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Quick guide

How to evaluate an Initial Clinical Trial Application: Assessment and Decision

CTIS Training Programme – Module 8
Version 1.1 – December 2020

Learning Objectives

- Remember the phases and associated timelines for evaluating an initial Clinical trial application (CTA).
- Understand the process and the user roles involved in the Assessment of Part I of an initial CTA as a Reporting Member State (RMS) and as a Member State Concerned (MSC).
- Understand the process and the user roles involved in the Assessment of Part II of an initial CTA as a MSC.
- Understand the process and the user roles involved in the Decision regarding the authorisation of an initial CTA.
- Remember the workload management functionalities in CTIS that allow users to monitor their tasks during the evaluation of an initial CTA.

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Assessment Part I



The Assessment of Part I consists in determining the acceptability (or not) of conducting a clinical trial from the review of the scientific documentation provided by the sponsor in the application.

Overview of Assessment Part I

The assessment of Part I consists of the evaluation of scientific documentation related to the trial on the anticipated therapeutic intend and benefit for public health, potential risks for the subject, compliance with the manufacturing, import, and labelling requirements, amongst other documentation provided in the application dossier.

These aspects, are to be evaluated during the assessment of Part I and are reflected in the system in the sections displayed on the figure on the right side.

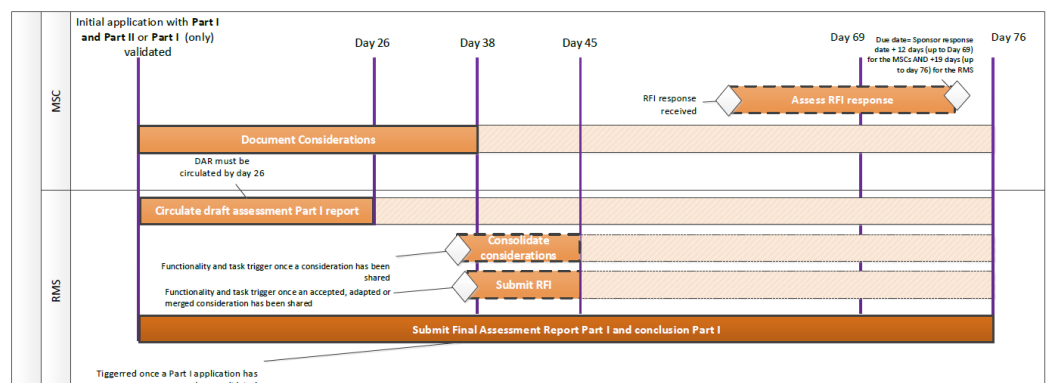
The joint review by the RMS and the MSC results in a Final Assessment Report (FAR) prepared by the RMS and in a conclusion for Part I, which will establish if the conduct of a clinical trial is acceptable; acceptable with conditions; or not acceptable.

Authorisation of manufacturing and import
Clock Stop
Content labelling of the IMPs
Cover letter
DSMB
Deferral Request
IMPD Quality
IMPD excluding Quality data
Investigator brochure
Justification low intervention
PIP
Product details
Proof of payment
Protocol
QP GMP certification
Scientific advice
Sponsor details
Study design
Summary of product characteristics (SmPC)
Synopsis

Figure 1 - Application sections in Part I where MSC can document considerations

Timelines

The assessment of Part I of an Initial application can take up to 45 days, or up to 76 days if Requests for Information (RFIs) are raised. The RMS may also extend the period up to 50 days for consultation with experts¹.



The dates shown in the figure above (see Annex) correspond to the maximum deadlines foreseen for each task and the maximum timeframes between the end of a task and the end of the following task. However, the system includes a dynamic workflow by which, if a task is completed before its deadline, the corresponding deadlines for the following tasks are recalculated, but the maximum timeframes are still respected.

The maximum deadlines foreseen for the tasks related to the assessment of Part I are:

- For hard tasks (mandatory tasks):
 - Submit Final Assessment Report (FAR) Part I and conclusion Part I– up to 45 days or 76 days (if RFIs are raised), from the Validation of the initial CTA. *Performed by the RMS.*
- For soft tasks (non-mandatory tasks):
 - Circulate Draft Assessment Report – up to 26 days from the Validation of the initial CTA. *Performed by the RMS.*
 - Document considerations – up to 38 days from the Validation of the initial

¹ For more information on how to extend the period for consultation with experts refer to the FAQs document of this module.



In the case of multinational trials, Part I part is jointly assessed by all MSCs, but the conclusion is submitted only by the RMS.



Assessment Part I – Draft Assessment Report



The Draft Assessment Report (DAR) is a preliminary assessment by the RMS of the scientific documentation of the application dossier. It is circulated to all the MSC.

CTA. *Performed by the RMS and MSC.*

- Consolidate considerations – up to 7 days after the considerations are shared. *Performed by the RMS.*
- Raise an RFI (if applicable) – up to 45 days from the validation of the Initial CTA. *Performed by the RMS.*
- Assess an RFI response – up to 12 days after the response is sent by the sponsor for the MSC, and up to 19 days for the RMS. *Performed by the RMS and MSC.*

Process to assess Part I

The assessment of Part I starts after the Validation of the Initial application is submitted by the RMS. The MSC will receive the following notice:

Notice	Validation conclusion recorded	Ref number	Source type	Evaluation process	Received	IMP	RMS	Sponsor
The validation conclusion of Valid has been recorded for the Initial application.		2020-500376-29-00	Initial	Validation	16/10/2020	Paracetamol	Austria	Test Organisation Demo

First, the RMS will **circulate the Draft Assessment Report (DAR)** of Part I among the MSC. This document includes a preliminary assessment of the scientific documentation of the application dossier. It consists of seven parts:

- Introduction
- Quality assessment
- Pre-clinical assessment
- Clinical assessment
- Statistical methodological assessment
- Regulatory assessment
- Conclusion

The RMS uploads a separate document for each part of the DAR (*see Article 6 of the CT Regulation²*). However, it is not mandatory to upload them all. To perform this task, the user with the appropriate role (*see section Roles and permissions below*) from the RMS needs to follow these steps:

1. Access the Tasks tab and click on the 'Circulate Draft Assessment Part I report' task. The task can be assigned to him/her by a CT Coordinator or if the user has the appropriate role, the user can select 'Assign to myself'. The system will redirect the user automatically to the relevant Evaluation section.

Circulate Draft Assessment Part I report	RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
Pending 2020-500376-29-00	AUSTRIA	INITIAL	Test Organisation Demo	Assess part I	16/10/2020	11/11/2020	26	

IMP1: Paracetamol - PARACETAMOL

2. Templates for each of the 7 parts of the DAR are available and can be retrieved by selecting the desired DAR part and clicking on the 'Generate template' button (*see image below*). The document is downloaded and saved on the user's local disk, ready to be used. It contains some prepopulated information about the trial. From there, the user can upload the documents in the corresponding part. Finally, users need to click on

² Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, *EU Official Journal* L158. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf



The documents of the DAR need to be actively shared by the RMS for the other MSC to view them. If the RMS uploads and shares documents for each of the 7 parts of DAR, the system will automatically deem this task as complete. If not, the RMS user must click on the 'Complete' button in the Tasks tab.



MSC

Assessment Part I – Document considerations

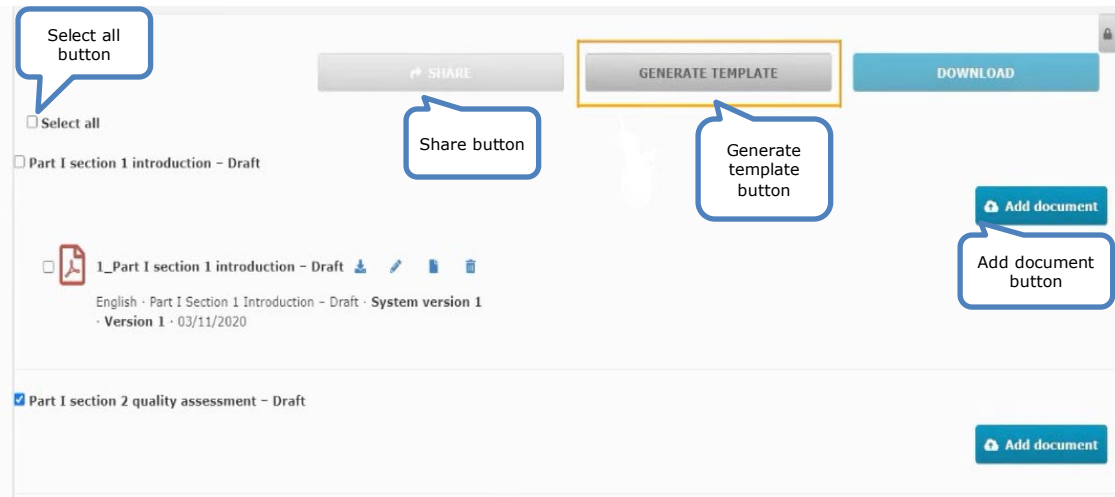


Considerations are the comments/corrections or questions that the MSC may have after reviewing the scientific documentation of an initial CTA and the DAR. These considerations are taken into account by the RMS when raising RFIs to the sponsor.



Considerations that are not shared will not be visible to other MSCs or the RMS and thus cannot be consolidated.

'select all', and then click on the share button.



In parallel, all MSCs can **document their considerations** for Part I of the application dossier from the moment the application has been validated. Moreover, MSCs can also document considerations regarding the DAR, up until 12 days after it has been circulated by the RMS.

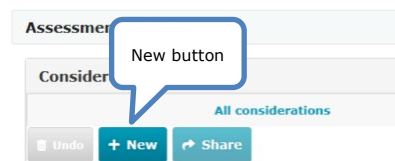
To perform this task MSC users with the appropriate permissions which have been assigned this task (see section Roles and Permissions below) need to follow these steps:

1. Access the Tasks tab and click on the 'Document Considerations Assess Part I' task. The task can be assigned to him/her by a CT Coordinator or if the user has the appropriate role, the user can select 'Assign to myself'. The system will redirect users to the relevant Evaluation section where they can document their considerations.

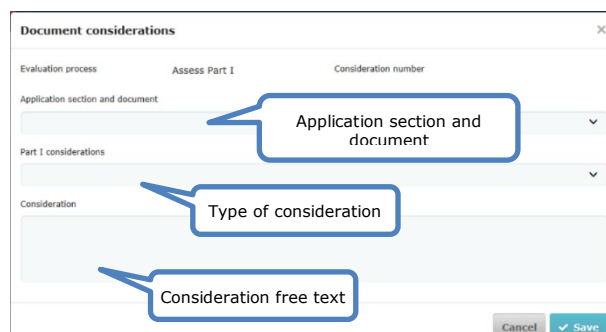
Document Considerations Assess Part I	RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
Pending 2020-500376-29-00	AUSTRIA	INITIAL	Test Organisation Demo	Assess part I	16/10/2020	23/11/2020	38	

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2. Select the '+ New' button to create a new consideration.



3. Select the application section and document for which the user wishes to document the consideration (see figure 1, page 1), select the type of consideration (clinical, non-clinical, regulatory, statistical, or quality-related), and describe the consideration in the form of free text, and finally click on save.



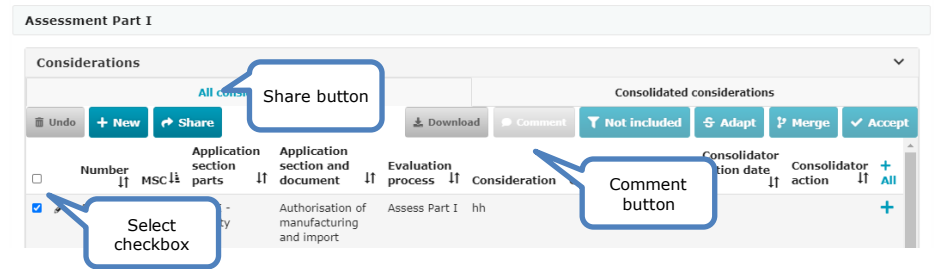


Assessment Part I - Consolidate considerations



The purpose of this task is to enable the RMS to spot any missing information in the application or error in the application and to send an RFI to the sponsor requesting its clarification or correction.

- After having saved the consideration the user can still work on it and edit it as needed. When it is ready, it must be shared with the other MSCs by clicking on the 'Share' button.



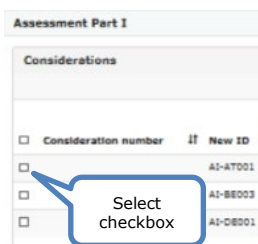
- MSC can comment considerations and establish an effective communication. If a consolidation is commented, the RMS will receive an alert regarding the comment.

After the considerations have been shared, the RMS will **consolidate them**. To perform this task RMS users with appropriate permissions who have been assigned this task (see section Roles and Permissions below) need to follow these steps:

- Access the Tasks tab and click on the 'Consolidate Considerations' task. The task can be assigned to him/her by a CT Coordinator or if the user has the appropriate role, the user can select 'Assign to myself'. The system will redirect the user automatically to the relevant Evaluation section where the considerations are stored.

Consolidate Considerations	RMS:	Application and Non-SM type:	Sponsor/Co-sponsor:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
Assigned 2020-500376-29-00	AUSTRIA	INITIAL	Total Organisation Demo	Asses part I	18/10/2020	30/11/2020	45	unays_m3

- To consolidate the considerations, the RMS should first select them via the checkbox displayed on the left side.



- Select one of the four following buttons:



- Not included:** allows the RMS to reject a consideration deemed not applicable.
 - Adapt:** allows the RMS to adapt a consideration shared by a MSC. In this case, the RMS must include the final wording of the consideration.
 - Merge:** allows the RMS to merge similar or identical considerations. In this case, the RMS must include the final wording of the consideration.
 - Accept:** allows the RMS to accept a specific consideration as it is.
- View the result by clicking on the tab 'Consolidated considerations'.



When users finish a soft-task, they will need to actively click on the 'Complete' button on the right side of the task for it to be deemed as finished.. This will trigger a Notice to the RMS and will allow to proceed to the following task.



Assessment Part I – Create, submit and assess an RFI

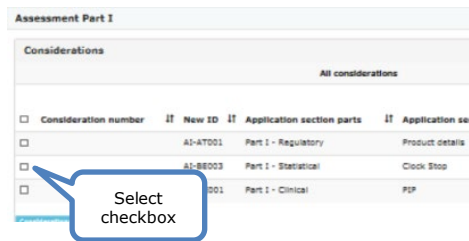


Requests for Information (RFIs) are requests sent by the RMS to the sponsor to provide additional information in the context of the validation and/or the assessment phases of an initial CTA.

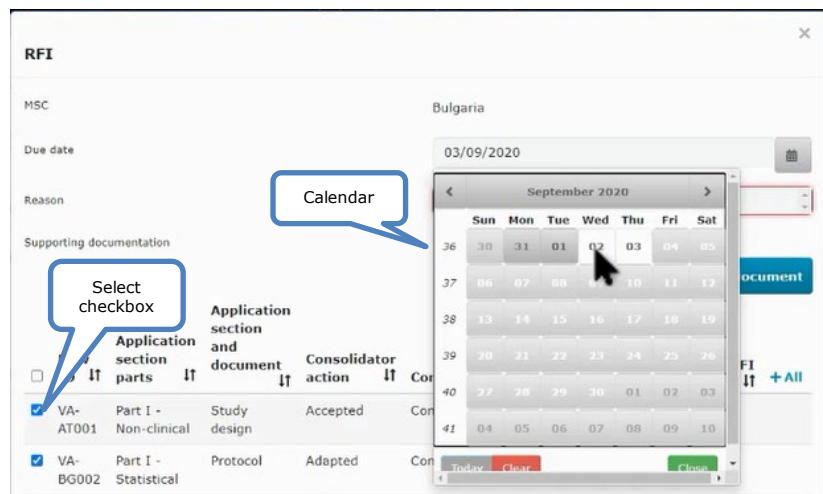
After reviewing and consolidating all the considerations, if the RMS considers that certain information is missing or needs clarification in the application documentation, it can **submit an RFI** to the sponsor.

To perform this task RMS users with appropriate permissions who have been assigned this task (see section *Roles and Permissions below*) need to follow these steps:

1. Select the considerations that need further clarification and click on the button 'share' to make them visible to the other MSCs after that they have been consolidated.

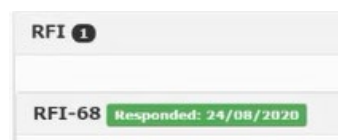


2. Click on '+Create RFI' on the top-right corner of the consolidated considerations section.
3. Establish the date by which the RFI response should be provided by the sponsor (a maximum period of 12 days can be given to the sponsor).



The MSCs have a maximum of 12 days after the submission of an RFI response to assess it. The RMS has a maximum of 19 days to do so.

4. The MSC can assess the response to the RFI submitted by the sponsor by selecting the alert 'Response to RFI Submitted' or the task 'Assess response to RFI'³. This will redirect the MSC to the dedicated RFI area of the Evaluation section on the application page. There the MSC can assess the response and submit comments for the other MSCs, including the RMS, to see.



³ The process of assessing a response to an RFI is similar in all phases of the evaluation. To view how this task is performed, please refer to video-clip CTTM06_Clip 3_Validation - RFI and issue validation decision in *Module 6: Assess a clinical trial application (RMS selection and Validation)*.



Assessment Part I – Final Assessment Report



The FAR provides the final assessment of the scientific documentation of the application dossier. It includes a part on the quality documentation and a part concerning the rest of the documentation.

After the RFI response has been assessed, the RMS needs to submit the **Final Assessment Report (FAR) and Part I conclusion.**

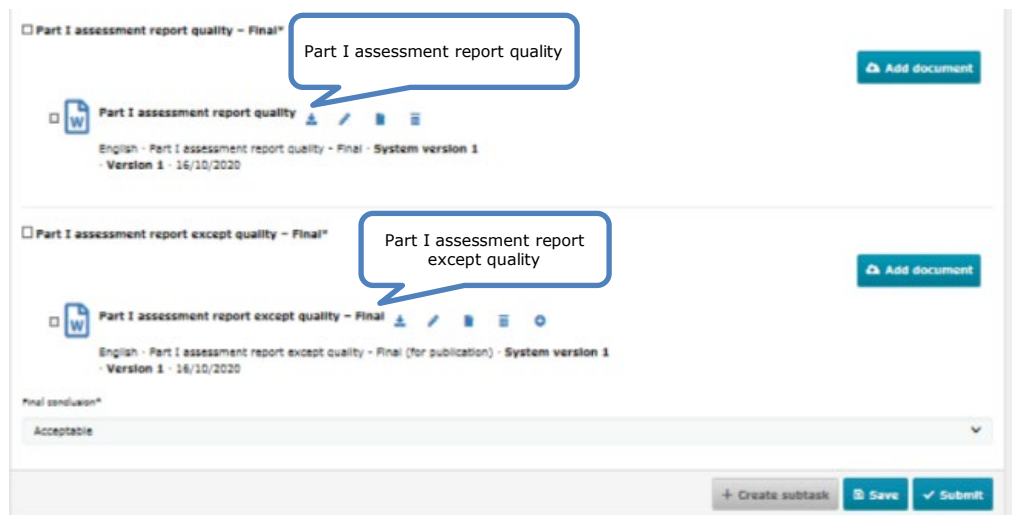
To perform this task RMS users with appropriate permissions who have been assigned this task (see section Roles and Permissions below) need to follow these steps:

1. Access the Tasks tab and click on the 'Submit Part I Conclusion' task. The task can be assigned to him/her by a CT Coordinator or if the user has the appropriate role, the user can select 'Assign to myself'.

Submit Part I Conclusion	RMS:	Application and Non-SM type:	Sponsor/Co-sponsors:	Evaluation process:	Created:	Due:	Remaining days:	Assignee:
Pending 2020-500376-29-00	AUSTRIA	INITIAL	Test Organisation Demo	Assess part I	16/10/2020	30/11/2020	45	

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2. In the Conclusion area of the relevant Evaluation section the RMS needs to upload:
 - a. A FAR for the quality part of the application.
 - b. A FAR for the rest of the application, excluding quality.
3. Select the conclusion in the drop-down menu among the options: 'acceptable', 'acceptable with conditions', or 'not acceptable'.
4. Click on the 'Submit' button on the bottom-left.



If the RMS does not complete the task 'Submit Part I conclusion' by the deadline, the application will be labelled as 'No conclusion'. The application will nonetheless proceed to the Decision phase.

Assessment Part I - Roles



There are three roles involved in the Assessment of Part I:

- 1) Assessor Part I Preparer full rights
- 2) Assessor Part I Preparer restricted rights (excluding quality)
- 3) Assessor Part I submitter full rights.

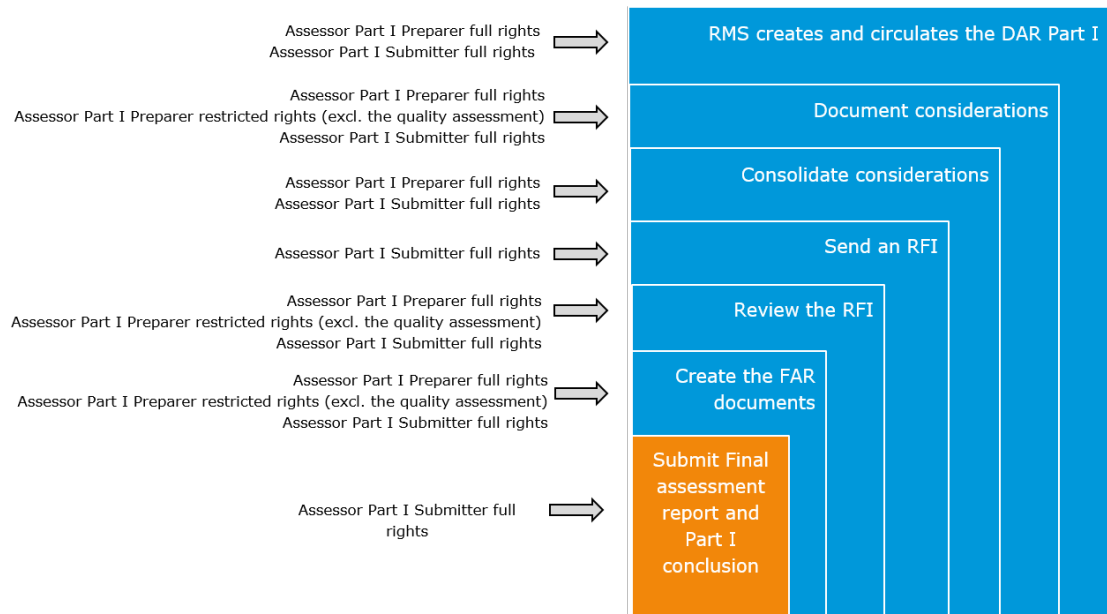
Roles and permissions

Only the Assessor Part I submitter full rights is able to perform the following tasks: circulate the DAR of Part I, send the RFI to the sponsor, and submit the Final assessment report and conclusion of Part I.

Users with preparer full rights may document considerations, consolidate considerations, review an RFI response, and create the FAR documents.

Users with preparer restricted rights (excluding the quality assessment) can document considerations of all sections except those related to quality, review the RFI response, and create the FAR documents not related to quality.

The roles are the same for all MSC, but the Assessor Part I roles of the RMS will be the leading roles of the assessment of Part I.



For the task Consolidate considerations, only the role of the Assessor Part I Submitter can share the consolidated considerations.

Annex Part I

