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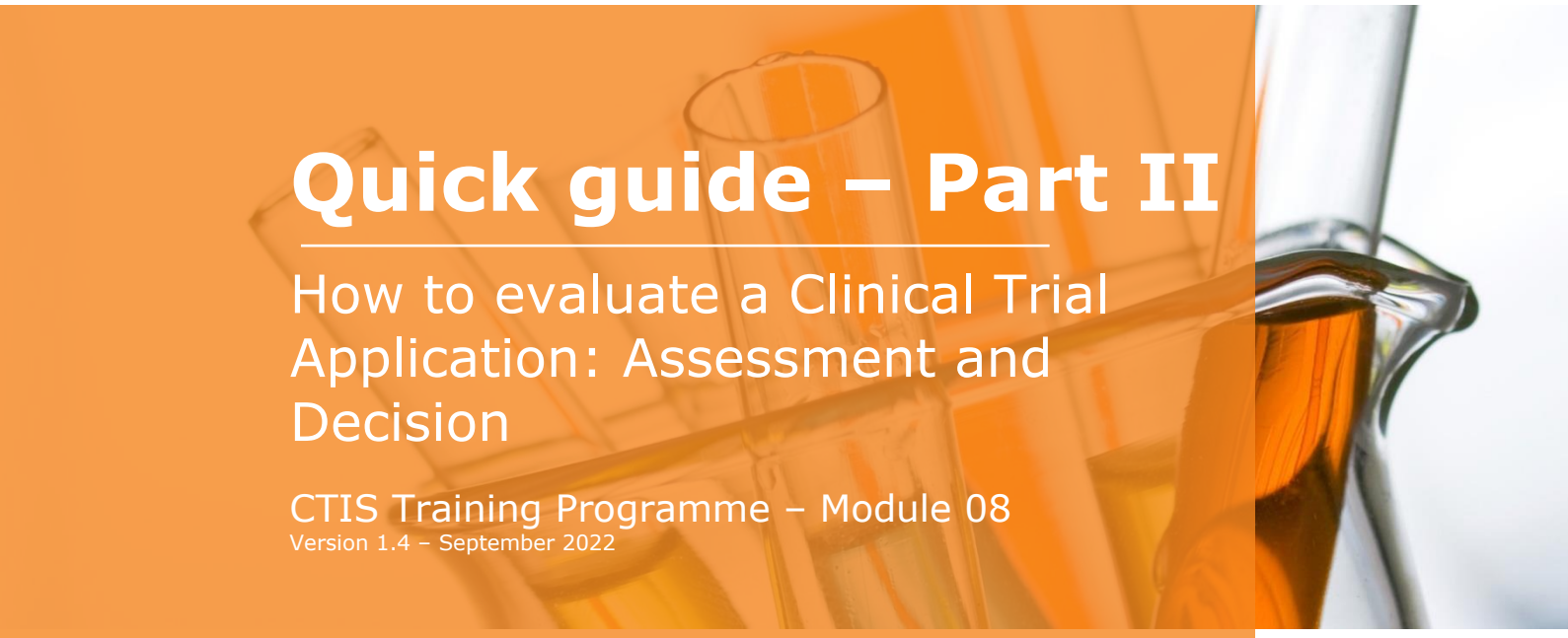

Quick guide – Part II

How to evaluate a Clinical Trial Application: Assessment and Decision

CTIS Training Programme – Module 08

Version 1.4 – September 2022

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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Record of updated versions

The table below describes the updated versions after CTIS go-live (January 2022):

Version	Version description	Date
1.4	New information related to how to upload documents 'Not for publication'	September 2022
1.3	Roles and permissions updates.	May 2022
1.2	Training material version published at CTIS go-live.	December 2021

Assessment Part II

The Assessment of Part II aims at determining the acceptability (or not) of conducting a clinical trial, from the revision of its regulatory documentation by each MSC separately (in case of multinational applications).

Overview of Assessment Part II

The assessment of Part II consists in the evaluation of the application by each MSC, for its territory, regarding the following aspects set out in Article 7 of the CT Regulation[1] and the General Data Protection Regulation[2]:

- Requirements for gathering the informed consent of the subjects.
- Arrangements for rewarding or compensating subjects and investigators.
- Arrangements for the recruitment of subjects.
- Protection of personal data.
- Suitability of individuals involved.
- Suitability of clinical trial sites.
- Damage compensation.
- Collection, storage, and future use of biological samples of the subject.

These aspects are to be reflected in the documents of the application dossier, which are evaluated as part of the Assessment of Part II (see figure on the right).

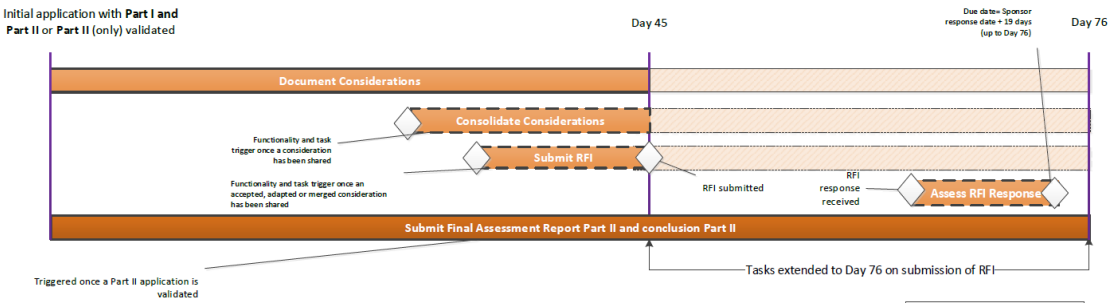
Clock Stop
Compliance with national requirements on Data Protection
Compliance with use of Biological samples
Cover letter
Deferral Request
Financial arrangements
Proof of insurance
Proof of payment
Recruitment arrangements
Subject information and informed consent form
Suitability of the clinical trial sites facilities
Suitability of the investigator

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

The sponsor can submit a partial application dossier including only Part I to launch the evaluation process, and may leave the submission of Part II for a later stage. However, if the sponsor does not submit Part II to an MSC within two years after the notification of the conclusion of Part I, the application will lapse.
If Part II is submitted to an MSC, that MSC shall complete its assessment and submit, through CTIS, an assessment report for Part II, including its conclusion, to the sponsor.

Timelines

The assessment of Part II can run in parallel to the assessment of Part I and can take up to 45 days, and up to 76 days if RFIs are submitted (from the validation of the Initial CTA).



#CTIS insights

Part I and II assessment phases share a similar workflow. The difference is that in Part II the process takes place within the users of the MSC. For Part I the RMS leads the process (e.g. consolidates considerations and raises RFI). In Part II, users can view draft considerations, and they are consolidated by the preparer or submitter role. For Part II, MSC can raise their RFIs.

[1] 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
[2] Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, *EU Official Journal*, L 119/1. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN

Assessment Part II - *Document considerations*

Part II considerations are comments/corrections or questions that MSCs may have while reviewing the regulatory documentation of an initial CTA. These considerations are taken into account when an MSC raises an RFI.

#CTIS insights

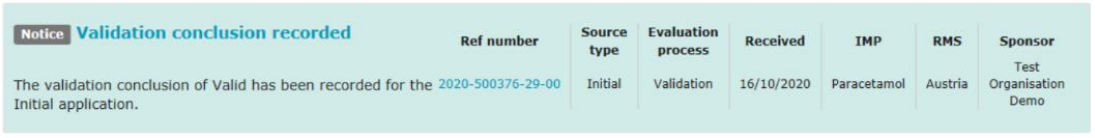
The DAR of Part II is different to the DAR of Part I. In Part II the DAR is not shared with the rest of MSC. It is an internal task that will be performed outside of CTIS and will be uploaded ultimately in CTIS.

The main dates shown in the figure above (see Annex) correspond to the evaluation of an initial CTA. If the tasks are completed earlier, the maximum timeframes between the end of a task and the end of the subsequent one will be respected, but the overall deadlines will be recalculated.
The maximum deadlines foreseen for the tasks related to the assessment of Part II are:

- For hard tasks (mandatory tasks):
  - Submit Final Assessment Report Part II and conclusion Part II – 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):
  - Document considerations (application documents) – up to 45 days from the Validation of the initial CTA.
  - Consolidate considerations – up to 45 days after the validation of the initial CTA. *This task must be performed right after the considerations have been documented and before submitting an RFI to the sponsor.*
  - Submit RFI (if applicable) – up to 45 days from the validation of the Initial CTA. *This task will be performed after the considerations have been consolidated*.
  - Assess RFI response (if applicable) – up to 19 days after the response is sent by the sponsor.

Process to assess Part II

The assessment of Part II starts after the Validation has been submitted by the RMS, and can be performed in parallel to the assessment of Part I. The process is very similar to the one for Part I, but it is performed individually by each MSC. The MSC will receive the following notice:



From the moment the application has been validated, each MSCs can **document their considerations** for Part II of the application dossier.

To perform this task MSC users with appropriate permissions (*see section Roles and Permissions*) need to follow these steps:

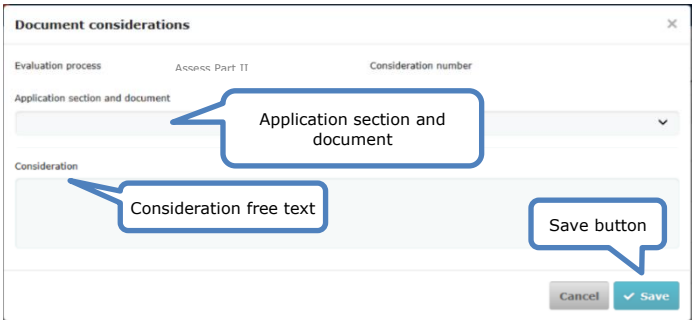
1. Access the Tasks tab and click on the 'Document Considerations Assess Part II' task. The task can be assigned to him/her by a CT Coordinator or if the user has the appropriate role, the user can select 'Assign to myself'.

Assessment Part II – *Consolidate considerations*

The purpose of the consolidate considerations task is to ensure if there is any information missing in the application and if there is an error in the application documentation that the sponsor should clarify or correct, respectively.

2. The system will redirect them to the relevant Evaluation section where they can document considerations.
3. Select the '+ New' button and fill in the pop-up form.

4. Select the application section *(see figure 1, page 1)* and document in which they have the consideration. Describe the consideration in the form of free text and finally click on 'Save'.

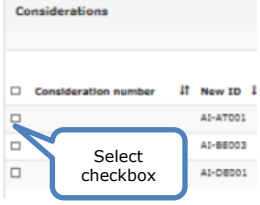


5. After saving the consideration the user can still work on it and edit it as needed. For Part II, all MSC users with the appropriate permissions can view draft considerations. They are shared to indicate they are 'finished'.

After the considerations have been shared, they need to be consolidated by the submitter or preparer role (*see section Roles and Permissions*). This task must be completed by day 45 from the validation of the initial application, in order to be able to raise an RFI.
To perform this task MSC users with appropriate permissions need to follow these steps:

1. 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'.

2. The system will redirect the user automatically to the relevant Evaluation section where the document considerations are stored.
3. To consolidate the considerations, the MSC should first select the considerations via the checkbox on the left of each of them.



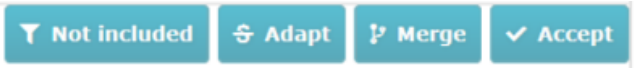
#CTIS insights

When users finish a soft task, they will need to click on the 'Complete' button on the right side of the task to mark it as completed. This will trigger a Notice and will allow to proceed to the following task.

Assessment Part II - *Create, submit and assess an RFI*

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

4. Select one of the four following buttons:

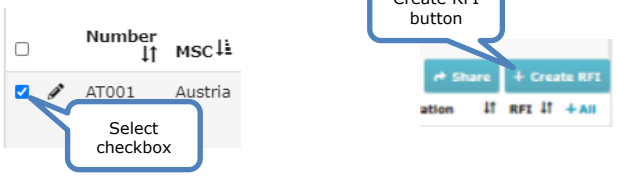


- *Not included*: allows the user to reject a consideration deemed not applicable.
- *Adapt*: allows the user to adapt a consideration shared by an MSC. In this case, the MSC must must include the final wording of the consideration.
- *Merge*: allows the user to merge similar or identical considerations.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

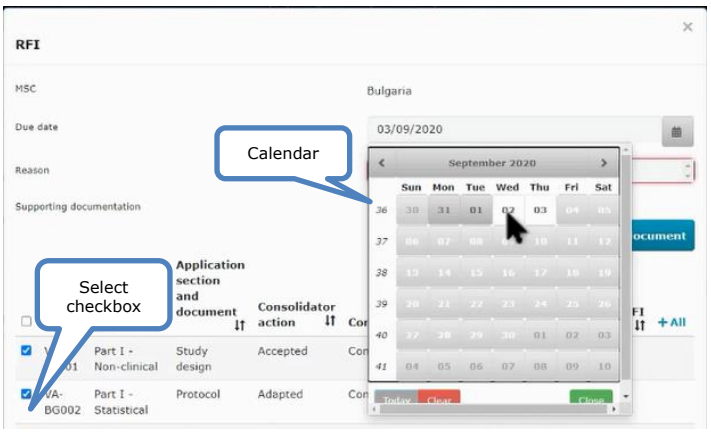
5. View the result by clicking on the tab 'Consolidated considerations'.

After reviewing and consolidating all the considerations, if the MSC deems that certain information from the application is missing, or that a document needs clarification, the MSC can **raise an RFI** to the sponsor.
To perform this task MSC users with appropriate permissions (*see section Roles and Permissions*) need to follow these steps:

1. Create an RFI by selecting the relevant considerations and click on the button '+Create an RFI' on the top-right corner of the consolidated considerations section.



2. Establish the date by which the RFI response should be provided (a maximum period of 12 days can be selected).



3. MSCs 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'. This will redirect the MSC to the dedicated RFI section of the evaluation on the application page. There the MSC can assess the response and submit comments[3].

#CTIS insights

The MSCs have 19 days after the submission of an RFI response by the sponsor to assess it.

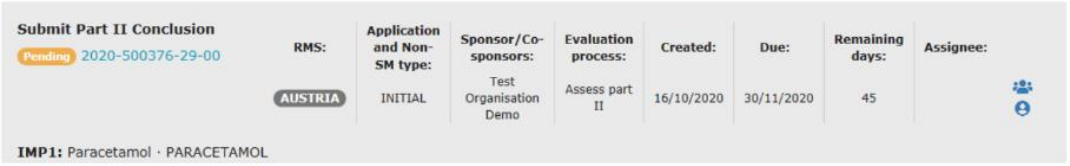
[3] The process of assessing a response to an RFI is similar in all phases of the evaluation. To view how this task is performed please refer to video-clip CTTM06_Clip 3_Validation - RFI and issue validation decision in *Module 6: Assess a clinical trial application (RMS selection and Validation).*

Assessment Part II - *Final Assessment Report*

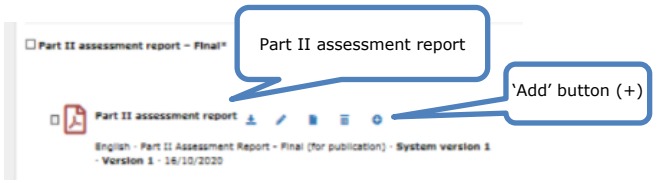
The FAR is the final assessment of the regulatory documentation of the application dossier. The MSCs can engage in an internal discussion between then regarding the FAR and the conclusion of Part II.

After the RFI has been assessed, each MSC needs to submit the **Part II Final Assessment Report (FAR) and Part II conclusion**.
To perform this task MSC users with appropriate permissions (*see section Roles and Permissions*) need to follow these steps:

1. Access the Tasks tab and click on the 'Submit Part II 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'.

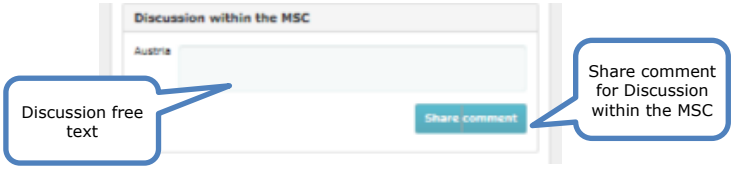


2. Once in the Evaluation section of the assessment of Part II corresponding to the Conclusion, the MSC needs to upload the Part II FAR.

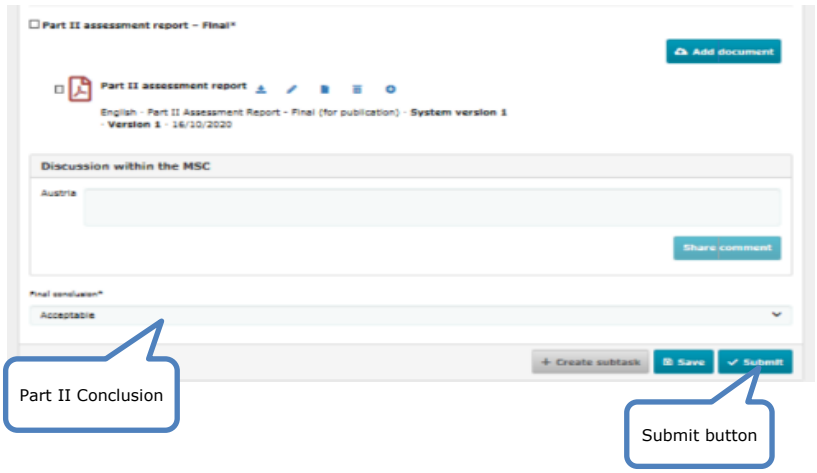


A 'Not for Publication' version of a FAR can be uploaded using the 'Add button (+)', that appears after uploading the first version of the document intended for publication. It is only available in CTIS sections where the documents to be uploaded are published.
More information can also be found in Module 06 - Evaluate a clinical trial application: Selection of reporting Member State (RMS) and validation of the clinical trial application e-learning

3. MSC users can discuss amongst themselves before submitting the Part II FAR and conclusion, by using a discussion functionality.



4. Select the conclusion in the drop-down menu among the options: 'acceptable', 'acceptable with conditions', or 'not acceptable'.



#CTIS insights

If the MSC does not submit the Part II conclusion by day 45 the Part II assessment will be considered as with 'No conclusion'. The application will nonetheless proceed to the Decision phase.

Assessment Part II - *Roles*

There are two roles in each MSC that take part in the Assessment of Part II of the application dossier:

1) Assessor Part II Preparer.

2) Assessor Part II Submitter.

Roles and permissions

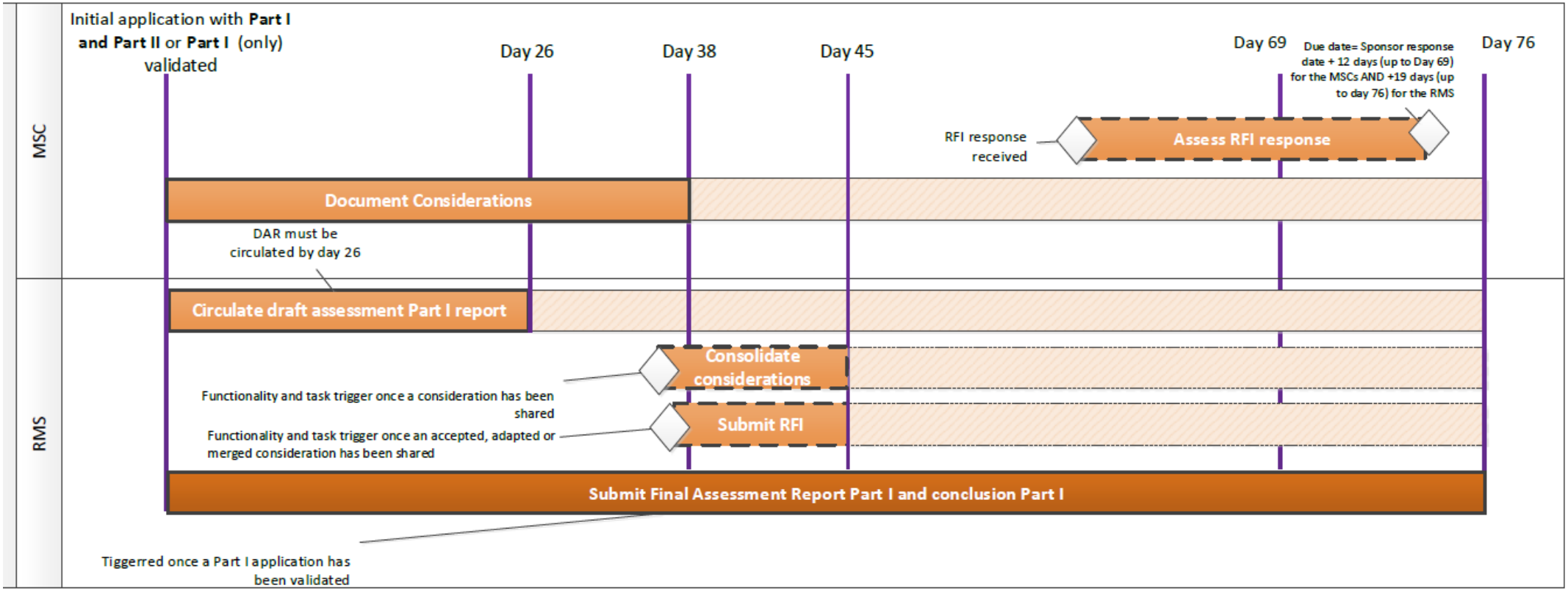
Two roles are involved in the Assessment of Part II: Assessor Part II preparer and Assessor Part II submitter. Both take part in all the tasks related to the Assessment of Part II, except for the following two: send an RFI and submit the Final assessment report and conclusion of Part II. These tasks can only be performed by the Assessor Part II Submitter.

Assessor Part II Submitter	Submit Part II assessment report; Submit RFI Part II
Assessor Part II Preparer	Create/Delete Part II assessment report; Create comments on Part II assessment report; Create/Delete/Share considerations Part II; Create/Delete/Share consolidated considerations Part II; Create/Share comments on assessment of the response to RFI Part II

#CTIS insights

Since Part II is assessed individually by each MSC, the DAR cannot be circulated with other MSC and hence no task is displayed in the Tasks tab, as opposed to Part I. However, it is important that each MSC creates the DAR and discusses it among the users of that MSC, before raising considerations on the Part II documentation of the application.

Annex


MSC
RMS
Initial application with **Part I and Part II** or **Part I** (only) validated
Day 26
Day 38
Day 45
Day 69
Due date= Sponsor response date + 12 days (up to Day 69) for the MSCs AND +19 days (up to day 76) for the RMS
Day 76
RFI response received
Assess RFI response
Document Considerations
DAR must be circulated by day 26
Circulate draft assessment Part I report
Consolidate considerations
Functionality and task trigger once a consideration has been shared
Submit RFI
Functionality and task trigger once an accepted, adapted or merged consideration has been shared
Submit Final Assessment Report Part I and conclusion Part I
Tiggerred once a Part I application has been validated

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