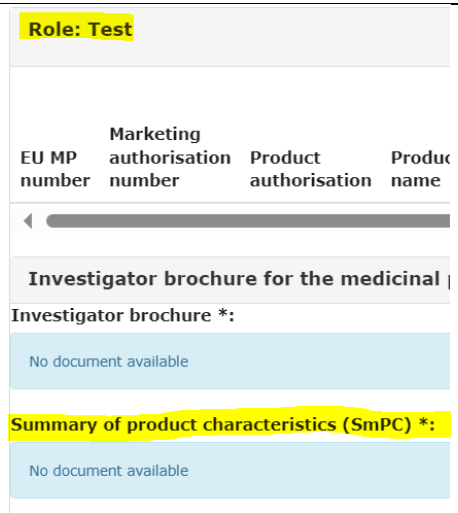
*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

	E2_SmPC Product name	CCMO Website - IB NL EN CTAG recommendations on AxMPs in clinical trials (europa.eu)	-If applicable -Update only if needed -The RSI should be section 4.8 -To be published for category 2 and 3 trials

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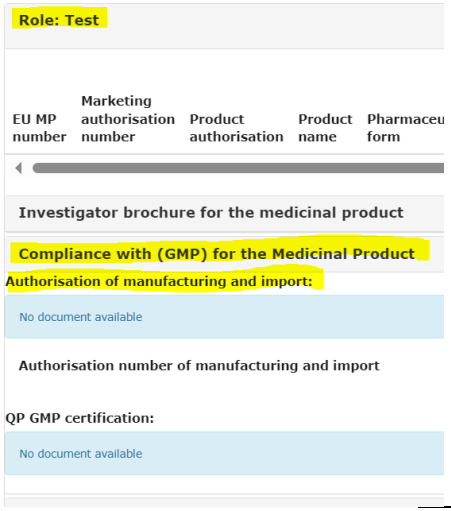
*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

	F1_ MIA product name abbreviated name manufacturer/importer	CCMO Website – GMP Documents NL EN	-If applicable -If new batches are expected after the authorization under the CTR, update the documentation related to compliance with GMP for the IMP for those batches
	F2_QP GMP declaration product name abbreviated name manufacturer/importer	CCMO Website – GMP Documents NL EN	-If applicable -Update only if needed

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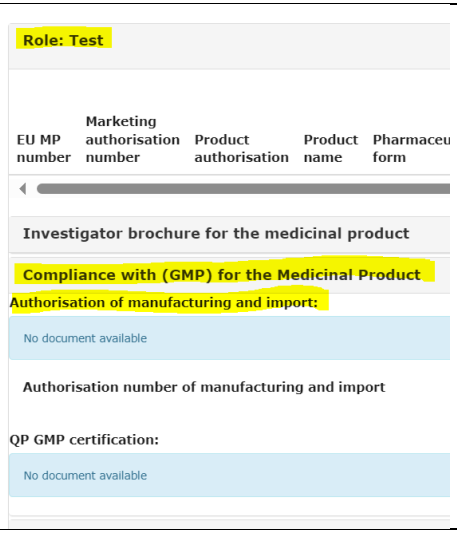
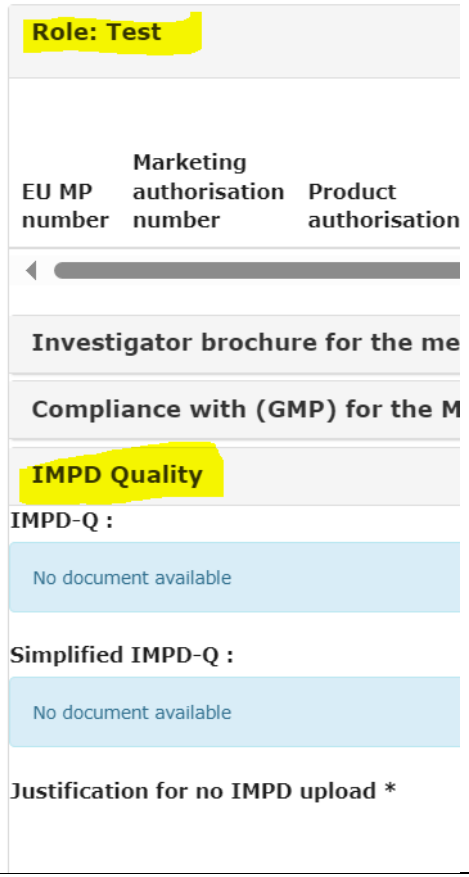
	F3_ Other statements/licences product name abbreviated name manufacturer/importer	CCMO Website – GMP Documents NL EN	-If applicable -Eg import licence or Certificate of GMP compliance -Update only if needed

*Please note this information is subject to change.

*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

	G1_IMPD_Q product name *OR* G1_Simplified IMPD_Q product name	CCMO Website - IMPD NL EN	-If applicable -Update only if needed -PDF needs to be searchable

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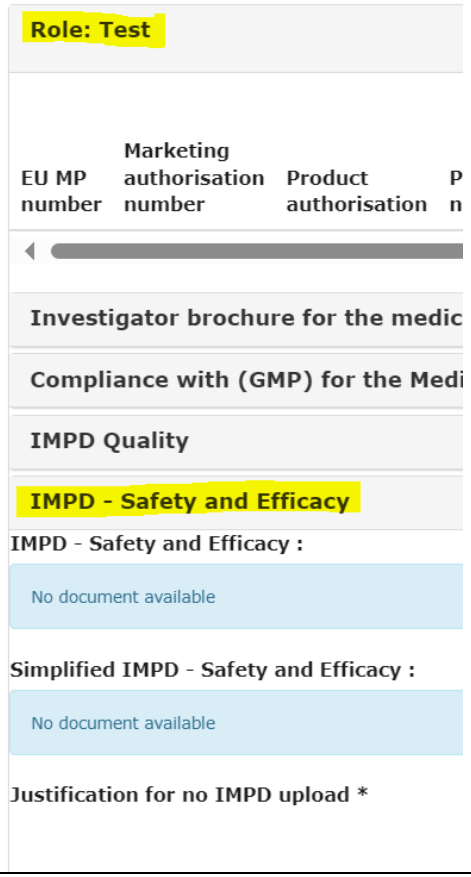
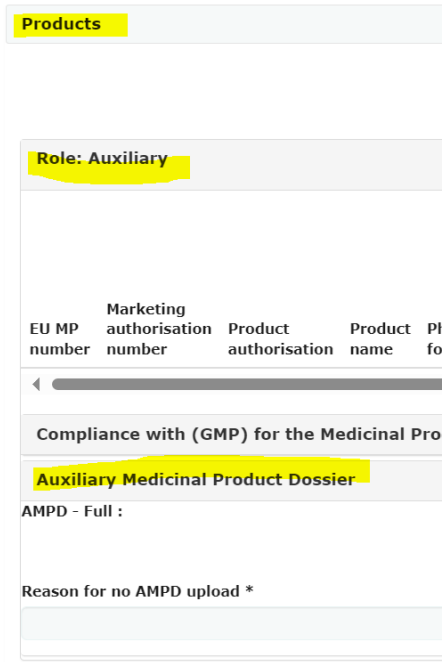
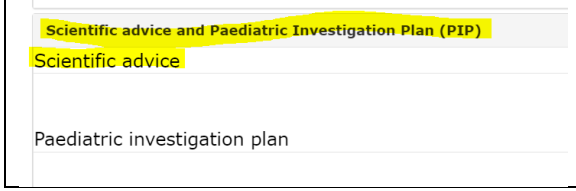
*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

	G1_IMPD_E-S product name *OR* G1_Simplified IMPD E-S product name	CCMO Website - IMPD NL EN	-If applicable -Update only if needed -PDF needs to be searchable

*Please note this information is subject to change.

*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

	H1_AxMPD product name	CCMO Website – AxMPD NL EN CTAG recommendations on AxMPs in clinical trials (europa.eu)	-If applicable -Update only if needed
	I1_Scientific advice name organization	CCMO Website – Scientific advice and PIP NL EN	-If applicable -If scientific advice was submitted and authorized under the CTD, provide the document, unchanged, in CTIS

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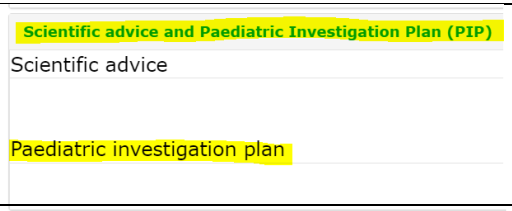
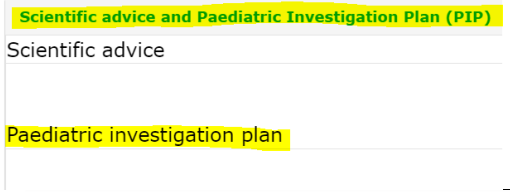
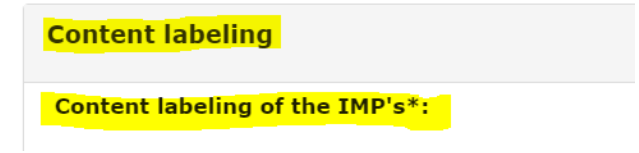
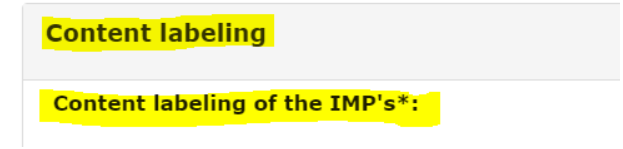
	I2_PedCo opinion	CCMO Website – Scientific advice and PIP NL EN	-If applicable
	I3_EMA PIP decision name agency	CCMO Website – Scientific advice and PIP NL EN	-If applicable -If a PIP was submitted and authorized under the CTD, provide the document, unchanged, in CTIS
	J1_NL-NL_Label IMP_ product name (NL-NL= country code, language code)	CCMO Website – Labels NL EN	-If applicable -If new batches are expected after the authorization under the CTR, update the labels as per CTR Annex VI
	J2_ NL-NL_Label AxMP_product name (NL-NL= country code, language code)	CCMO Website – Labels NL EN	-If applicable -If new batches are expected after the authorization under the CTR, update the labels

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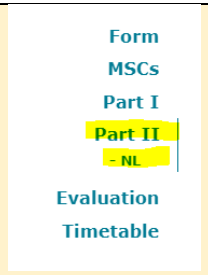
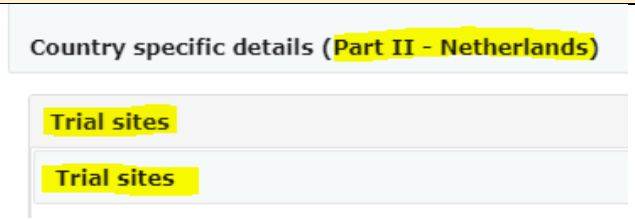
PART II 			
	NA	NA	-Ensure all sites that are still active and that were approved under the CTD as well as the approved Principal Investigator (PI) for each site is listed in this section. If new sites will be introduced during the first SM after the transition, add the trial site and PI here as well.
	K1_Recruitment arrangements	CCMO Website – Recruitment NL EN	**NEW DOCUMENT FOR CTR!** -Mandatory template -Add a sponsor version and date within the document for filing purposes -If recruitment has ended, add a pdf document stating this instead of the mandatory template -To be published for category 2 and 3 trials

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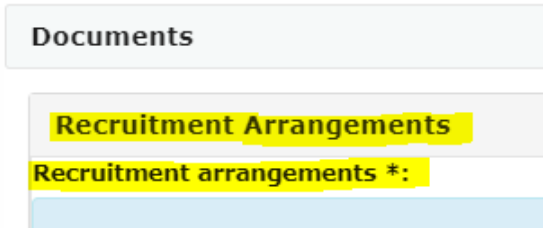	K2_ NL(NL)_Recruitment material_description (NL-NL= country code, language code)	CCMO Website – Recruitment NL EN	-Only submit Dutch, patient facing documents. -If recruitment materials were submitted and authorized under the CTD, provide the documents, unchanged, in CTIS. If updates have been made for this submission, make this clear in the modification description document and submit clean and track changes versions. -Besides the SIS-ICF all information and/or description of procedures related to informed consent that is given to the subjects *before* their decision to participate or abstain from participation shall be submitted together with the SIS-ICF (document code L2). **Recruitment materials are the only other patient-facing documents that may be submitted in Part II (document code K2, section Recruitment arrangements).** Any other patient-facing documents provided to patients *after* they have signed the informed consent should not be submitted. -To be published for category 2 and 3 trials

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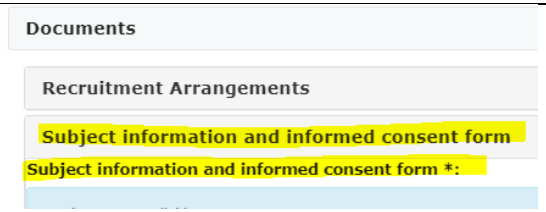
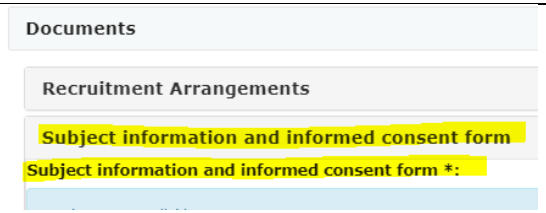
	L1_ NL-NL_SIS and ICF_description (NL-NL= country code, language code)	CCMO Website - ICF NLEN	-Update if needed. If updates have been made for this submission, make this clear in the modification description document and submit clean and track changes versions. -PDF needs to be searchable -Submit Dutch documents -To be published for category 2 and 3 trials
	L2_ NL-NL_Other subject information material_description (NL-NL= country code, language code)	CCMO Website - ICF NLEN	-If these documents were submitted and authorized under the CTD, provide the documents, unchanged, in CTIS. If updates have been made for this submission, make this clear in the modification description document and submit clean and track changes versions. -Besides the SIS-ICF all **information and/or description of procedures related to informed consent that is given to the subjects *before* their decision to participate or abstain from participation** shall be submitted together with the SIS-ICF (document code L2). Recruitment materials are the only other patient-facing documents that may be submitted in Part II (document code K2, section Recruitment

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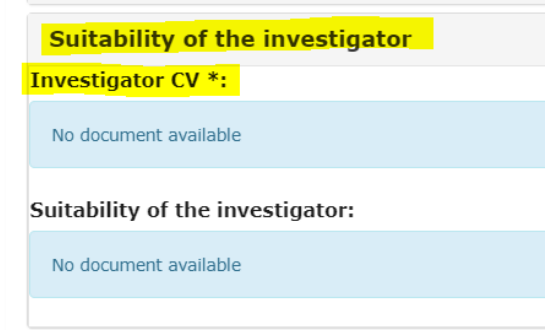
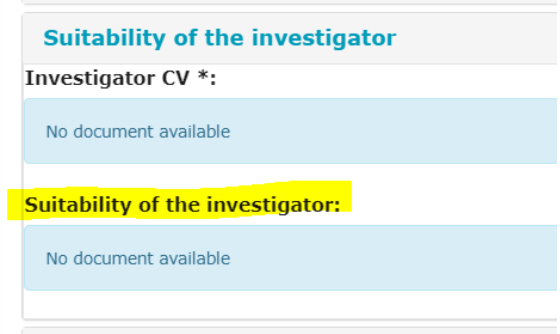
			arrangements). Any other patient-facing documents provided to patients *after* they have signed the informed consent should not be submitted. -Submit Dutch documents -To be published for category 2 and 3 trials
	M1_CV Investigator name investigator and clinical trial site	CCMO Website – Suitability of the Investigator NL EN	-Provide the CV(s) (submitted and authorized under the CTD) unchanged in CTIS -1 Principal Investigator per site -No GCP certificates should be submitted. Relevant training should be evident from the CV
	M2_DoI Investigator name investigator and clinical trial site	CCMO Website – Suitability of the Investigator NL EN	**NEW DOCUMENT FOR CTR!** -Mandatory Declaration of interest (DoI) template for trial sites previously approved under the CTD. Also mandatory for any new trial sites. -1 DoI per site

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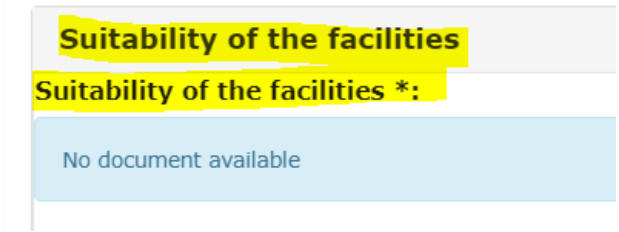
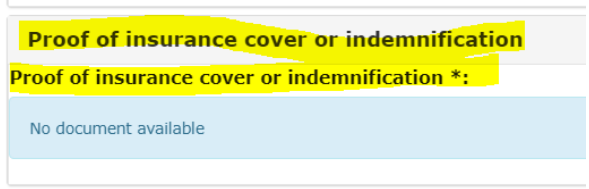
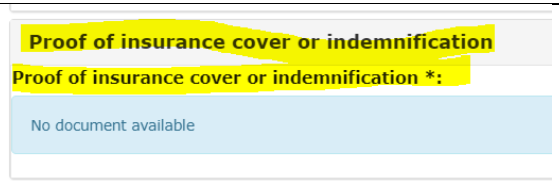
	N1_Site suitability form name clinical trial site	CCMO Website – Suitability of the facilities NL EN	-Provide the Research Declaration / VGO (submitted and authorized under the CTD) unchanged in CTIS. -Submit page 1 only -1 form per site -Clinical Trial Agreements should not be submitted
	O1_Trial participant insurance certificate	CCMO Website – Insurance NL EN	- WMO participant insurance (bewijs proefpersonenverzekering) -Provide the participant insurance (submitted and authorized under the CTD) unchanged in CTIS. However, if the insurance is/is almost expired, submit an updated document
	O2_Proof of coverage sponsor or investigator name sponsor/trial site	CCMO Website – Insurance NL EN	-Liability insurance which covers general liability or both general and product liability -Not required for submission in CTIS if each site has their own insurance and this is clearly stated on page one of the VGO form -Provide the liability insurance (submitted and authorized under the CTD) unchanged in CTIS. However, if the insurance is/is almost expired, submit an updated document

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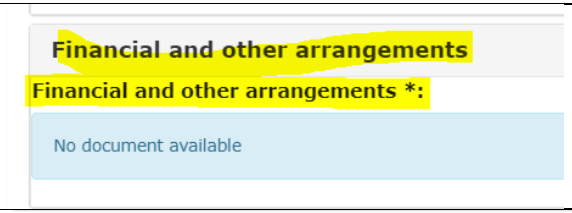
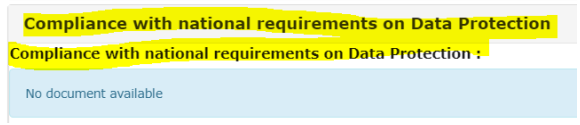
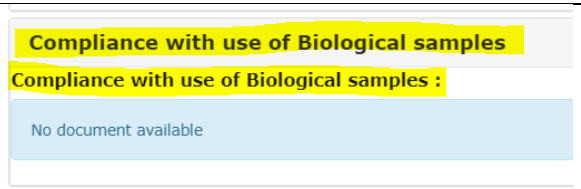
	P1_Compensation trial participants, investigator, funding and other arrangements	CCMO Website – Financial arrangements NL EN	**NEW DOCUMENT FOR CTR!** -Mandatory template - Add a sponsor version and date within the document for filing purposes
	R1_Compliance on the collection and use of personal data	CCMO Website – National Data protection NL EN	**NEW DOCUMENT FOR CTR!** -Mandatory template - Add a sponsor version and date within the document for filing purposes
	S1_Compliance on the collection, use and storage of biological samples	CCMO Website – Biological samples NL EN	**NEW DOCUMENT FOR CTR!** -Mandatory template -Add a sponsor version and date within the document for filing purposes -If no biological samples will be used in the study, upload a pdf stating this in this section instead of the mandatory template

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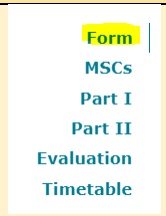
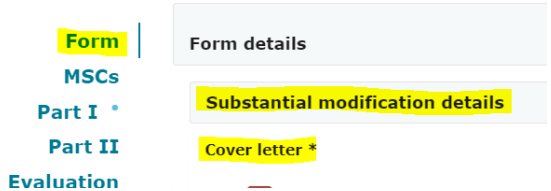
Centrale Commissie Mensgebonden Onderzoek

SUBSTANTIAL MODIFICATION (SM): Document List

Legend
Blue text: text needs to be completed by sponsor.
Green text: Document subject to publication (depending on trial category). See the Guidance document and Annex 1 found under transparency.

Location in CTIS	Document & Naming Convention	Link	Additional Information
FORMS 			
	B1_Cover letter SM# EU CT number	Clinical Trials Coordination Group website (hma.eu) Template under Key Documents List – Substantial Modification (SM). Template name: *Cover letter*	-Mandatory European template- agreed to by all Member States -Clearly describe the location of the RSI if updated

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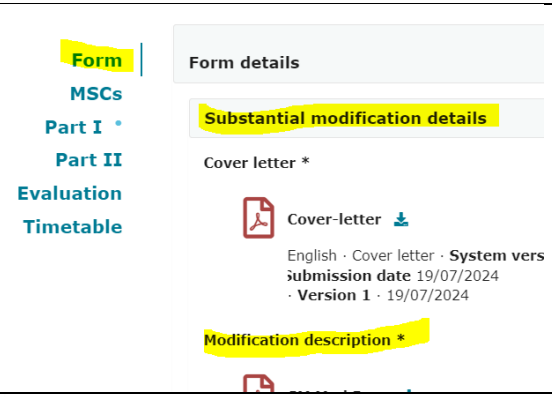
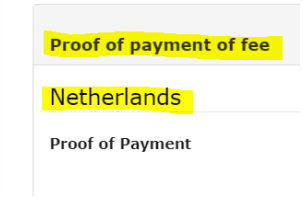
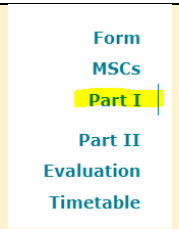
	B1_Description of the modification	Clinical Trials Coordination Group website (hma.eu) Template under Key Documents List – Substantial Modification (SM). Template name: *Modification description*	-Mandatory European template- agreed to by all Member States
	B2_NL-NL_Proof of Payment (NL-NL= country code, language code)	CCMO Website - Proof of Payment NL EN	-Mandatory template -Complete all fields (except KvK if not applicable) -Ensure that a reference, purchase or order number is included in section Payment Characteristics (not the EU CT number)
Part I 			

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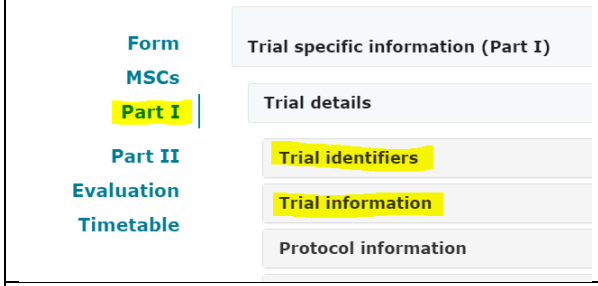
*For submissions in other Member States Concerned (MSCs), please research the country specific requirements for that MSC (please see Q&A document – Regulation (EU) 536/2014 Annex II and III as well as the Overview part II requirements by MedEthicsEU).

	NA	EudraLex - Volume 10 - European Commission (europa.eu) -See Annex II of the *Questions and Answers Document – Regulation (EU) 536/2014*	-If not yet done, enter all information in English and add the Dutch translations for the full and public study title (Part I, Trial Identifiers) and for the Medical condition, Objectives, Inclusion/Exclusion criteria, Endpoints (Part I, Trial Information)
Any updated documents	Add "_TC" or "_SoC" to the end of your document name Example: D1_Protocol EU CT number_TC D1_Protocol EU CT number_SoC		- If you are submitting an updated protocol, IB or IMPD, always submit a searchable track changes version *and* a summary of changes version. -If you are submitting an updated ICF, always submit a searchable track changes version. -For all other documents (for eg, K1, P1, etc) always submit a track changes version, if possible. -Ensure any updated documents have a sponsor version and date within the document for filing purposes

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