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.

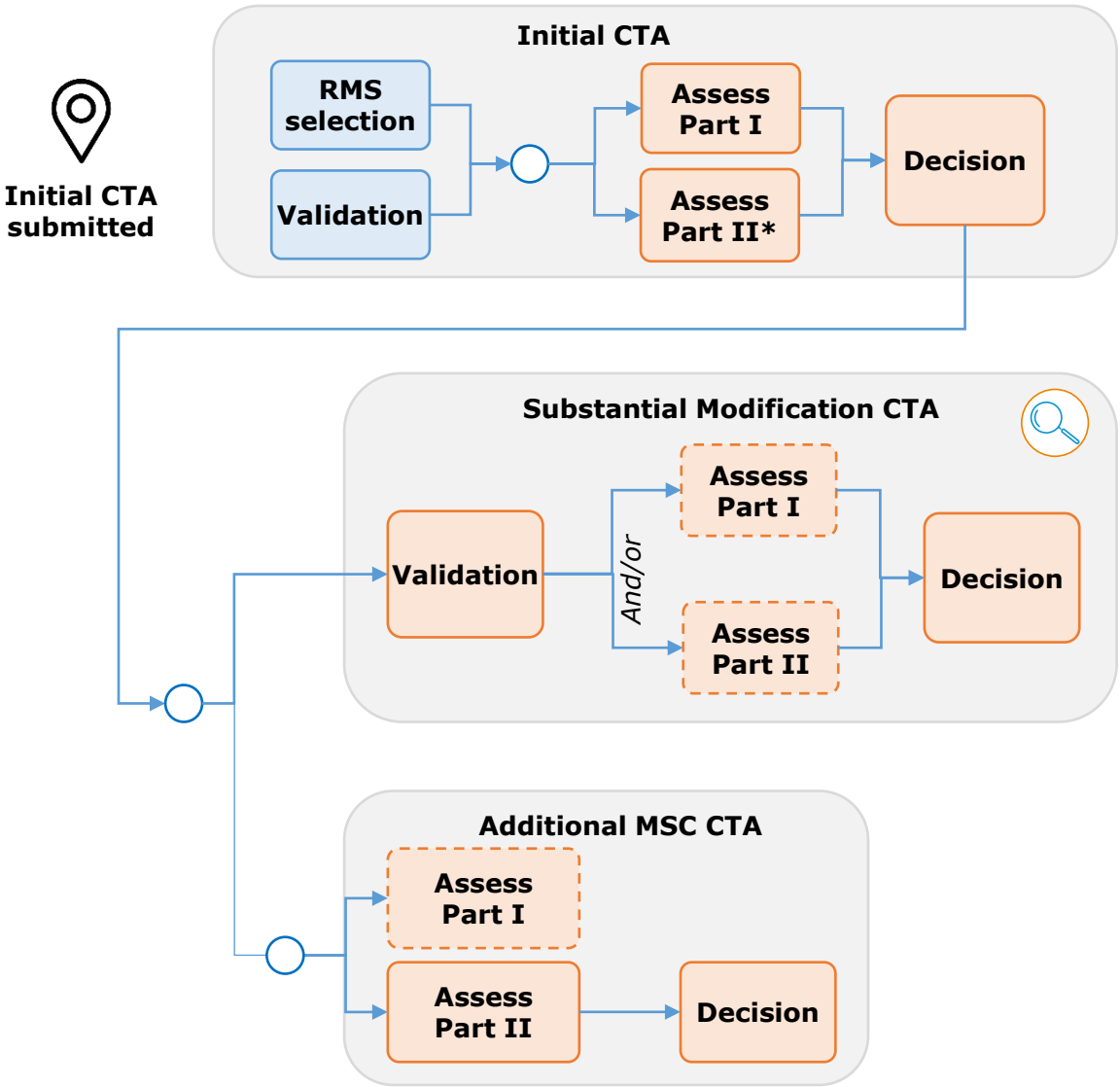
Decision of an SM

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.

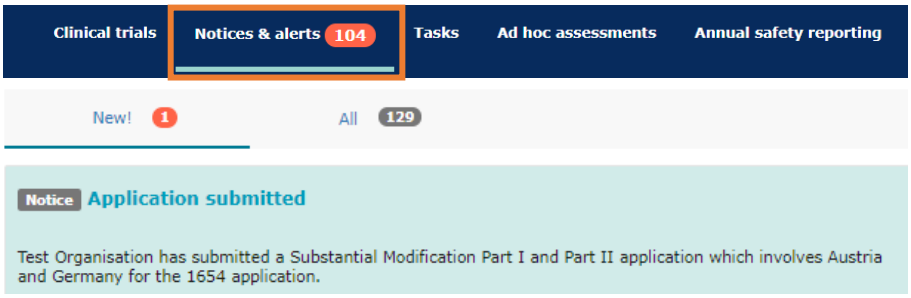
Step in the process that may occur depending on the CTA submitted. An SM CTA can include Part I and Part II, Part I only or Part II only. For an Add MSC CTA users may raise considerations for Part I, but the conclusion cannot be modified.

**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

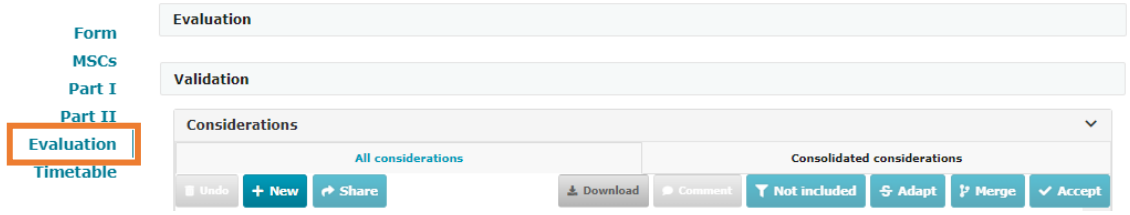
Access SM CTAs

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.



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.

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).



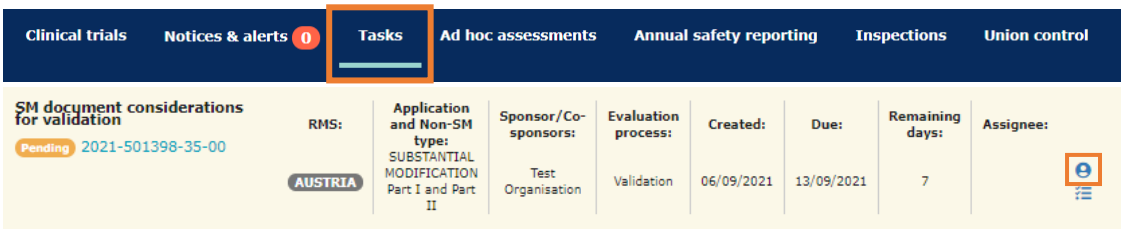
#CTIS insights

The Substantial Modifications (SM) include the whole process of evaluation: **Validation, Assessment (Part I and/or Part II), and Decision**. It should be noted that some SM may concern only Part I, Part II, or both, depending on the scope of the modification.

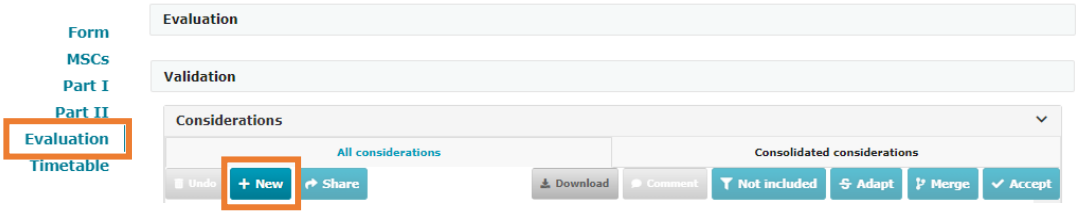
Validation and Assessment of an SM

Validate SM CTAs: create considerations

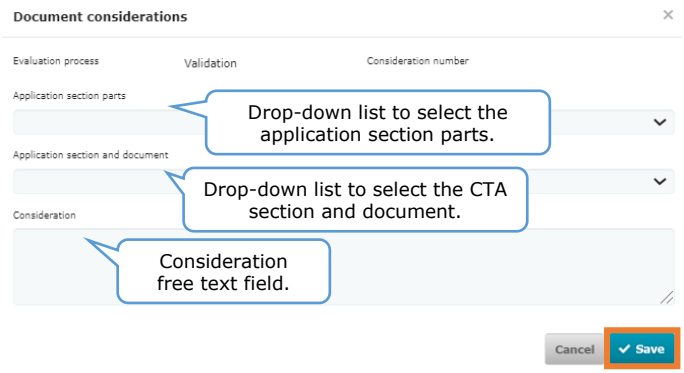
1. Users can start the validation of the SM CTA by completing the task of **documenting considerations for validation assigned to them**. they can assign the task to users, using the appropriate button on the right side of the task.



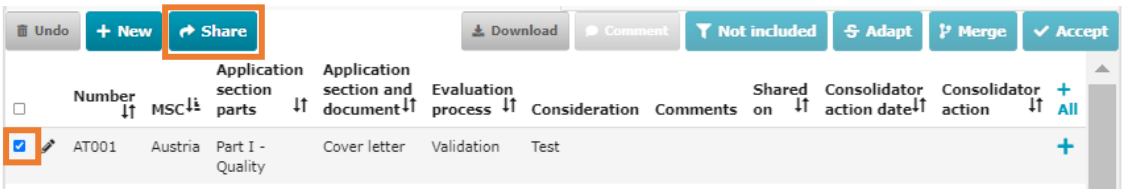
2. Users access the **'Evaluation'** section of the CTA where they are able to start documenting their considerations of the substantial modification by selecting the **'+ New'** button.



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



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



#CTIS insights

For considerations of Part I, users can document considerations regarding **Quality, Non-quality, Clinical, Regulatory or Statistical**.

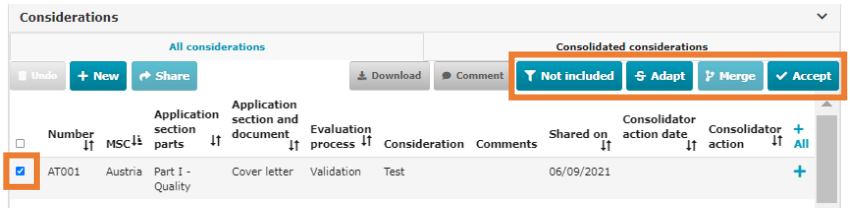
MSCs can comment on considerations. If a consideration is **commented on**, the **RMS will receive an alert** regarding the comment.

Validation and Assessment of an SM

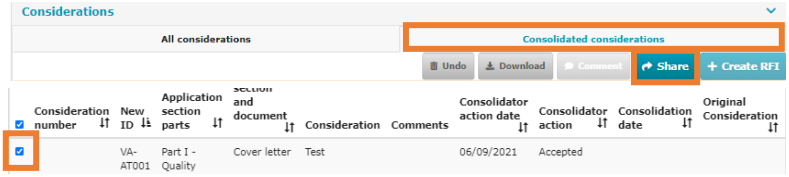
Validate SM CTAs: consolidate considerations and submit validation decision

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').

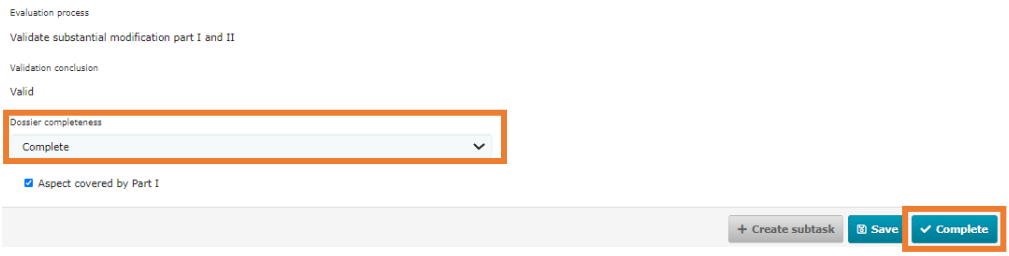


3. The RMS can select the consolidated considerations in the **'Consolidated considerations'** sub-tab and click on the '**Share**' button.



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.



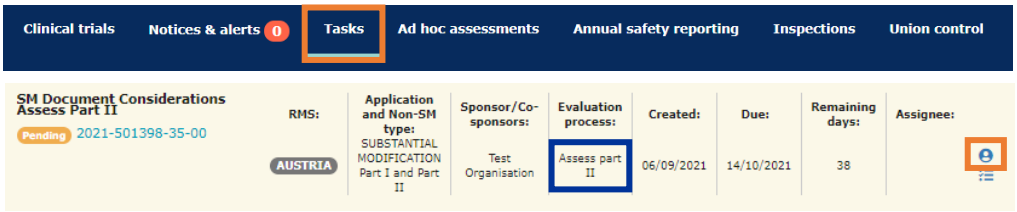
#CTIS insights

After reviewing and consolidating all the considerations, if the RMS considers that certain information is missing or needs clarification in the application documentation, it can **submit an RFI** to the sponsor.

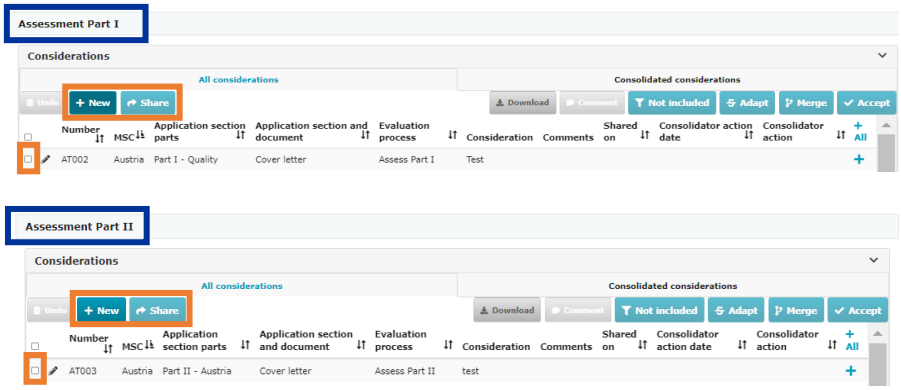
Validation and Assessment of an SM

Assess Part I and Part II: create considerations

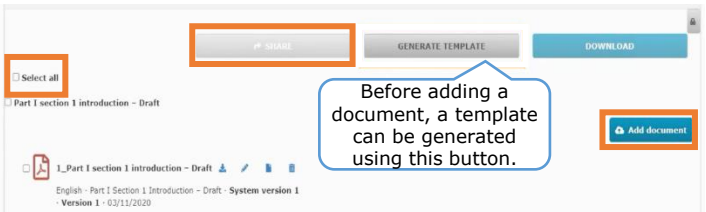
1. On the **'Tasks'** tab, MSCs can view the tasks related to the assessment and select the 'SM Document consideration Assess Part I' and/or 'SM Document consideration Assess Part II' task by assigning the task to users, using the appropriate button on the right side of the task..



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.



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.



#CTIS insights

Templates are available for each of the 7 parts of the DAR. Users can select the desired part and click on the '**Generate template**' button.

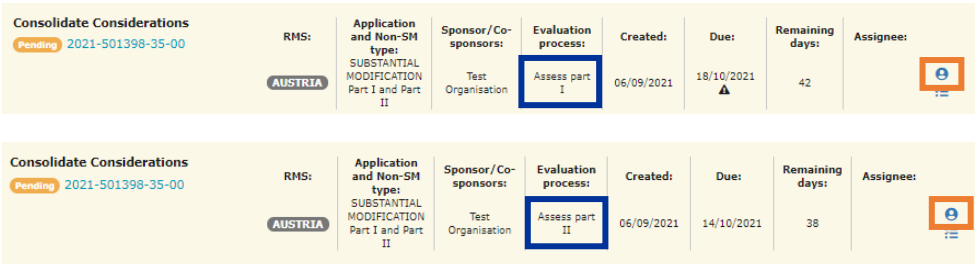
MSCs can discuss amongst themselves during the assessment phase, by using the **discussion functionality**.

Considerations can be **created even after the circulation of the DAR.**

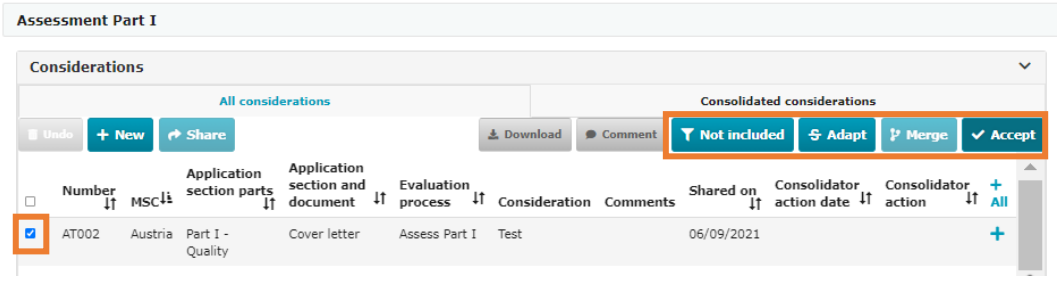
Validation and Assessment of an SM

Assess Part I and Part II: consolidate considerations

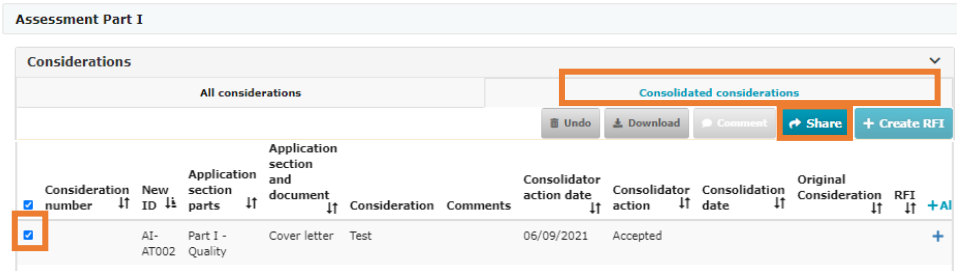
1. The RMS can consolidate the considerations for Part I by selecting the '**Consolidate Considerations**' task. For Part II, each MSC will perform this task individually (if applicable).



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').



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



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.

#CTIS insights

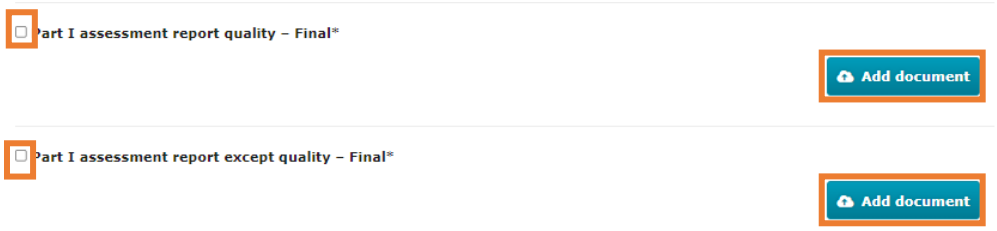
If the substantial modification applies to Part I only or Part II only, **the assessment will be limited to Part I or Part II respectively**.

If the SM involves Part II of the application dossier, **each MSC performs its own assessment**. Only if the substantial modification involves **Part I**, the **RMS** will have a **leading role in the assessment**.

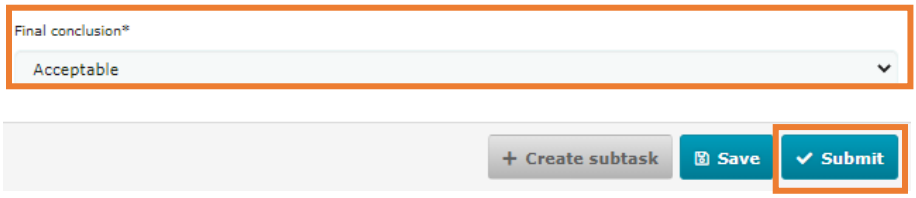
Validation and Assessment of an SM

Assess Part I and Part II: submit assessment conclusions

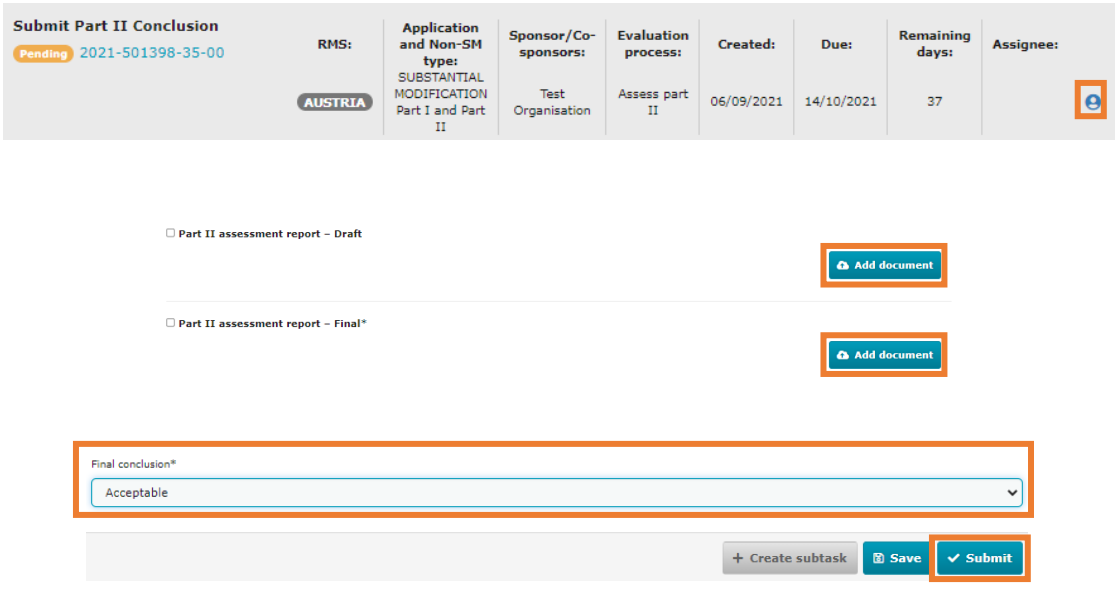
5. In the '**Submit Part I Conclusion**' task, the user of the RMS uploads **two documents**: one for the assessment of the Part I quality documentation and another one not related to all the Part I documentation, except quality.



6. 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.



7. 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.



#CTIS insights

The **conclusions on Part I and the Final Assessment Report (FAR)** should be based in the content of the DAR. The final conclusion values can be: **Acceptable, Acceptable with conditions** and **Not acceptable.**

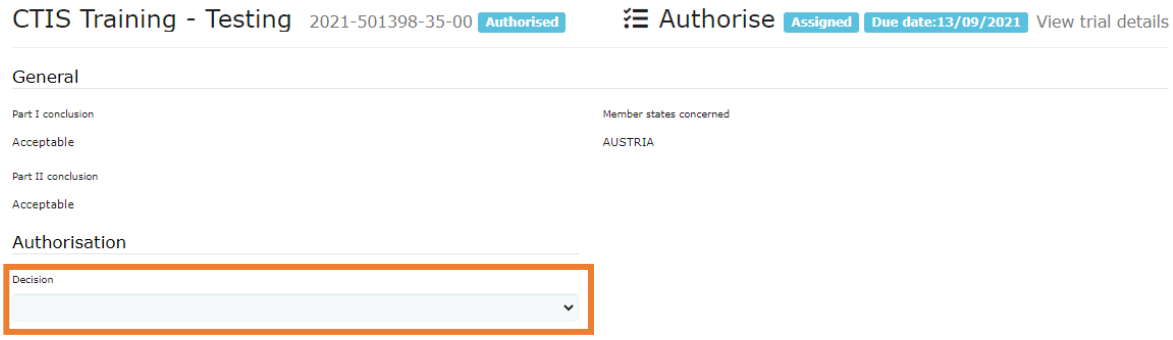
When submitting the FAR, **users need to upload both documents** (quality and excluding quality) **regardless of whether there are any quality parts**.

Decision of an SM

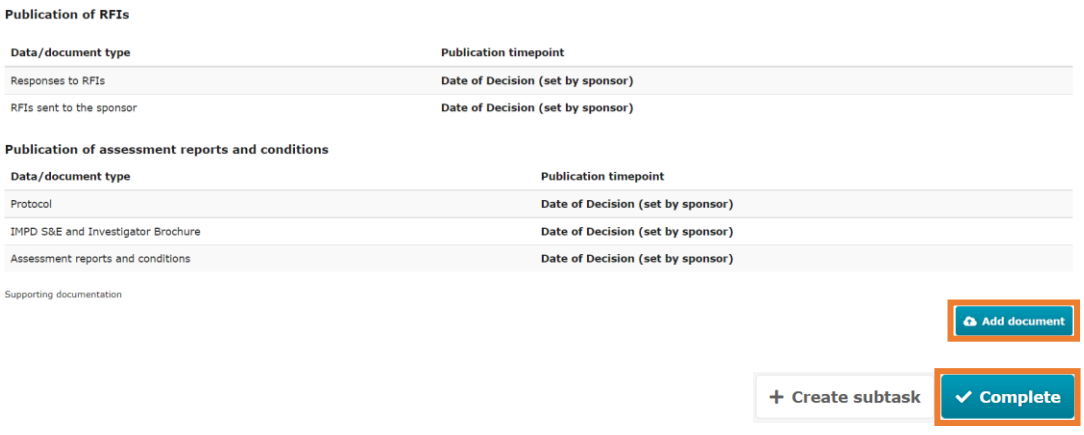
Submit a Decision

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.

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'**.



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



#CTIS insights

For each **SM type there will be a conclusion** (Part I / Part II) followed by a MSC decision.

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