



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Step-by-step guide

How to evaluate a Substantial Modification clinical trial application

CTIS Training Programme – Module 08

Version 1.1 – March 2022

Learning Objectives

- Understand the process involved in the assessment of Substantial Modification Clinical Trial Application (SM CTA).
- Remember the workload management functionalities in CTIS that allow users to monitor their tasks during the evaluation of an SM CTA.

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Substantial Modification

A Substantial Modification (SM) is an application to apply a change to any aspect of the Clinical Trial (CT), which is made after the decision on a previously submitted application and which is likely to either:

- Have a substantial impact on the safety or rights of the subjects; or
- On the reliability and robustness of the data generated in the CT.

In all cases, a modification is regarded as 'substantial' when one or both of the above criteria are met.

The evaluation process of SM CTAs is established in the Regulation (EU) No 536/2014 on Clinical Trials (CT Regulation). This process includes **Validation, Assessment of Part I and/or Assessment of Part II**, and the **Decision**. Some SMs may concern Part I only, Part II only, or both, depending on the scope of the modification.

Users of the Member State Concerned (MSC) will be able to see what has been modified from the relevant section of the clinical trial application page (i.e. Form, MSC, Part I and/or Part II), under the 'Substantial modification details'.

This Step-by-step guide includes:



Evaluation of a Clinical Trial Application (CTA)

This section outlines an overview of the evaluation of a clinical trial application process.



Validation and Assessment of an SM

This section outlines the steps that the MSC of the CTA has to follow to validate and assess an SM CTA.



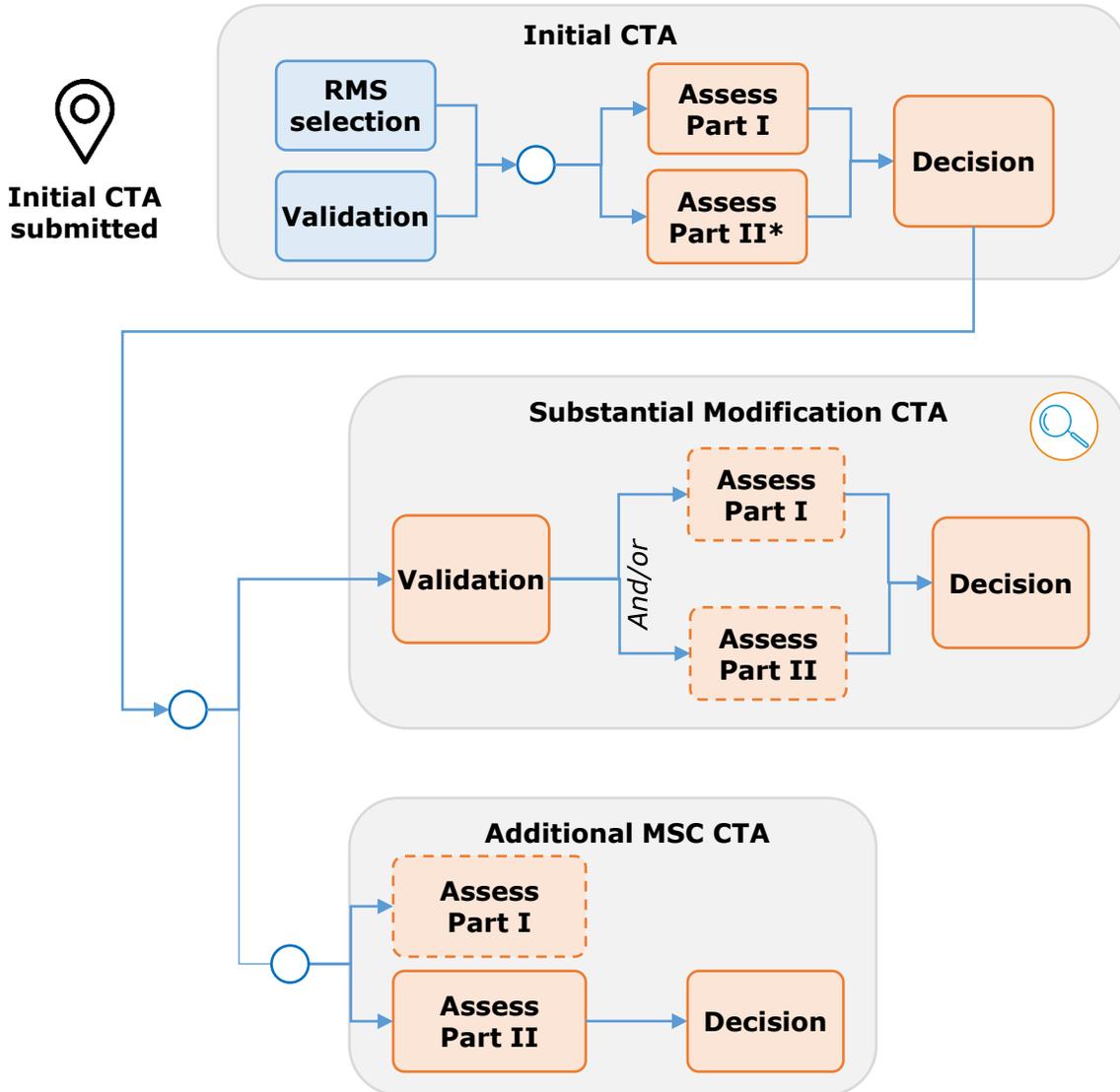
Decision of an SM

This section outlines the steps that each MSC performs to submit a Decision regarding the Substantial modification CTA (i.e. whether the trial is 'Authorised', 'Authorised with conditions', or 'Not authorised').

Evaluation of a CTA

The evaluation process starts **once the sponsor has submitted an initial Clinical Trial Application (CTA)**. The MSCs can **evaluate the documentation** provided by the sponsor to ensure the compliance with the CT Regulation. The evaluation is performed for the following types of CTAs: Initial CTA, Substantial Modification (SM) and Additional MSC CTA (Add MSC).

EVALUATION OF A CLINICAL TRIAL APPLICATION



Focus of this document.



Content included in module 06 eLearning | Step-by-step guide RMS selection.



Content included in module 08 Quick guide | Step-by-step guide SM | Step-by-step guide Add MSC.



Step in the process that may occur depending on the CTA submitted. An SM CTA can include Part I and Part II, Part I only or Part II only. For an Add MSC CTA users may raise considerations for Part I, but the conclusion cannot be modified.

*In case of applications limited to Part I, the sponsor has two years from the notification of the conclusion of Part I to submit an application limited to Part II.

Validation and Assessment of an SM

Access SM CTAs

1. Similar to **other types of CTA**, MSCs receive a notice establishing that a Substantial Modification **application has been submitted**. Users can access the tasks through the notice received, the **'Task'** tab or the **'Evaluation'** section.

The screenshot shows a navigation bar with tabs: Clinical trials, Notices & alerts (104), Tasks, Ad hoc assessments, and Annual safety reporting. The 'Notices & alerts' tab is selected and highlighted with an orange box. Below the navigation bar, there are filters for 'New!' (1) and 'All' (129). A notification card is displayed with the title 'Notice Application submitted' and the text: 'Test Organisation has submitted a Substantial Modification Part I and Part II application which involves Austria and Germany for the 1654 application.'

2. On the **'Tasks'** tab, users can view the tasks related to the validation and assign the **'SM document consideration for validation'** task to users, using the appropriate button on the right side.

The screenshot shows the 'Tasks' tab selected in the navigation bar. Below the navigation bar, there is a table with the following columns: SM document considerations for validation, RMS, Application and Non-SM type, Sponsor/Co-sponsors, Evaluation process, Created, Due, Remaining days, and Assignee. The 'Assignee' column has a button with a person icon and a list icon, which is highlighted with an orange box.

SM document considerations for validation	RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
Pending 2021-501398-35-00	AUSTRIA	SUBSTANTIAL MODIFICATION Part I and Part II	Test Organisation	Validation	06/09/2021	13/09/2021	7	

3. Users perform the evaluation of the SM in the **'Evaluation'** section of the CTA; regardless of the way they accessed the application (i.e. via **'Notice & alert'** or **'Task'** tabs).

The screenshot shows the 'Evaluation' section of the CTA. On the left, there is a sidebar with a list of options: Form, MSCs, Part I, Part II, Evaluation (highlighted with an orange box), and Timetable. The main content area shows a form with the following sections: Evaluation, Validation, and Considerations. The 'Considerations' section is expanded, showing a table with columns for 'All considerations' and 'Consolidated considerations'. Below the table, there are buttons for 'Undo', '+ New', 'Share', 'Download', 'Comment', 'Not included', 'Adapt', 'Merge', and 'Accept'.

Validation and Assessment of an SM

Validate SM CTAs: create considerations

- Users can start the validation of the SM CTA by completing the task of **documenting considerations for validation assigned to them**. they can assign the task to users, using the appropriate button on the right side of the task.

Clinical trials	Notices & alerts 0	Tasks	Ad hoc assessments	Annual safety reporting	Inspections	Union control		
SM document considerations for validation Pending 2021-501398-35-00								
RMS:	AUSTRIA	Application and Non-SM type: SUBSTANTIAL MODIFICATION Part I and Part II	Sponsor/Co-sponsors: Test Organisation	Evaluation process: Validation	Created: 06/09/2021	Due: 13/09/2021	Remaining days: 7	Assignee:

- Users access the '**Evaluation**' section of the CTA where they are able to start documenting their considerations of the substantial modification by selecting the '**+ New**' button.

Form
MSCs
Part I
Part II
Evaluation
Timetable

Evaluation

Validation

Considerations

All considerations

Consolidated considerations

Undo **+ New** Share Download Comment Not included Adapt Merge Accept

- Users can **populate the fields of the pop-up form** and click on the '**Save**' button.

Document considerations

Evaluation process: Validation Consideration number

Application section parts: Drop-down list to select the application section parts.

Application section and document: Drop-down list to select the CTA section and document.

Consideration: Consideration free text field.

Cancel **Save**

- After documenting the consideration, users can select the consideration and click on the '**Share**' button.

Undo **+ New** **Share** Download Comment Not included Adapt Merge Accept

	Number	MSC	Application section parts	Application section and document	Evaluation process	Consideration	Comments	Shared on	Consolidator action date	Consolidator action	
<input checked="" type="checkbox"/>	AT001	Austria	Part I - Quality	Cover letter	Validation	Test					+

Validation and Assessment of an SM

Validate SM CTAs: consolidate considerations and submit validation decision

1. After the considerations of the MSCs have been documented and shared, the Reporting Member State (RMS) can access the considerations from the **'Consolidate Considerations'** task in the **'Tasks'** tab and assign the task to users, using the appropriate button on the right side of the task.

2. The RMS can select the considerations **using the checkbox** on the left, and **click one of the four buttons to consolidate them** (i.e. 'Not Included', 'Adapt', 'Merge', 'Accept').

3. The RMS can select the consolidated considerations in the **'Consolidated considerations'** sub-tab and click on the **'Share'** button.

4. After consolidating the consideration, the RMS can submit the validation decision by accessing the **'Submit validation decision'** from the **'Tasks'** tab and assigning the task to users, using the appropriate button on the right side of the task.

5. Then the RMS can determine if the application dossier is complete or incomplete from the drop-down menu and select the **'Complete'** button.

Validation and Assessment of an SM

Assess Part I and Part II: create considerations

1. On the 'Tasks' tab, MSCs can view the tasks related to the assessment and select the 'SM Document consideration Assess Part I' and/or 'SM Document consideration Assess Part II' task by assigning the task to users, using the appropriate button on the right side of the task..

Clinical trials Notices & alerts 0 Tasks Ad hoc assessments Annual safety reporting Inspections Union control									
SM Document Considerations Assess Part I		RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
Pending 2021-501398-35-00		AUSTRIA	SUBSTANTIAL MODIFICATION Part I and Part II	Test Organisation	Assess part I	06/09/2021	11/10/2021	35	

Clinical trials Notices & alerts 0 Tasks Ad hoc assessments Annual safety reporting Inspections Union control									
SM Document Considerations Assess Part II		RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
Pending 2021-501398-35-00		AUSTRIA	SUBSTANTIAL MODIFICATION Part I and Part II	Test Organisation	Assess part II	06/09/2021	14/10/2021	38	

2. Similarly to the validation phase, users can document their considerations for Part I and/or Part II by selecting the '+ New' button and then selecting the 'Share' button.

Assessment Part I

Considerations

All considerations

+ New Share

Number	MSC	Application section parts	Application section and document	Evaluation process	Consideration	Comments	Shared on	Consolidator action date	Consolidator action
AT002	Austria	Part I - Quality	Cover letter	Assess Part I	Test				

Assessment Part II

Considerations

All considerations

+ New Share

Number	MSC	Application section parts	Application section and document	Evaluation process	Consideration	Comments	Shared on	Consolidator action date	Consolidator action
AT003	Austria	Part II - Austria	Cover letter	Assess Part II	test				

3. The RMS can circulate the Draft Assessment report for Part I by assigning the 'Circulate Draft Assessment Part I report' task, **uploading** one, many or all the Draft Assessment Report (DAR) documents, as applicable, for the application dossier sections; **selecting** the 'Select all' button, and then **clicking** the 'Share' button.

Circulate Draft Assessment Part I report									
Pending 2021-501398-35-00		RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
		AUSTRIA	SUBSTANTIAL MODIFICATION Part I and Part II	Test Organisation	Assess part I	06/09/2021	27/09/2021	21	

Select all

Part I section 1 introduction - Draft

1_Part I section 1 introduction - Draft

English - Part I Section 1 Introduction - Draft - System version 1 - Version 1 - 03/11/2020

GENERATE TEMPLATE

DOWNLOAD

Add document

Before adding a document, a template can be generated using this button.

Validation and Assessment of an SM

Assess Part I and Part II: consolidate considerations

1. The RMS can consolidate the considerations for Part I by selecting the '**Consolidate Considerations**' task. For Part II, each MSC will perform this task individually (if applicable).

Consolidate Considerations Pending 2021-501398-35-00	RMS: AUSTRIA	Application and Non-SM type: SUBSTANTIAL MODIFICATION Part I and Part II	Sponsor/Co-sponsors: Test Organisation	Evaluation process: Assess part I	Created: 06/09/2021	Due: 18/10/2021	Remaining days: 42	Assignee:
Consolidate Considerations Pending 2021-501398-35-00	RMS: AUSTRIA	Application and Non-SM type: SUBSTANTIAL MODIFICATION Part I and Part II	Sponsor/Co-sponsors: Test Organisation	Evaluation process: Assess part II	Created: 06/09/2021	Due: 14/10/2021	Remaining days: 38	Assignee:

2. For Part I, the RMS can select the considerations **using the checkbox** on the left, and **click one of the four buttons** (i.e. 'Not Included', 'Adapt', 'Merge', 'Accept').

Assessment Part I										
Considerations						Consolidated considerations				
All considerations						Consolidated considerations				
Undo + New Share						Download Comment Not included Adapt Merge Accept				
Number	MSC	Application section parts	Application section and document	Evaluation process	Consideration	Comments	Shared on	Consolidator action date	Consolidator action	All
<input checked="" type="checkbox"/>	AT002	Austria	Part I - Quality	Cover letter	Assess Part I	Test	06/09/2021			

3. The RMS can select the consolidated considerations in the '**Consolidated considerations**' sub-tab and click on the '**Share**' button.

Assessment Part I										
Considerations						Consolidated considerations				
All considerations						Consolidated considerations				
Undo Download Comment						Share + Create RFI				
Consideration number	New ID	Application section parts	Application section and document	Consideration	Comments	Consolidator action date	Consolidator action	Consolidation date	Original Consideration	RFI
<input checked="" type="checkbox"/>	AI-AT002	Part I - Quality	Cover letter	Test		06/09/2021	Accepted			

4. After consolidating the considerations of Part I, the user of the RMS selects the '**Submit Part I Conclusion**' and click on the '**Assign to me**' button. If the RMS considers that certain information is missing or needs clarification in the application documentation, an **RFI can be submitted** to the sponsor.

Submit Part I Conclusion Pending 2021-501398-35-00	RMS: AUSTRIA	Application and Non-SM type: SUBSTANTIAL MODIFICATION Part I and Part II	Sponsor/Co-sponsors: Test Organisation	Evaluation process: Assess part I	Created: 06/09/2021	Due: 18/10/2021	Remaining days: 41	Assignee:
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Validation and Assessment of an SM

Assess Part I and Part II: submit assessment conclusions

- In the 'Submit Part I Conclusion' task, the user of the RMS uploads **two documents**: one for the assessment of the Part I quality documentation and another one not related to all the Part I documentation, except quality.

Part I assessment report quality – Final*

[Add document](#)

Part I assessment report except quality – Final*

[Add document](#)

- Once the two assessment reports have been uploaded, the user of the RMS can select a final conclusion from the dropdown menu and click on the 'Submit' button.

Final conclusion*

Acceptable

[+ Create subtask](#)
[Save](#)
[Submit](#)

- If the SM involves Part II of the application dossier, **each MSC provides its own individual Part II conclusion** by selecting the 'Submit Part II Conclusion' task, uploading one Part II assessment report and submitting the final conclusion.

Submit Part II Conclusion	RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
Pending 2021-501398-35-00	AUSTRIA	SUBSTANTIAL MODIFICATION Part I and Part II	Test Organisation	Assess part II	06/09/2021	14/10/2021	37	

Part II assessment report – Draft

[Add document](#)

Part II assessment report – Final*

[Add document](#)

Final conclusion*

Acceptable

[+ Create subtask](#)
[Save](#)
[Submit](#)

Decision of an SM

Submit a Decision

1. After the assessment report has been submitted, users can assign the 'Authorise' task to users, using the appropriate button on the right side of the task.

Clinical trials	Notices & alerts 0	Tasks	Ad hoc assessments	Annual safety reporting	Inspections	Union control
Authorise Pending 2021-501398-35-00						
RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:
AUSTRIA	SUBSTANTIAL MODIFICATION Part I and Part II	Test Organisation	Decision	07/09/2021	13/09/2021	6
						Assignee:

2. On the Decision page, users can view information on the conclusions of the different parts to which the corresponding SM can provide their decision via a drop-down list to establish if the trial is 'Authorised', 'Authorised with conditions', or 'Not authorised'.

CTIS Training - Testing 2021-501398-35-00 Authorised Authorise Assigned Due date:13/09/2021 [View trial details](#)

General

Part I conclusion: Acceptable
 Member states concerned: AUSTRIA

Part II conclusion: Acceptable

Authorisation

Decision:

3. MSCs can **add supporting documentation to the Decision** and ultimately, click on the 'Complete' button to finalise the evaluation of an SM.

Publication of RFIs

Data/document type	Publication timepoint
Responses to RFIs	Date of Decision (set by sponsor)
RFIs sent to the sponsor	Date of Decision (set by sponsor)

Publication of assessment reports and conditions

Data/document type	Publication timepoint
Protocol	Date of Decision (set by sponsor)
IMPD S&E and Investigator Brochure	Date of Decision (set by sponsor)
Assessment reports and conditions	Date of Decision (set by sponsor)

Supporting documentation

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Send a question

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Clinical Trials Information System (CTIS)

Step-by-step guide: How to evaluate a Substantial Modification: Assessment and Decision

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