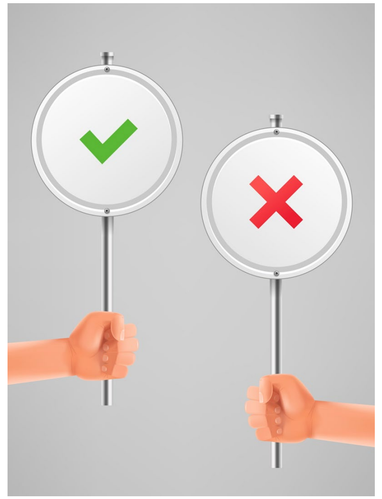
Centrale Commissie Mensgebonden Onderzoek

Best practices for transitional trials and their management in CTIS

Monique Al, special advisor CCMO, The Netherlands
vice-chair CTCG, co-chair MedEthicsEU



DO!

START TO TRANSITION YOUR CLINICAL TRIAL NOW!

DON’T!

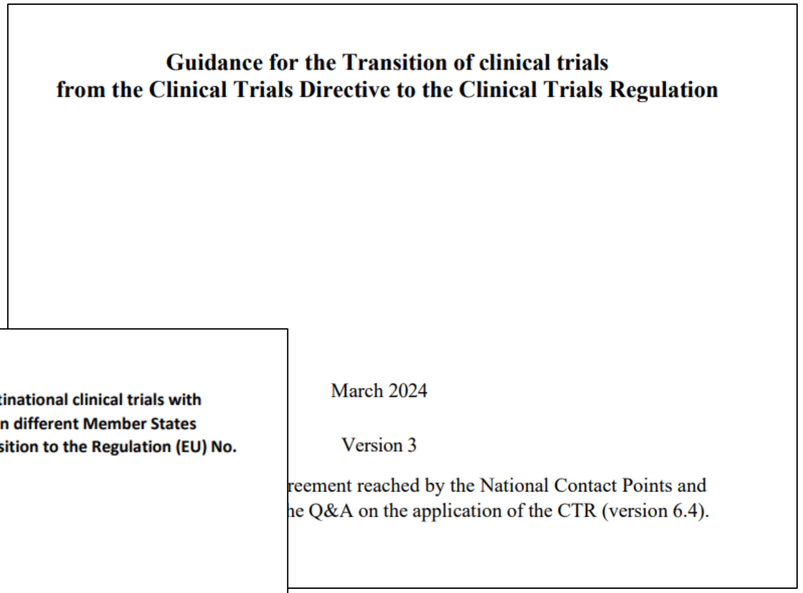
POSTPONE TRANSITION TO THE END OF TRANSITIONAL PERIOD

END (PREMATURE) THE TRIAL TO PREVENT TRANSITION

GUIDANCE and BEST PRACTICE GUIDE ON TRANSITION TRIALS

- Commission guidance on transition trials (Eudralex volume 10): https://health.ec.europa.eu/document/download/10c83e6b-2587-420d-9204-d49c2f75f476_en?filename=transition_ct_dir-reg_guidance_en.pdf

- CTCG best practice transition multinational clinical trials and template cover letter at CTCG website, key document list, section transitional trials: https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html

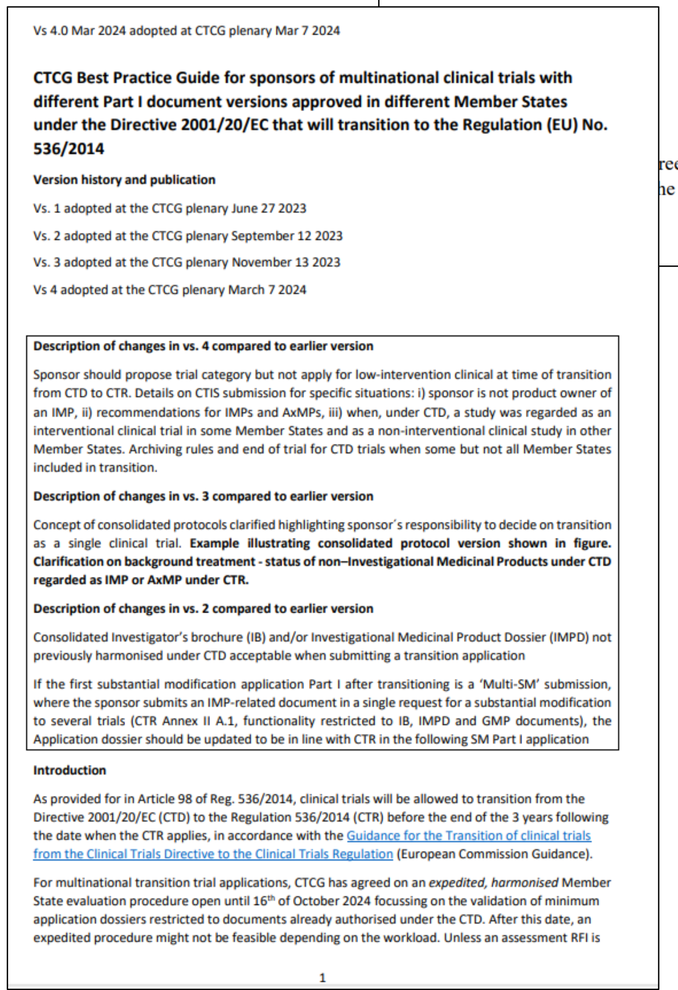


Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation

March 2024

Version 3

reement reached by the National Contact Points and he Q&A on the application of the CTR (version 6.4).



Vs 4.0 Mar 2024 adopted at CTCG plenary Mar 7 2024

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

Version history and publication

Vs. 1 adopted at the CTCG plenary June 27 2023

Vs. 2 adopted at the CTCG plenary September 12 2023

Vs. 3 adopted at the CTCG plenary November 13 2023

Vs 4 adopted at the CTCG plenary March 7 2024

Description of changes in vs. 4 compared to earlier version

Sponsor should propose trial category but not apply for low-intervention clinical at time of transition from CTD to CTR. Details on CTIS submission for specific situations: i) sponsor is not product owner of an IMP, ii) recommendations for IMPs and AxMPs, iii) when, under CTD, a study was regarded as an interventional clinical trial in some Member States and as a non-interventional clinical study in other Member States. Archiving rules and end of trial for CTD trials when some but not all Member States included in transition.

Description of changes in vs. 3 compared to earlier version

Concept of consolidated protocols clarified highlighting sponsor´s responsibility to decide on transition as a single clinical trial. **Example illustrating consolidated protocol version shown in figure. Clarification on background treatment - status of non–Investigational Medicinal Products under CTD regarded as IMP or AxMP under CTR.**

Description of changes in vs. 2 compared to earlier version

Consolidated Investigator's brochure (IB) and/or Investigational Medicinal Product Dossier (IMPD) not previously harmonised under CTD acceptable when submitting a transition application

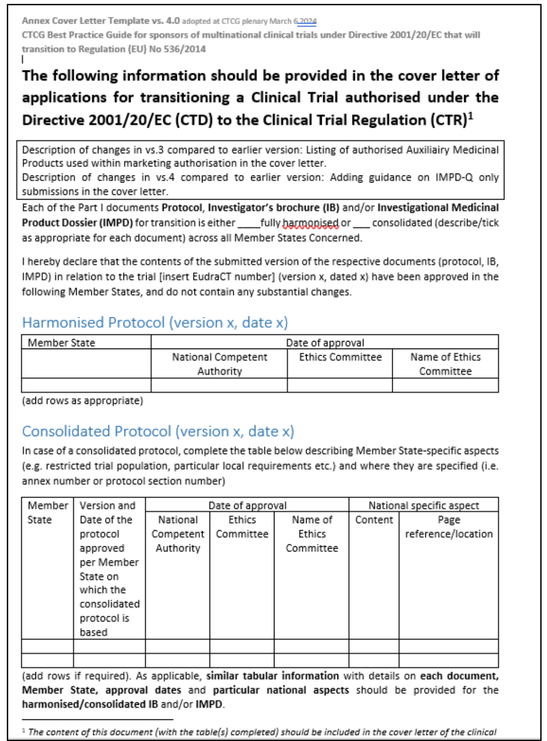
If the first substantial modification application Part I after transitioning is a 'Multi-SM' submission, where the sponsor submits an IMP-related document in a single request for a substantial modification to several trials (CTR Annex II A.1, functionality restricted to IB, IMPD and GMP documents), the Application dossier should be updated to be in line with CTR in the following SM Part I application

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 Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation (European Commission Guidance).

For multinational transition trial applications, CTCG has agreed on an *expedited, harmonised* Member State evaluation procedure open until 16th of October 2024 focussing on the validation of minimum application dossiers restricted to documents already authorised under the CTD. After this date, an expedited procedure might not be feasible depending on the workload. Unless an assessment RFI is

1



Annex Cover Letter Template vs. 4.0 adopted at CTCG plenary March 6 2024
CTCG Best Practice Guide for sponsors of multinational clinical trials under Directive 2001/20/EC that will transition to Regulation (EU) No 536/2014

The following information should be provided in the cover letter of applications for transitioning a Clinical Trial authorised under the Directive 2001/20/EC (CTD) to the Clinical Trial Regulation (CTR)[1]

Description of changes in vs.3 compared to earlier version: Listing of authorised Auxiliairy Medicinal Products used within marketing authorisation in the cover letter.
Description of changes in vs.4 compared to earlier version: Adding guidance on IMPD-Q only submissions in the cover letter.

Each of the Part I documents **Protocol**, **Investigator's brochure (IB)** and/or **Investigational Medicinal Product Dossier (IMPD)** for transition is either ____fully harmonised or ___ consolidated (describe/tick as appropriate for each document) across all Member States Concerned.

I hereby declare that the contents of the submitted version of the respective documents (protocol, IB, IMPD) in relation to the trial [insert EudraCT number] (version x, dated x) have been approved in the following Member States, and do not contain any substantial changes.

Harmonised Protocol (version x, date x)

Member State	Date of approval		
	National Competent Authority	Ethics Committee	Name of Ethics Committee

(add rows as appropriate)

Consolidated Protocol (version x, date x)

In case of a consolidated protocol, complete the table below describing Member State-specific aspects (e.g. restricted trial population, particular local requirements etc.) and where they are specified (i.e. annex number or protocol section number)

Member State	Version and Date of the protocol approved per Member State on which the consolidated protocol is based	Date of approval			National specific aspect	
		National Competent Authority	Ethics Committee	Name of Ethics Committee	Content	Page reference/location

(add rows if required). As applicable, **similar tabular information** with details on **each document, Member State, approval dates** and **particular national aspects** should be provided for the **harmonised/consolidated IB** and/or **IMPD**.

[1] *The content of this document (with the table(s) completed) should be included in the cover letter of the clinical*

FIRST SM (part I and/or part II) after TRANSITION

CTCG Best practice on first SM after transition (including templates cover letter and substantial modification description: See key documents list at CTCG website!!!

https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html

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

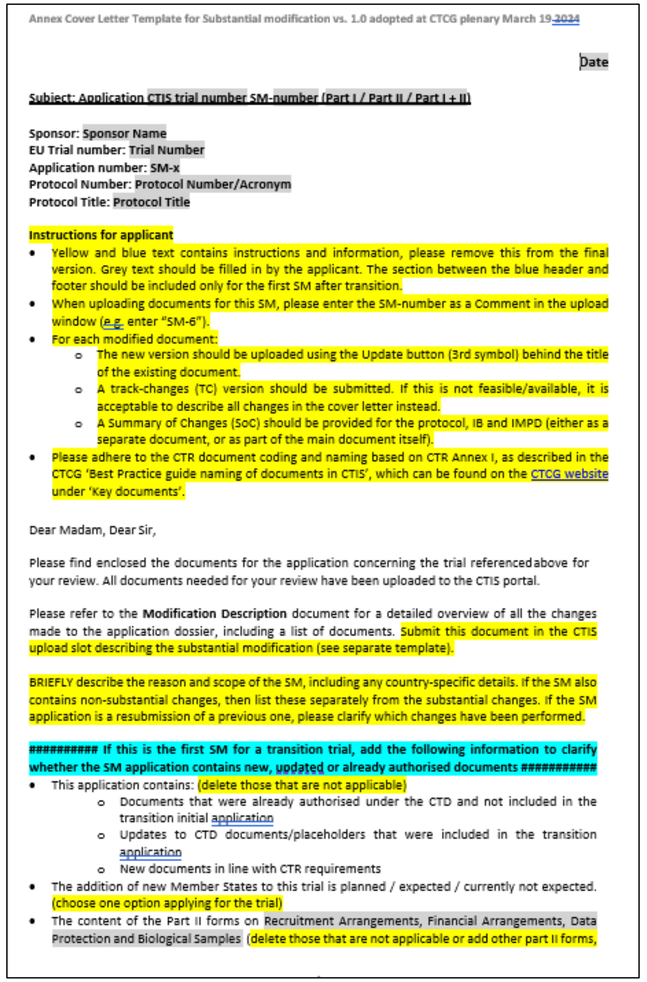
The first substantial modification application Part I after transition should update documents in line with the requirements of the Clinical Trials Regulation EU no 536/2014 (CTR) at the time there is a need for the sponsor to update any of the documents in the Application Dossier Part I through a planned 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 Annex II of Regulation (EU) No 536/2014 and question 3.8 of the COM Q&A CTR). 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 requirements of the CTR before an additional Member State Concerned (addMSC) is added[1]. This update should be done through an SM part I application, unless completed at the time of the initial transition or a previous SM part I.

With the aim to harmonise requirements in EU/EEA, the table below lists different stages of the clinical trial after transition (horizontal) and the agreement in CTCG on which documents/structured data (vertical) need to be updated to be in line with CTR (vertical) at the time of the first SM Part I after transition of a minimum trial dossier in line with guidance by the European Commission[1] and CTCG[2].

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 new transparency rules (see Questions and Answers document on future transparency rules[3]

	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 procedures**
Cover letter	See Cover Letter Template for First SM after transition (as well as template for Substantial Modification Description)	See Cover Letter Template for First SM after transition (as well as template for Substantial Modification Description)	See Cover Letter Template for First SM after transition (as well as



Annex Cover Letter Template for Substantial modification vs. 1.0 adopted at CTCG plenary March 19 2024

Date

Subject: Application CTIS trial number SM-number (Part I / Part II / Part I + II)

Sponsor: Sponsor Name
EU Trial number: Trial Number
Application number: SM-x
Protocol Number: Protocol Number/Acronym
Protocol Title: Protocol Title

Instructions for applicant

- Yellow and blue text contains instructions and information, please remove this from the final version. Grey text should be filled in by the applicant. The section between the blue header and footer should be included only for the first SM after transition.
- When uploading documents for this SM, please enter the SM-number as a Comment in the upload window (e.g. enter "SM-6").
- For each modified document:
  - The new version should be uploaded using the Update button (3rd symbol) behind the title of the existing document.
  - A track-changes (TC) version should be submitted. If this is not feasible/available, it is acceptable to describe all changes in the cover letter instead.
  - A Summary of Changes (SoC) should be provided for the protocol, IB and IMPD (either as a separate document, or as part of the main document itself).
- Please adhere to the CTR document coding and naming based on CTR Annex I, as described in the CTCG 'Best Practice guide naming of documents in CTIS', which can be found on the CTCG website under 'Key documents'.

Dear Madam, Dear Sir,

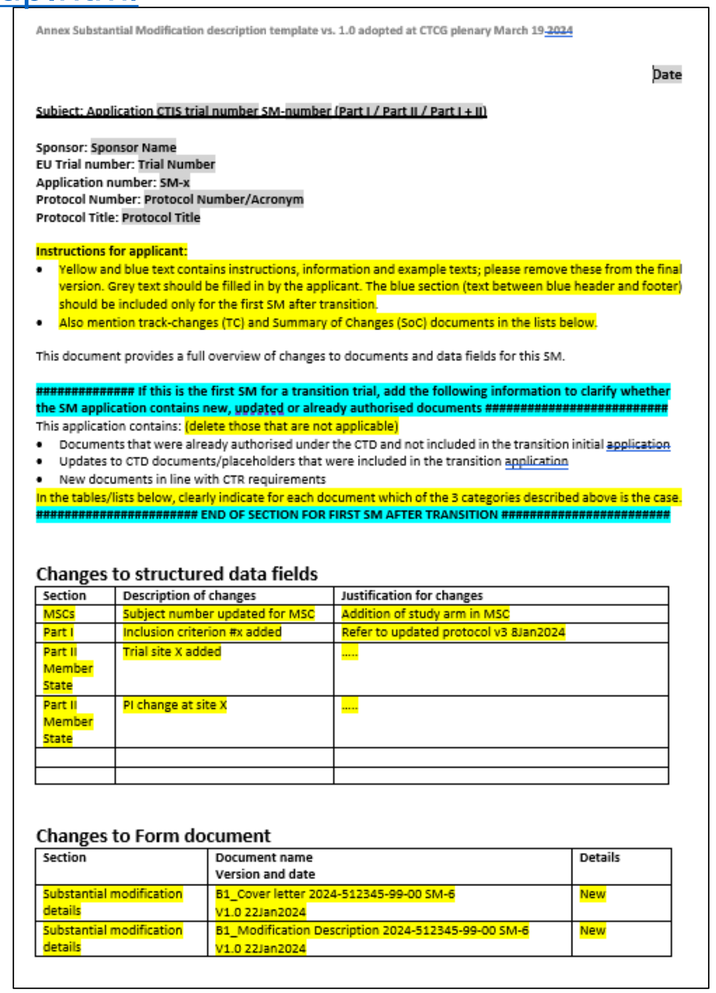
Please find enclosed the documents for the application concerning the trial referenced above for your review. All documents needed for your review have been uploaded to the CTIS portal.

Please refer to the **Modification Description** document for a detailed overview of all the changes made to the application dossier, including a list of documents. Submit this document in the CTIS upload slot describing the substantial modification (see separate template).

BRIEFLY describe the reason and scope of the SM, including any country-specific details. If the SM also contains non-substantial changes, then list these separately from the substantial changes. If the SM application is a resubmission of a previous one, please clarify which changes have been performed.

########## If this is the first SM for a transition trial, add the following information to clarify whether the SM application contains new, updated or already authorised documents ##########

- This application contains: (delete those that are not applicable)
  - Documents that were already authorised under the CTD and not included in the transition initial application
  - Updates to CTD documents/placeholders that were included in the transition application
  - New documents in line with CTR requirements
- The addition of new Member States to this trial is planned / expected / currently not expected. (choose one option applying for the trial)
- The content of the Part II forms on Recruitment Arrangements, Financial Arrangements, Data Protection and Biological Samples (delete those that are not applicable or add other part II forms,



Annex Substantial Modification description template vs. 1.0 adopted at CTCG plenary March 19 2024

Date

Subject: Application CTIS trial number SM-number (Part I / Part II / Part I + II)

Sponsor: Sponsor Name
EU Trial number: Trial Number
Application number: SM-x
Protocol Number: Protocol Number/Acronym
Protocol Title: Protocol Title

Instructions for applicant:

- Yellow and blue text contains instructions, information and example texts; please remove these from the final version. Grey text should be filled in by the applicant. The blue section (text between blue header and footer) should be included only for the first SM after transition.
- Also mention track-changes (TC) and Summary of Changes (SoC) documents in the lists below.

This document provides a full overview of changes to documents and data fields for this SM.

############ If this is the first SM for a transition trial, add the following information to clarify whether the SM application contains new, updated or already authorised documents ##########
This application contains: (delete those that are not applicable)

- Documents that were already authorised under the CTD and not included in the transition initial application
- Updates to CTD documents/placeholders that were included in the transition application
- New documents in line with CTR requirements

In the tables/lists below, clearly indicate for each document which of the 3 categories described above is the case.
########## END OF SECTION FOR FIRST SM AFTER TRANSITION ##########

Changes to structured data fields

Section	Description of changes	Justification for changes
MSCs	Subject number updated for MSC	Addition of study arm in MSC
Part I	Inclusion criterion #x added	Refer to updated protocol v3 8Jan2024
Part II Member State	Trial site X added	.....
Part II Member State	PI change at site X	.....

Changes to Form document

Section	Document name Version and date	Details
Substantial modification details	B1_Cover letter 2024-512345-99-00 SM-6 V1.0 22Jan2024	New
Substantial modification details	B1_Modification Description 2024-512345-99-00 SM-6 V1.0 22Jan2024	New

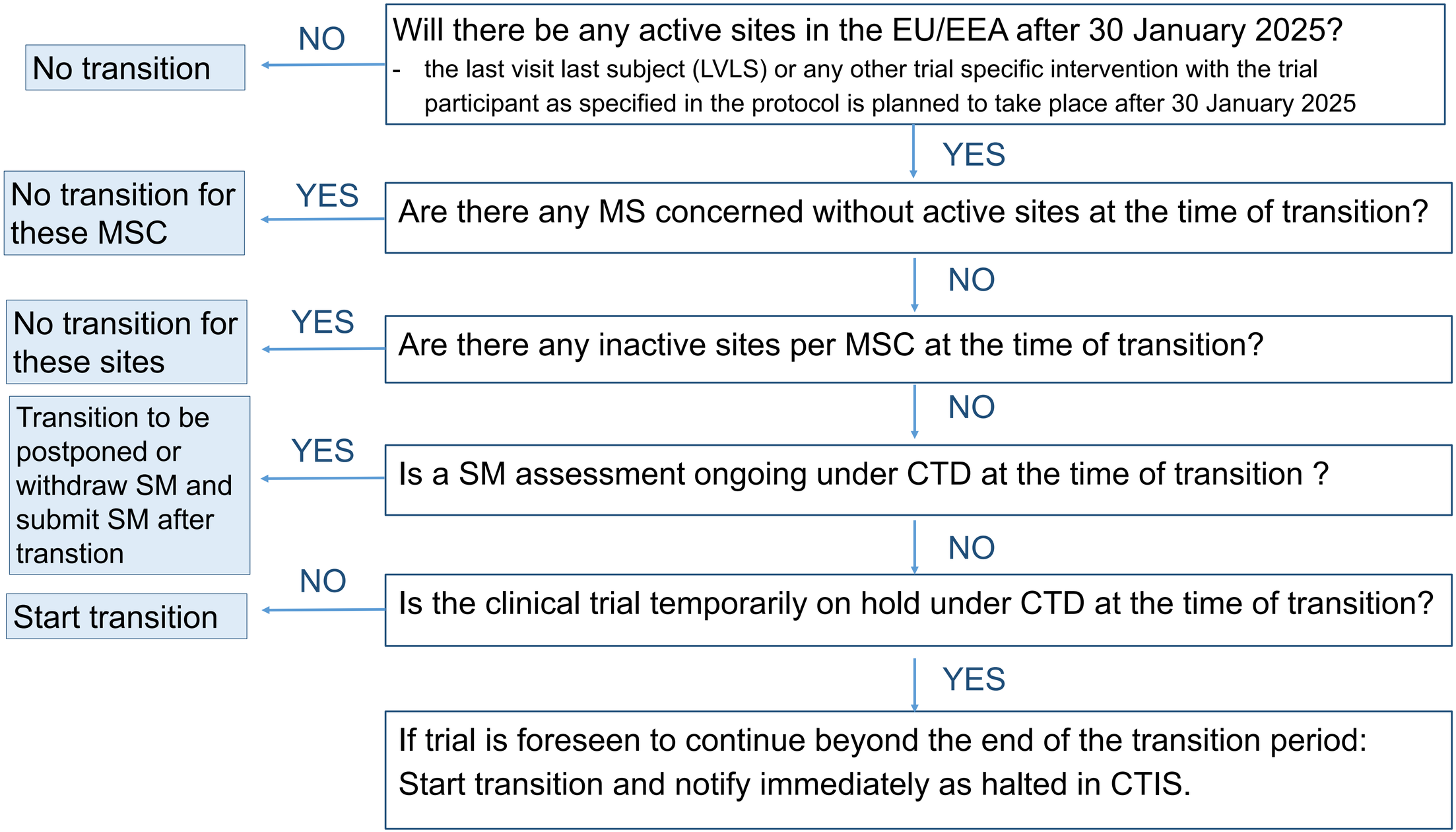
CRITERIA TRANSITION from CTD to CTR and CONCEPT of ACTIVE SITES

- Trials that can be transitioned: Only trials authorised under the CTD and likely to be ongoing beyond 30 January 2025 need to be transitioned if they meet these criteria:
  - are interventional clinical trials in humans;
  - involve **at least one active site** in the EU/EEA where the trial is still ongoing;
  - there are no substantial amendments ongoing in any Member State Concerned (MSC) under CTD.

- **Active site**: the concept active site implies that if the **last visit last subject** (LVLS) or any other **trial specific intervention with the subject** as specified in the protocol **took place before** this date, the trial does **not** have **to be transitioned**.

- **At the time of transition: all active sites have to be transitioned!**

Decision tree administrative transition clinical trial



EudraCT for clinical trials with no active sites and not transitioned

- If there are **no active sites in EU/EEA** but the EoT has not yet been notified, the trial should **not be transitioned**
- **EudraCT remains open** beyond the end of the transition period for sponsors:

➢to notify (global) end of the trial and submission of summary results of trials completed under the Directive.

➢to keep registering in EudraCT trials conducted exclusively outside of the EU/EEA that are part of a Paediatric Investigation Plan (PIP) and/or in scope of Article 46 of the Paediatric Regulation (EC) 1901/2006, until a relevant functionality is delivered in CTIS.

Documentation: minimum set of documents

Sponsor needs to submit an initial application relying on the **existing CTD dossier**, already assessed and **authorised**.

The following minimum set of data/documentation is required:

Structured fields and forms

- ✓ All mandatory application structured data fields in CTIS need to be completed.
- ✓ Statement on GDPR compliance (*new, required for users CTIS*)
- ✓ Cover Letter. The cover letter should follow the format of the CTCG template cover letter for transition trials

Part I

- ✓ Protocol (consolidated/harmonised)
- ✓ Investigator's Brochure (consolidated/harmonised) or SmPC for marketed product
- ✓ IMPD (consolidatd/harmonised)
- ✓ GMP relevant documents
- ✓ Documents related to auxilliary medicinal products* (non-IMPs under CTD)

Part II

- ✓ Subject information sheet and informed consent form

- Auxilliary medicinal products in clinical trials, update 3 March 2024: https://health.ec.europa.eu/document/download/47ad006a-6ad4-488d-bb51-ab91d11e2871_en?filename=2017_06_28_recommendation_on_axmps.pdf

Documentation: minimum set of documents

- ✓ Only the **latest approved versions** should be included in the transition application
- ✓ The sponsor may choose to **include additional part I documents** (not listed in previous slide) as outlined in CTR annex I, provided that these have been **authorised under CTD**
- ✓ A **list of the minimum set of documents part II per MS** have been published in annex to the Commission guidance on transition trials (Eudralex volume 10): https://health.ec.europa.eu/document/download/10c83e6b-2587-420d-9204-d49c2f75f476_en?filename=transition_ct_dir-reg_guidance_en.pdf
- ✓ All **other part I or II documents** (not listed), the sponsor **replace them with a document clarifying "Assessed by National Competent Authority (NCA) and/or ethics committee** who has given a positive opinion on the clinical trial under the CTD" and therefore **covered by the conclusion of the assessment under the CTD**.
- ✓ **Additional documents Part I documents approved in some, but not all MSCs** (e.g. the **DSMB Charter** for Part I or layperson **synopsis in national language**) can be included as well, provided that these have been **authorised under the CTD** and they are clearly **indicated in the cover letter** as applicable for those MSs only.

Harmonised or consolidated protocol, IB, IMPD

- Transition of **multiple versions** of these part I documents within one clinical trial application under a single EU CT number is **NOT possible**
- Only **one single document** should be uploaded.
- A **harmonised protocol, IB and/or IMPD** means that the respective document(s) is **identical** and includes the same trial procedures/ information in all countries **approved across all EU Member States under the CTD**.

- A **consolidated protocol, IB and/or IMPD** means that there are **differences** in the respective document(s) **in different Member States**, but the document itself is identical, i.e. **Member State-specific differences are outlined within the document text or in an appendix** to the respective document.
- **Non-substantial modifications** (in line with annex IV of the Commission Q&A on Eudralex volume 10), can also be included in a **consolidated** document for transition.

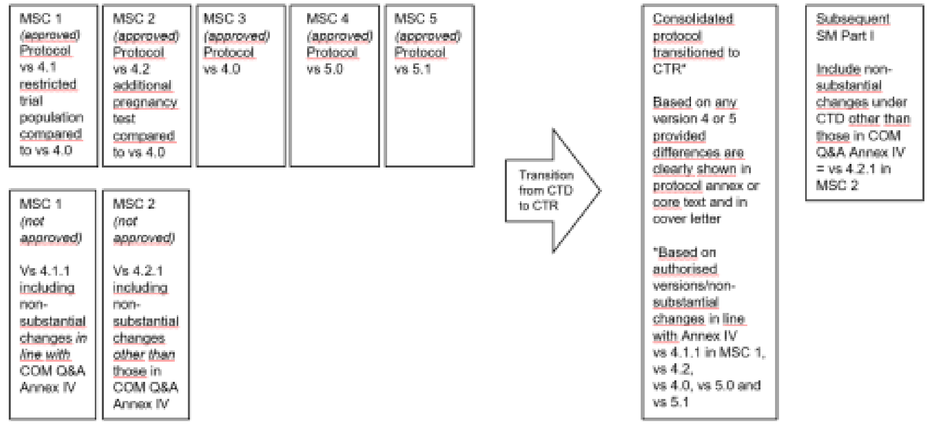
INITIAL TRANSITION CT APPLICATION

DO!

CONSOLIDATED PROTOCOL, IB or IMPD in case of DIFFERENT authorised versions in MULTINATIONAL clinical trials

ANNEX

An example illustrating transition of a CTD trial to CTR with different protocol versions approved in the Member States Concerned – for some MSCs including additional non-substantial changes



Documentation/structured data: some specifications

- ✓ Category **low-intervention clinical trials** is **not applicable** for transition clinical trial at the time of transition.
- ✓ **Categorisation AxMP (non-IMP under CTD) vs IMP,** if not harmonised among MSC under CTD: **harmonisation at the time of transition** – administrative procedure, see page 5 in CTCG best practice for sponsors on transition (https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html)
- ✓ The **approved IMPD** can 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.
- ✓ If **sponsor** is **not the product owner of the IMP** and no reference trial in CTIS**: no IMPD-Q submission in the initial transition step** but with next SM part I (link to IMPD-Q only submission or reference trial, if applicable)
- ✓ **Documentation labelled with EudraCT trial number** (=approved under CTD) is acceptable and does not have to be updated with EU CT number before transition (e.g. protocol, QP declaration or IMP labels)
- ✓ **No update of templates** needed
- ✓ **No need to retro-spectively create a site suitability form**
- ✓ **Mandatory use of CTCG template cover letter** (annex to CTCG best practice guidance for sponsors).

EXPEDITED ADMINISTRATIVE TRANSITION OPEN UNTIL16 OCTOBER 2024!

After this date an expedited administrative transition might not be feasible anymore!!

Validation
max 25 days
(with RFI)

Assessment
Max ± 7 days
(no RFI)

Decision
max 5 days

- Validation phase in line with article 5 CTR (no RFI max 10 days; with RFI max 25 days)
- Assessment phase max ±7 days – no re-assessment of clinical trial
- If there are errors in trial category/deferrals as proposed by sponsor → RFI → timelines for assessment phase fall back on max timelines article 6 CTR (max 76 days)
- No tacit conclusion part II – assessment phase also max ±7 days
- Decision phase in line with article 8 CTR (max 5 days)
- During transition, the clinical trial can continue under the CTD

Please keep an eye in CTIS in order for your application not to lapse!

AFTER TRANSITION CT IS APPROVED

DO!

CONDUCT CT according to rules CTR

COMPLETE CT DOSSIER PART I with next SUBSTANTIAL MODIFICATION PART I

COMPLETE CT APPLICATION PART II with next SUBSTANTIAL MODIFICATION PART II

FIRST SM (part I and/or part II) after TRANSITION

CTCG Best practice on first SM after transition (including templates cover letter and substantial modification description: See key documents list at CTCG website!!!

https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html

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

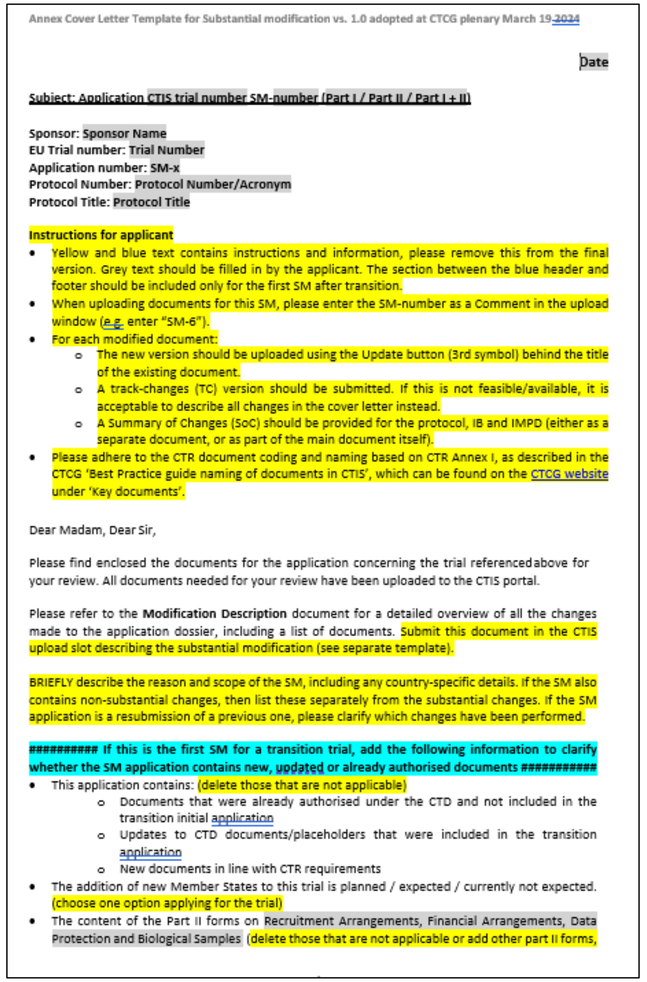
The first substantial modification application Part I after transition should update documents in line with the requirements of the Clinical Trials Regulation EU no 536/2014 (CTR) at the time there is a need for the sponsor to update any of the documents in the Application Dossier Part I through a planned 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 Annex II of Regulation (EU) No 536/2014 and question 3.8 of the COM Q&A CTR). 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 requirements of the CTR before an additional Member State Concerned (addMSC) is added[1]. This update should be done through an SM part I application, unless completed at the time of the initial transition or a previous SM part I.

With the aim to harmonise requirements in EU/EEA, the table below lists different stages of the clinical trial after transition (horizontal) and the agreement in CTCG on which documents/structured data (vertical) need to be updated to be in line with CTR (vertical) at the time of the first SM Part I after transition of a minimum trial dossier in line with guidance by the European Commission[1] and CTCG[2].

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 new transparency rules (see Questions and Answers document on future transparency rules[3]

	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 procedures**
Cover letter	See Cover Letter Template for First SM after transition (as well as template for Substantial Modification Description)	See Cover Letter Template for First SM after transition (as well as template for Substantial Modification Description)	See Cover Letter Template for First SM after transition (as well as



Annex Cover Letter Template for Substantial modification vs. 1.0 adopted at CTCG plenary March 19 2024

Date

Subject: Application CTIS trial number SM-number (Part I / Part II / Part I + II)

Sponsor: Sponsor Name
EU Trial number: Trial Number
Application number: SM-x
Protocol Number: Protocol Number/Acronym
Protocol Title: Protocol Title

Instructions for applicant

- Yellow and blue text contains instructions and information, please remove this from the final version. Grey text should be filled in by the applicant. The section between the blue header and footer should be included only for the first SM after transition.
- When uploading documents for this SM, please enter the SM-number as a Comment in the upload window (e.g. enter "SM-6").
- For each modified document:
  - The new version should be uploaded using the Update button (3rd symbol) behind the title of the existing document.
  - A track-changes (TC) version should be submitted. If this is not feasible/available, it is acceptable to describe all changes in the cover letter instead.
  - A Summary of Changes (SoC) should be provided for the protocol, IB and IMPD (either as a separate document, or as part of the main document itself).
- Please adhere to the CTR document coding and naming based on CTR Annex I, as described in the CTCG 'Best Practice guide naming of documents in CTIS', which can be found on the CTCG website under 'Key documents'.

Dear Madam, Dear Sir,

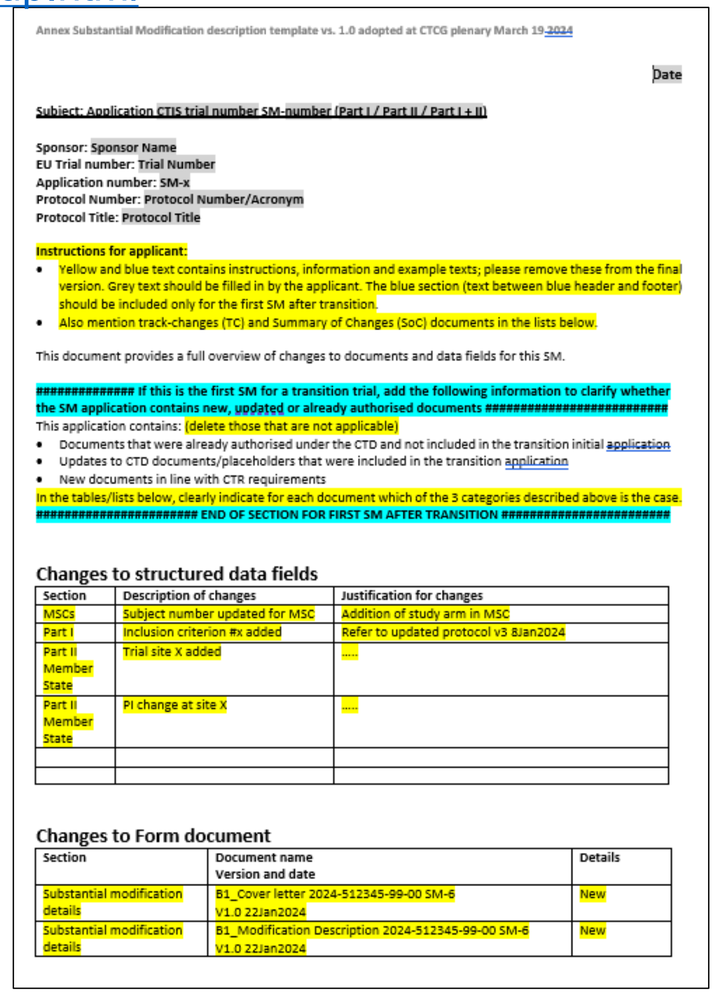
Please find enclosed the documents for the application concerning the trial referenced above for your review. All documents needed for your review have been uploaded to the CTIS portal.

Please refer to the **Modification Description** document for a detailed overview of all the changes made to the application dossier, including a list of documents. Submit this document in the CTIS upload slot describing the substantial modification (see separate template).

BRIEFLY describe the reason and scope of the SM, including any country-specific details. If the SM also contains non-substantial changes, then list these separately from the substantial changes. If the SM application is a resubmission of a previous one, please clarify which changes have been performed.

########## If this is the first SM for a transition trial, add the following information to clarify whether the SM application contains new, updated or already authorised documents ##########

- This application contains: (delete those that are not applicable)
  - Documents that were already authorised under the CTD and not included in the transition initial application
  - Updates to CTD documents/placeholders that were included in the transition application
  - New documents in line with CTR requirements
- The addition of new Member States to this trial is planned / expected / currently not expected. (choose one option applying for the trial)
- The content of the Part II forms on Recruitment Arrangements, Financial Arrangements, Data Protection and Biological Samples (delete those that are not applicable or add other part II forms,



Annex Substantial Modification description template vs. 1.0 adopted at CTCG plenary March 19 2024

Date

Subject: Application CTIS trial number SM-number (Part I / Part II / Part I + II)

Sponsor: Sponsor Name
EU Trial number: Trial Number
Application number: SM-x
Protocol Number: Protocol Number/Acronym
Protocol Title: Protocol Title

Instructions for applicant:

- Yellow and blue text contains instructions, information and example texts; please remove these from the final version. Grey text should be filled in by the applicant. The blue section (text between blue header and footer) should be included only for the first SM after transition.
- Also mention track-changes (TC) and Summary of Changes (SoC) documents in the lists below.

This document provides a full overview of changes to documents and data fields for this SM.

############ If this is the first SM for a transition trial, add the following information to clarify whether the SM application contains new, updated or already authorised documents ##########
This application contains: (delete those that are not applicable)

- Documents that were already authorised under the CTD and not included in the transition initial application
- Updates to CTD documents/placeholders that were included in the transition application
- New documents in line with CTR requirements

In the tables/lists below, clearly indicate for each document which of the 3 categories described above is the case.
########## END OF SECTION FOR FIRST SM AFTER TRANSITION ##########

Changes to structured data fields

Section	Description of changes	Justification for changes
MSCs	Subject number updated for MSC	Addition of study arm in MSC
Part I	Inclusion criterion #x added	Refer to updated protocol v3 8Jan2024
Part II Member State	Trial site X added	.....
Part II Member State	PI change at site X	.....

Changes to Form document

Section	Document name Version and date	Details
Substantial modification details	B1_Cover letter 2024-512345-99-00 SM-6 V1.0 22Jan2024	New
Substantial modification details	B1_Modification Description 2024-512345-99-00 SM-6 V1.0 22Jan2024	New

REQUIREMENTS FIRST SM PART I: THREE DIFFERENT STAGES OF CLINICAL TRIALS

	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 procedures**
Cover letter and description of changes	Mandatory templates	Mandatory templates	Mandatory templates
Protocol	Update protocol with EU CT number, sponsor statement CTR compliance, result reporting and, if applicable, DSMB and emergency situations (art 35). Other changes only if in conflict with CTR, e.g. text on notifications (art 52-54), archiving (art 58)	See column A	Update (see column A) only if SM concerns this document
Protocol synopsis	Update protocol synopsis in English or national language (if applicable) – *needed to provide later translations for the addMSC*	See column A	Update (see column A) only if SM concerns this document
Patient facing documents	Update patient facing document in English or national language (if applicable)	See column A	Update (see column A) only if SM concerns this document
IB, Scientific advice, PIP	Update IB, Scientific advice or PIP only if SM concerns this document	See column A	Update (see column A) only if SM concerns this document
IMPD/AxMPD	Update IMPD/AxMPD only if SM concerns this document or in case of alignment IMP/AxMP (non-IMP)	See column A	-
GMP compliance/ QP declar.	Update in case of new IMP batches	See column A	-
Labeling	Update in case of new IMP batches	See column A	-
Structured data	Update if sponsor considers trial to be a low-intervention clinical trial	See column A	-

REQUIREMENTS FIRST SM PART II after TRANSITION

✓Submit the authorised versions of the documents not uploaded at initial transition step;

✓Use the template cover letter and template description of changes for the SM application package: [CTCG website]

✓All sections of part II dossier as indicated in annex I CTR EU no 536/2014 should be completed taken into account the following:

- templates of forms authorised under CTD do not need to be updated eg. CV principal investigator;
- if recruitment has closed in a MSC, no need to upload recruitment material for this MSC;
- no need to retrospectively create a site suitability form. The site suitability form authorised under CTD can be uploaded
- new templates of forms under CTR, with content (new or updated) not authorised under CTD, should be submitted
- new templates of forms with content authorised under CTD: no need to update to the new templates.
- check the websites of the MSC for the full list of required documents part II for this MS (see annex III of the Commission Q&A on CTR: https://health.ec.europa.eu/document/download/bd165522-8acf-433a-9ab1-d7dceae58112_en?filename=regulation5362014_qa_en_0.pdf

TRANSPARANCY RULES TRANSITION TRIALS

ACT EU Q&A on protection of Commercially Confidential Information and Personal Data while using CTIS (europa.eu)

STEP 1: Initial transition dossier (Q11 of COMMISSION GUIDANCE, Eudralex volume 10)

PROTOCOL, **SUBJECT INFORMATION SHEET(s)** AND **INFORMED CONSENT FORM(s)**: REDACTED (for publication) and UNREDACTED (not for publication)

ALL OTHER DOCUMENTS: In slot 'for publication' upload document with text referring to NCA and/or ethics committee who assessed and authorised the document under the CTD.

STEP 2: after transition sponsors may already follow the principles of the revised rules (see Q&A on protection of CCI and PD) – CTIS update planned for mid 2024

A version 'for publication' (redacted) and 'not for publication' (unredacted) only for the documents in scope of the revised transparency rules:
CATEGORY 1/PIP:
PROTOCOL including PATIENT FACING DOCUMENTS (if applicable), **PROTOCOL SYNOPSIS**
CATEGORY 2,3
PROTOCOL including PATIENT FACING DOCUMENTS (if applicable), **PROTOCOL SYNOPSIS**, **SmPC (if applicable), RECRUIT MATERIAL, SUBJECT INFORMATION SHEET(s) AND INFORMED CONSENT FORM(s)**

- Documents outside scope of the revised transparency rules: in slot 'for publication' upload document with text that those documents no longer will be subject to publication, see wording suggested in Annex I of the Q&A: ACT EU Q&A on protection of Commercially Confidential Information and Personal Data while using CTIS (europa.eu)
- See for full overview: ACT EU Q&A on protection of Commercially Confidential Information and Personal Data while using CTIS (europa.eu)

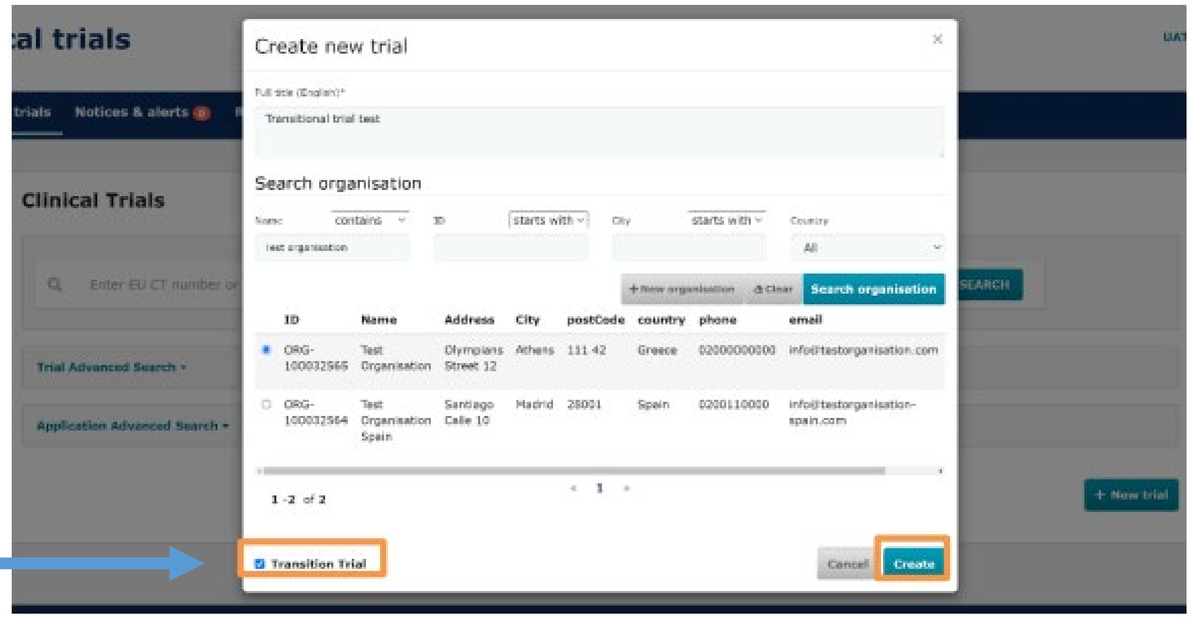
CTIS training modules:

[Clinical Trials Information System (CTIS): online training modules | European Medicines Agency (europa.eu)]

DO!

START TO TRANSITION YOUR CLINICAL TRIAL NOW!

Select the transition trial button in CTIS!



Centrale Commissie Mensgebonden Onderzoek

POSTADRES

POSTBUS 16302
2500 BH DEN HAAG

BEZOEKADRES

BEZUIDENHOUTSEWEG 30
2594 AV DEN HAAG

ccmo@ccmo.nl

+31 **(0)70** 340 6700

www.ccmo.nl

THANK YOU!

ctr@ccmo.nl