EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

CTIS Evaluation Timelines

CTIS Training Programme

Version 2.2 – February 2025

Learning Objectives

- Understand all the deadlines and timers applicable across the evaluation of a clinical trial application.

The European Medicines Agency developed this training material to enhance public access to information on the Clinical Trial Information System (CTIS). This material describes a preliminary version of CTIS and may therefore not entirely describe the system as it is at the time of use of this material. The Agency does not warrant or accept any liability in relation to the use (in part or in whole) or the interpretation of the information contained in this training material by third parties.

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Record of updated versions

The table below describes the updated versions after the first publication of the document (September 2022):

Version	Version description	Date
2.2	Clarification for the timeline of the task 'Submit Decision' of Substantial Modification for Part II has been added.	February 2025
2.1	Clarification for the timeline of the task 'Submit Decision' of Additional MSC applications has been added.	September 2024
2.0	Additional clarification on Assess Part II task (page 7) and SM Submit decision task (page 20) for SM Part II only. Clarifications regarding earlier completion of tasks/actions (pages 6-8). Examples of calculations of timelines in Annex (pages 35-38).	February 2024
1.2	Additional clarification on server time and Winter clock (pages 6 & 7).	January 2023
1.1	Small fix regarding Winter clock (page 7).	October 2022

Introduction

The purpose of this material is to provide Member States and sponsors with an **overview of the timelines and deadlines** across the Clinical Trial Application (CTA) process. As part of this document, references to other training materials have been included to provide a full overview of the process.

The Clinical Trials Information System (CTIS) requires Member States to undertake hard tasks (mandatory) and soft tasks (non-mandatory), and sponsors to perform actions. Both tasks and actions are reflected in the 'Timetable' section of the 'Clinical trials' tab. However, sponsors are not able to see the soft tasks of Member States.

- **Hard tasks (mandatory)**
  - Hard tasks can only be executed by the users they have been assigned to.
  - If the hard task is not executed, the system applies a tacit decision.
  - The system automatically deems them as completed as soon as they are executed.
- **Soft tasks (non-mandatory)**
  - Soft tasks can be executed by other users than the assignee with the same profile.
  - If the soft task is not executed, the system does not apply immediate consequences on the process.
  - The task assignee must click on 'Complete' to finalise them.

In CTIS, the completion of the task or an action by a Member State or sponsor respectively might affect the timeline of the application process (i.e. timers in CTIS are dynamic). Therefore, users are advised to check CTIS on a daily basis during crucial times in their clinical trials application process.

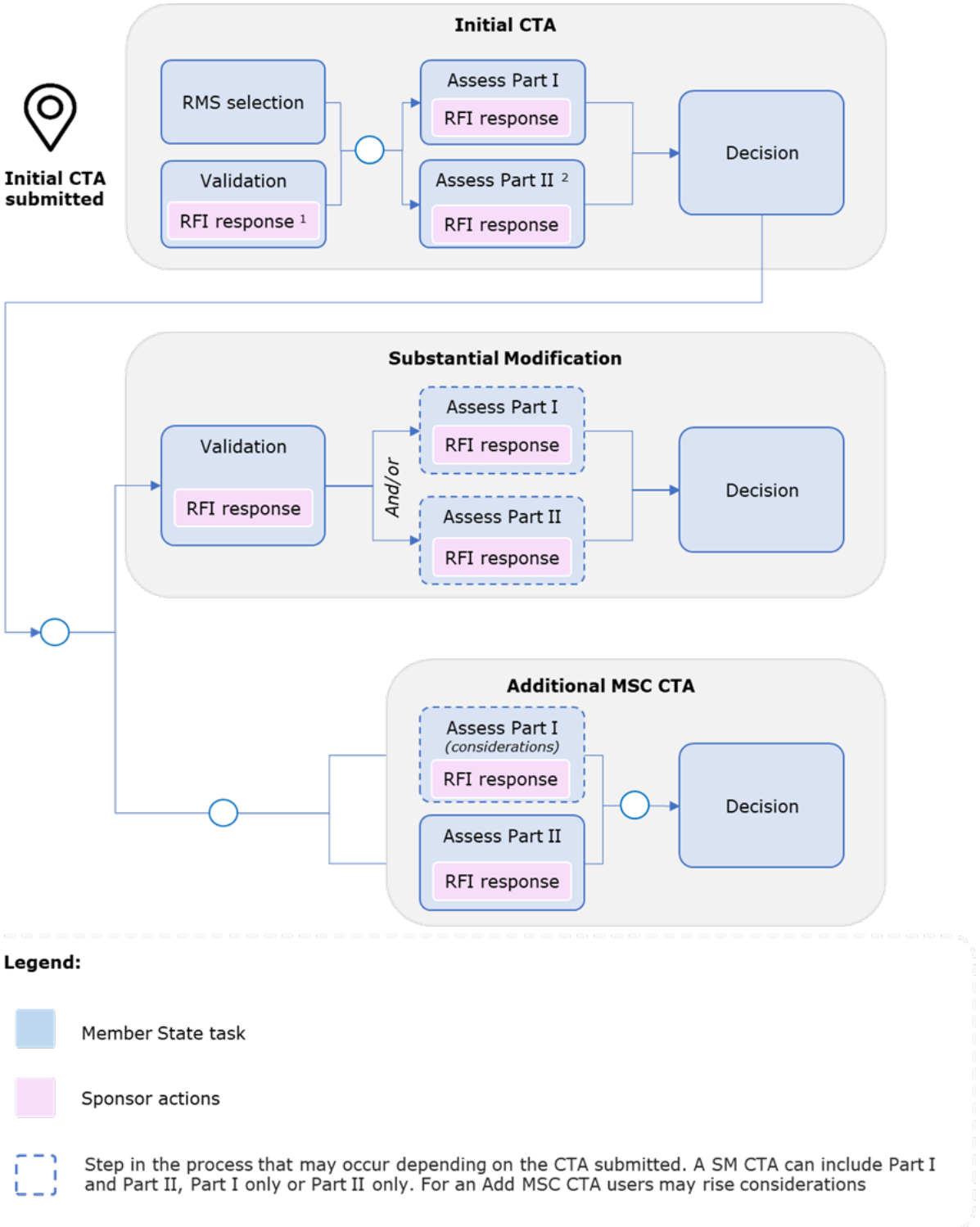
- *For more information on workload management functionalities (tasks and timetable) for Member states, refer to the eLearning of Module 4: Support with workload management (authority workspace).*
- *For more information on workload management functionalities (timetable) for sponsors, refer to the eLearning of Module 4: Support with workload management (sponsor workspace).*

The process of evaluation of a CTA by Member States is established in the Clinical Trials Regulation[1] (CT Regulation). This process starts once the **sponsor has submitted a CTA.**

The evaluation of the clinical trial application is performed for the following **types of CTAs**: Initial CTA; Substantial Modification CTA (SM); Additional Member State Concerned CTA (Add MSC). Each application has its own **timelines** and **activities** to be performed.

In this document, the **timelines for Member States and sponsors in all types of applications within the evaluation of a clinical trial** are explained in detail.

[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf



[1] RFI response action will only take place in case the Member state raise an RFI.

[2] 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.

Timelines overview

In order to have a complete overview of the timelines, it is important to take into account the following aspects. Some examples with calculations of due dates of tasks are presented in the Annex:

- **Dynamic workflow:** The timelines shown in CTIS correspond to the maximum deadlines foreseen for each task/action and the maximum timeframes between the end of a task and the end of the following one. CTIS includes a dynamic workflow by which, if a task/action is completed before its deadline, the corresponding deadlines for the following tasks/actions are recalculated. For **certain tasks, performed by MSC** (see page 7), their earlier completion will result in shorter timelines of the following tasks/actions and potentially, in shorter evaluation period.
- **Lapse of the CTA:** Sponsors need to check the deadlines given by the Member State Concerned (MSC) for responding to the Request for Information (RFIs) in the system, as MSCs **can determine a shorter period** for sponsors to respond to the RFIs. In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application.
- **Tasks' expirations:** The functionality for soft tasks will be available until the completion of the submission's tasks.
- **Timers' calculation:** Task timer calculation is based on the following rules stemmed from Regulation 1182/71 [2], which defines how timelines should be calculated for legally defined delays, and taking into account a winter clock stop (see below):
    - Depending on the **type of application and the process**, the system takes one calendar into account for any given task as presented in the following table:

Process	Day Count Starts	Day Count Ends	Calendar		
			Initial CTA	Substantial modification	Additional MSC CTA
Select Reporting Member State (RMS)	Application submitted	RMS selected	Longest calendar[3]	-	-
Validate Application	Application submitted	Validation concluded	RMS[4]	RMS (for Substantial modification Part I/II or Part I only) MSC (SM for Part II only)	-
Assess Part I	Application validated	Part I concluded	RMS calendar	RMS calendar	RMS calendar
Assess Part II	Application validated	Part II concluded	Each MSC calendar	Each MSC calendar	Each MSC calendar
Submit Decision	Application Part I Concluded Application Part II Concluded	Decision on the application	Each MSC calendar	Each MSC calendar	Each MSC calendar

    - **System time zone:** The time zone to be used for the system is Central European Time (CET).
    - **Start of task timer:** Timers are calculated starting from the next day following the creation of the task.
    - **Due dates:**

[2] Regulation (EEC, EURATOM) No 1182/71 of the Council of June 1971, determining the rules applicable to periods, dates and time limits. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31971R1182&from=nl

[3] Each MSC has a different holiday calendar. In case of a multi-national trial, the process of the RMS selection will follow the longest calendar of the MSCs involved.

[4] Reporting Member State (RMS).

- **End of timer:** All activities with a due date shall be due at 23:59:59 on that day, according to the specified time zone.
- **Working day due date:** The due date must fall on a working day.
- **Two consecutive working days:** There must be a minimum of two consecutive working days at any time during the task timer.

- **Winter Clock stop:** If there is a winter clock stop scheduled, then all timers within the evaluation of that clinical trial application will stop on 22nd December at 23:59:59 and will resume on 8th January the following year at 00:00:01. Tasks won't have their due date falling during that period. Any days during that period are not counted towards the timelines.
- **Creation of task:** A task is created when the precondition of the task specified in the respective workflow is met. The respective workflows are RMS selection, validation, assessment part I, assessment part II and decision.
- **Completion of task**: A task completed **earlier will shorten the timelines only** in the following cases:

Process	Task	Timers for an initial application	Shorten the due date of the next workflow if completed earlier?
Validate Application	Submit validation conclusion	Day 10 + 15	Yes
Assess Part I*	Submit part I conclusion	Day 45 + 31	Yes, if the assess part II is also completed earlier
Assess Part II**	Submit part II conclusion	Day 45 + 31	Yes, if the assess part I is also completed earlier
Submit Decision***	Submit decision	Day 5	-

* Within the flow part I assessment, if the soft task 'Document considerations' is completed earlier than day 38, it will trigger the next task 'Consolidate considerations' earlier than the initial projected due date. However, the due date for the final task of that flow 'Submit part I conclusion' will remain as originally calculated but the RMS can conclude earlier than the indicated due date.

** Task is 'Completed' after Part II conclusion is made. For SM Part II the timer is: Day 33 + 31, in case of RFI and for Additional MSC the timer is: Day 47 + 31, in case of RFI.

*** The timeline for the task 'Submit Decision' of Additional MSC applications and SM Part II only will **not** be shortened if the previous task in the evaluation process (Submit part II conclusion) is completed earlier.

Initial clinical trial application – Timelines

Actors involved: **Member States** **Sponsors**

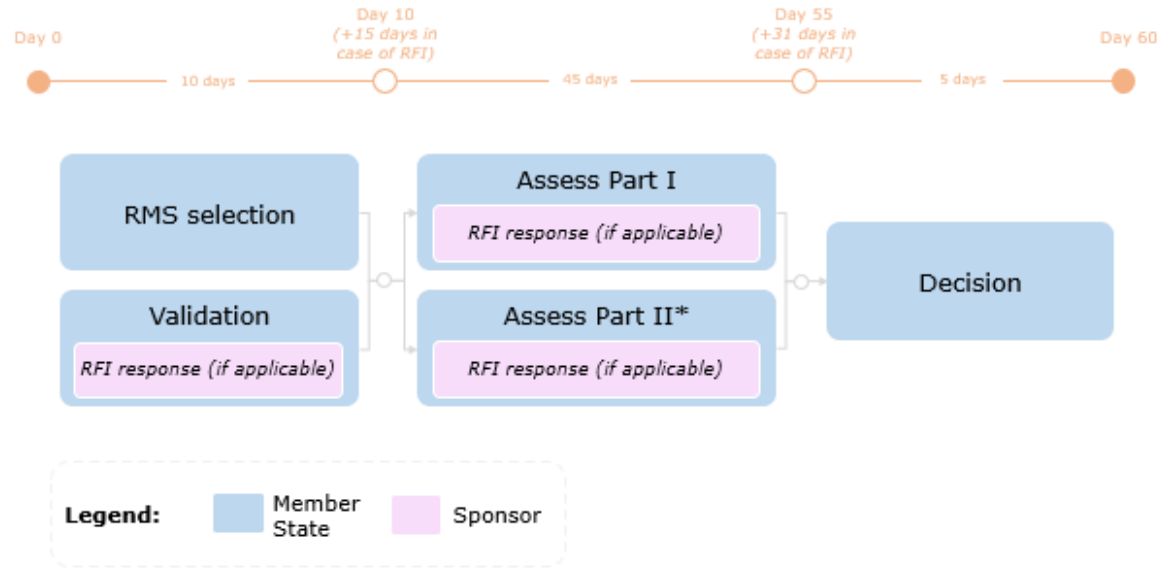
The CT Regulation[5] introduced a harmonised procedure for the submission of Clinical Trial Applications (CTAs) regarding Clinical Trials (CTs) to be conducted in the EU (whether they are mono-national or multinational).

The CT Regulation establishes an **overall timeline of 60 days for the Member States** to evaluate an Initial application. This deadline **may be extended in case that Requests for Information (RFIs)** are raised by a Member State Concerned (MSC) throughout the evaluation process.

Timelines can be extended up to 15 days for RFIs raised in the Validation phase (10 days for the sponsor to respond and 5 days for MSC to review the response), **and up to 31 days for RFIs raised in the Assessment phases**. Multiple RFIs can be raised during the different phases of the evaluation process. However, it should be noted that when multiples RFIs are raised during an assessment phase, the overall timeline will be only extended once despite each RFI having its own due date.

The dates shown in the figures above correspond to the **maximum deadlines foreseen for each task/action**. However, the system includes a **dynamic workflow** by which, if a task/action is completed before its deadline, the corresponding deadlines for the following tasks are recalculated.

Initial CTA



* 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 to Part II.

[5] European Commission, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, EU Official Journal L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol1/reg_2014_536/reg_2014_536_en.pdf

Initial CTA: RMS selection

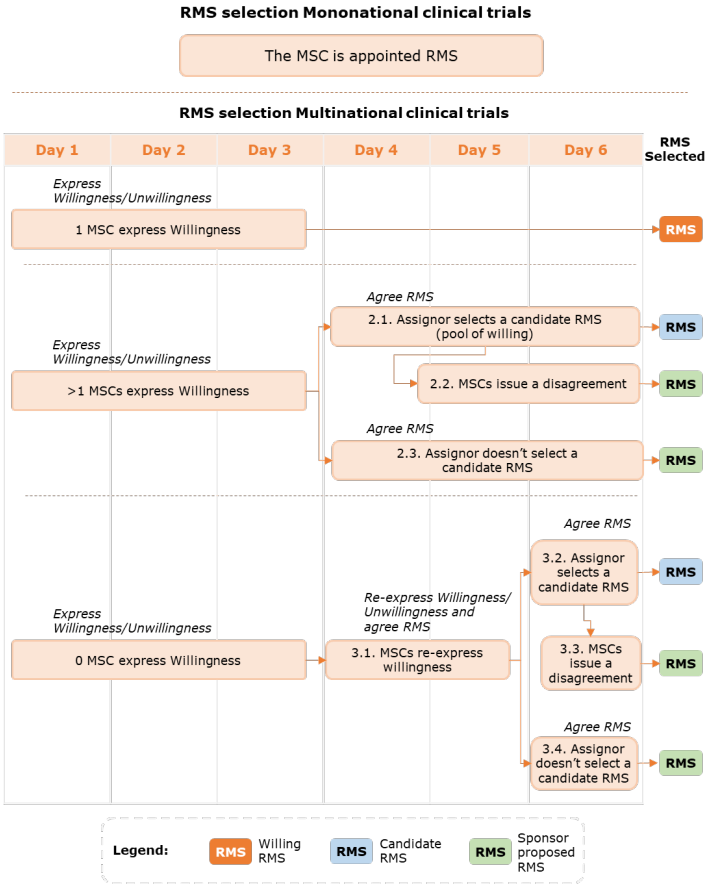
Actors involved: **Member States**

The **Reporting Member State (RMS) selection process** is **triggered as soon as the initial application dossier is submitted by the sponsor**.

- In **multinational trials**, this process occurs in parallel to the validation phase. However, an RMS needs to be selected to be able to complete this phase, as the RMS is responsible for consolidating the considerations made by the MSCs and submitting the validation conclusion. The selection of the RMS can occur within **6 days after the submission** of the application dossier by the sponsor, in line with Article 5(1) of the Regulation (EU) No 536/2014 on Clinical Trials (CT Regulation[6]).
- In **mono-national trials** the MSC will be automatically appointed to be the RMS after the submission of the application dossier, therefore, the following tasks are not applicable for this type of trial: Express willingness/unwillingness, RMS discussion and Agree RMS.

For more information on the RMS selection, refer to the Step-by-step guide of Module 6: How to evaluate an Initial CTA – RMS selection.

The different scenarios within the RMS selection process for multinational and mono-national clinical trials are shown in the image and table below:



[6] European Commission, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, EU Official Journal L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol1/reg_2014_536/reg_2014_536_en.pdf

Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
MSC	Express willingness/ unwillingness	**Hard task**	Up to day 3 (day 0+3), or earlier if all MSCs conclude the 'Express willingness' task and if more than 1 MSC is willing at day 3. If no MSCs are willing at day 3, the task is labelled 're-express willingness and agree RMS'. Having two consecutive working days and not falling on a non-working day (longest MSC calendar)
MSC	Agree RMS	Hard task	Up to day 6 (day 0+6) or at the end of 'Express willingness/unwillingness' task if completed earlier. Having two consecutive working days and not falling on a non-working day (longest MSC calendar)
MSC	Re-express willingness and Agree RMS	**Hard task**	Up to day 6 once all MSCs have concluded the 'Express willingness' task. Having two consecutive working days and not falling on a non-working day (longest MSC calendar)

Initial CTA: Validation

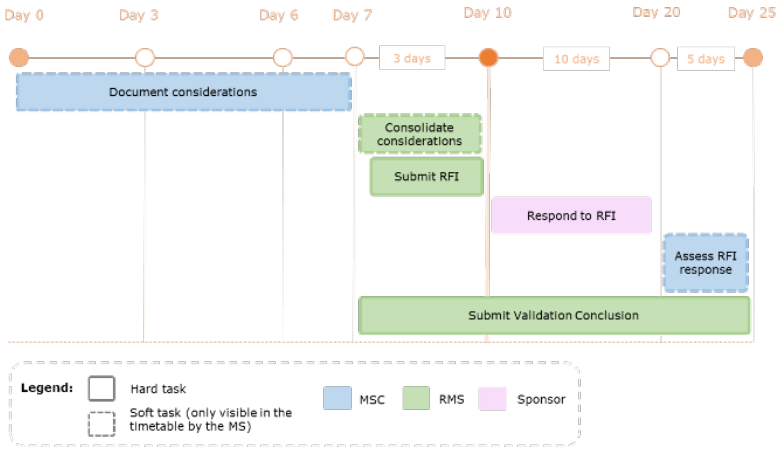
Actors involved: **Member States** **Sponsors**

The validation **starts as soon as the application dossier is submitted**. In an initial CTA, MSCs can start documenting the considerations about the application dossier before the RMS is selected.

Article 5 of the CT Regulation[7] establishes that the **validation phase** for an initial CTA should take **up to 10 days**. This timeline can be further **extended by a maximum addition of 15 days if an RFI is submitted** (this deadline comprises an additional time for the sponsor to reply (10 days) and MSC to assess RFI responses (5 days)). Sponsors need to check the deadlines given by the MSC for responding to the RFIs in the system, as MSCs can determine a shorter period for sponsors to respond to the RFIs. In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application (see image and table below for further reference).

For more information on: Validation phase, *refer to the eLearning of Module 6: How to evaluate a CTA; How to Respond an RFI, refer to eLearning of Module 11: How to respond to RFIs received during the evaluation of a CTA.*

Initial CTA: Validation



Note: In mono-national trials, the MSC and RMS is the same actor and does not have to document and consolidate considerations since it is the only user evaluating the trial.

[7] European Commission, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, EU Official Journal L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol1/reg_2014_536/reg_2014_536_en.pdf

Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
MSC	Document Considerations	Soft task	Day 7 (day 6 + 1 day): Up to 7 days after the initial application with Part I and Part II or Part I (only) has been submitted by the sponsor.
			In case of multinational trials: 1 day after the RMS has been agreed, not falling on a non-working day. Note that there is no necessity of 2 consecutive working days rule, because the lifecycle of this task started at Day 0 so this rule is already satisfied between Day 0 and 7.
			In case of mono-national trials: Day 7 is calculated as Day 0 + 7 days, not falling on a non-working day and keeping the two consecutive working days rule.
RMS	Consolidate Considerations	Soft task	Day 10 (day 7 + 3 days): Up to day 10 from the application submission and after the consideration has been shared. Not falling on a non-working day.
			In case of multinational trials: Day 7 + 3 (Submit Validation decision) = Day 7 (document considerations for validation due date) + 3 days, keeping 2 consecutives working days during the task lifecycle and not falling on a non-working day (RMS calendar).
			In case of mono-national trials: Day 10 is calculated as Day 7 + 3 days, not falling on a non-working day.
RMS	Submit RFI (if applicable)	Soft task	Day 10 (day 7 + 3 days): Up to day 10 from the application submission, once an accepted, adapted, or merged consideration has been shared.
			In case of multinational trials: Day 7 + 3 (Submit Validation decision) = Day 7 (document considerations for validation due date) + 3 days, keeping 2 consecutives working days during the task lifecycle and not falling on a non-working day (RMS calendar).
			In case of mono-national trials: Day 10 is calculated as Day 7 + 3 days, not falling on a non-working day.
Sponsor	Respond to RFI (if applicable)	N/A	Day 20: (day 10 + 10 days). Sponsors have 10 days to respond once RFI has been submitted by the RMS. Note that if the Sponsor does not respond to an RFI before the due date set by the RMS for the sponsor to response, it will cause the lapse of the application (due date cannot fall on a weekend or during the clock stop).
MSC	Assess RFI response (if applicable)	Soft task	Day 25 (day 20 + 5 days). Up to day 25, task triggered if and when an RFI response is received. MSCs have up to 5 days to assess the RFI response.
RMS	Submit Validation Conclusion	**Hard task**	Day 10 or day 25 if an RFI is submitted. Triggered at day 7, or earlier if the RMS is selected. Up to 25 days from the application submission in case of RFI.

Initial CTA: Assessment of Part I

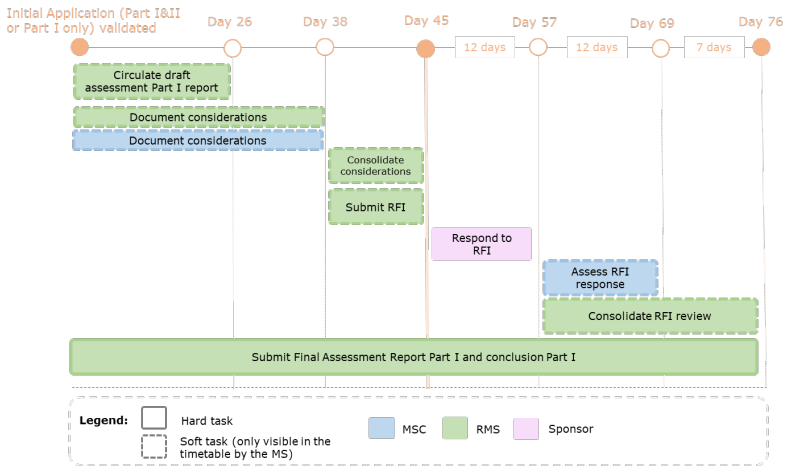
Actors involved: **Member States** **Sponsors**

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** (12 days for the sponsor to respond and 12 days for the MSCs to review the response, and additional 7 days for the RMS to consolidate the review). The RMS may also extend the period up to 50 days for consultation with experts. In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application (see image and table below for further reference).

If the RMS does not complete the task 'Submit Part I conclusion' by the due date, Part I will remain labelled as with 'No conclusion', and the overall application will remain 'Under evaluation'.

For more information on the Assessment of Part I, refer to the Quick Guide of Module 8: How to evaluate a Clinical Trial Application: Assessment and Decision - Part I.

Initial CTA: Assessment Part I



Note: In mono-national trials, the MSC and RMS is the same actor.

Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
RMS	Circulate Draft Assessment Report (DAR)	Soft task	Day 26 (day 0 + 26 days): Up to 26 days from the Validation of the initial CTA.
RMS & MSC	Document considerations	Soft task	Day 38 (day 26 + 12 days): Up to 38 days from the Validation of the initial CTA and once the RMS has completed the 'Circulate DAR' task.
RMS	Consolidate considerations	Soft task	Day 45 (day 38 + 7 days): Up to 7 days after the considerations are shared.
RMS	Submit the RFI (if applicable)	Soft task	Day 45 (day 38 + 7 days): Up to 45 days from the validation of the Initial CTA.
Sponsor	Respond to RFI (if applicable)	N/A	Day 57 (day 45 (or RFI submission date) + 12 days): Up to 12 days to respond from the RFI submission. Note that if the Sponsor does not respond to an RFI before the due date set by the RMS for the sponsor to response, it will cause the lapse of the application.
RMS & MSC	Assess an RFI response (if applicable)	Soft task	Day 69 (day 57 + 12 days): Up to 12 days after the response is sent by the sponsor for the MSC, and up to 19 days for the RMS.
RMS	Submit Final Assessment Report (FAR) Part I and conclusion Part I	**Hard task**	Day 45 or day 76: Up to 45 days or 76 days (if RFIs are raised), from the Validation of the initial CTA.

Initial CTA: Assessment of Part II

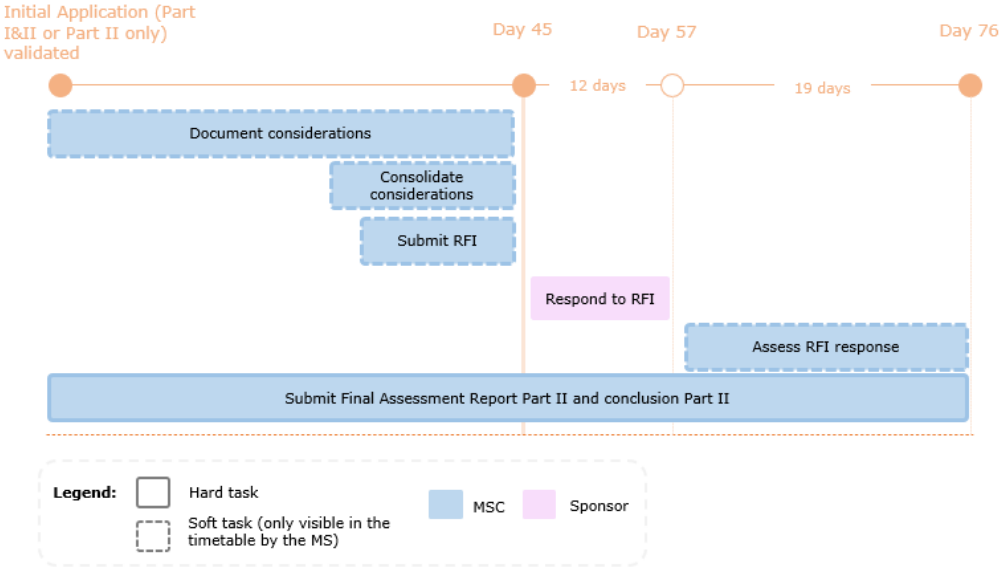
Actors involved: **Member States** **Sponsors**

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 (12 days for the sponsor to respond and additional 19 days for the MSCs to assess the RFI). In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application (see image and table below *for* further reference).

If the MSC does not complete the task 'Submit Part II conclusion', Part II of the application will remain as with 'No conclusion'. Nonetheless, the application will proceed to the Decision phase.

For more information on the Assessment of Part II, refer to the Quick Guide of Module 8 – How to evaluate a Clinical Trial Application: Assessment and Decision - Part II.

Initial CTA: Assessment Part II



Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
MSC	Document considerations (application documents)	Soft task	Day 45: Up to 45 days from the Validation of the initial CTA.
MSC	Consolidate considerations	Soft task	Day 45: Up to 45 days from 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.
MSC	Submit RFI (if applicable)	Soft task	Day 45: Up to 45 days from the validation of the Initial CTA. This task will be performed after the considerations have been consolidated.
Sponsor	Respond to RFI (if applicable)	N/A	Day 57 (day 45 (or RFI submission date) + 12 days): Up to 12 days to respond from the RFI submission. Note that if the Sponsor does not respond to an RFI before the due date set by the RMS for the sponsor to response, it will cause the lapse of the application.
MSC	Assess RFI response (if applicable)	Soft task	Day 76 (day 57 + 19 days): Up to 19 days after the response is sent by the sponsor.
MSC	Submit Final Assessment Report Part II and conclusion Part II	**Hard task**	Day 45 or day 76: Up to 45 days or 76 days (if RFIs are raised), from the Validation of the initial CTA.

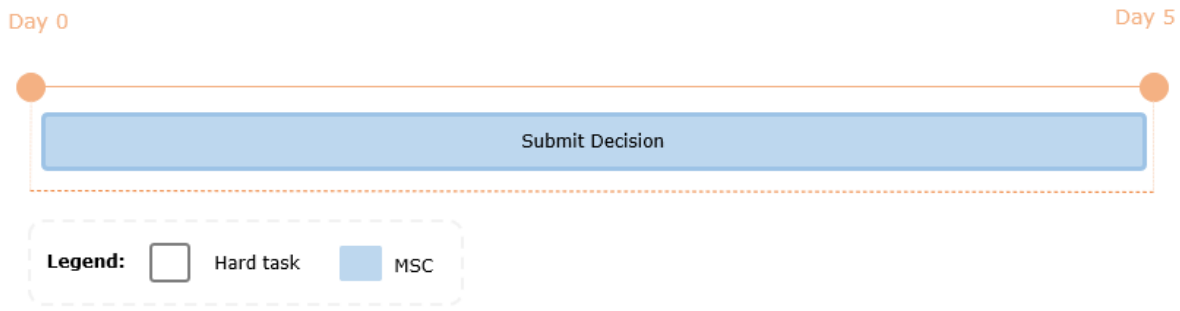
Initial CTA: Decision

Actors involved: **Member States**

Each MSC has a **maximum of 5 days to submit its Decision** after the conclusions of Part I and Part II assessment have been submitted. If no conclusion has been submitted, the task is still triggered. (see image and table below for further reference).

For more information on the Decision phase, refer to the Quick Guide of Module 8 – How to evaluate a Clinical Trial Application: Assessment and Decision - Decision.

Initial CTA: Decision



Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
MSC	Submit decision	**Hard task**	Day 5: 5 days later the trigger of the task, having two consecutive working days and not falling on a non-working day for each MSC calendar.

Substantial Modification clinical trial application – Timelines

Actors involved: **Member States** **Sponsors**

A Substantial Modification Clinical Trial Application (SM CTA) 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.

The CT Regulation[8] establishes an **overall timeline of 50 days for the Member States** to evaluate a substantial modification. This deadline **may be extended in case that Requests for Information (RFIs)** are raised by a Member State Concerned (MSC) throughout the evaluation process.

Timelines can be extended up to 15 days for RFIs raised in the Validation phase (10 days for sponsors to respond and 5 days for MSC to review the response), **and up to 31 days for RFIs raised in the Assessment phase**. Multiple RFIs can be raised during the different phases of the evaluation process. However, it should be noted that when multiples RFIs are raised each of them will have its own deadline, and the overall timeline will be only extended once (see image below for further reference).

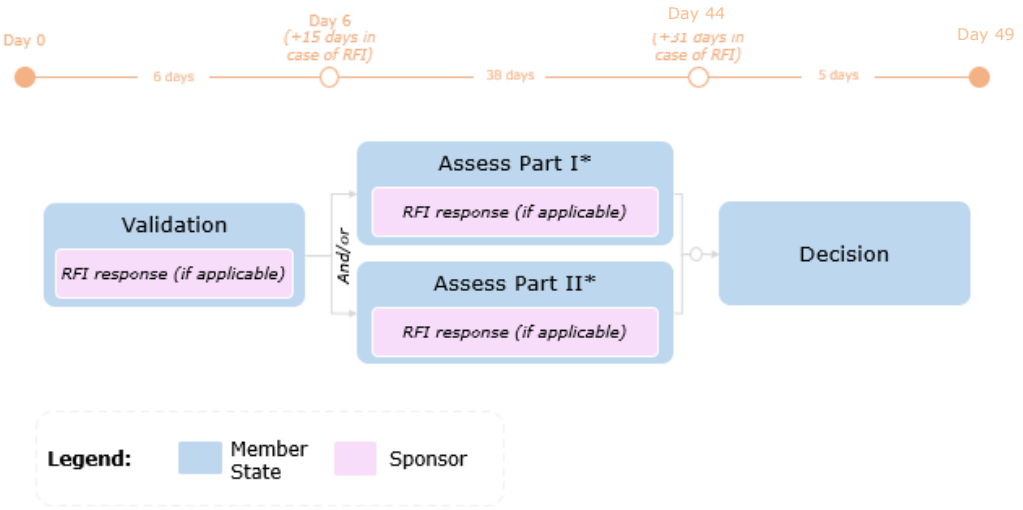
If a sponsor has received a request for a non-Substantial Modification, there are no specific deadlines, however, it should be handled efficiently to ensure the clinical trial application process can be concluded efficiently.

The dates shown in the figure above correspond to the **maximum deadlines foreseen for each task/action.** However, the system includes a **dynamic workflow** by which, if a task/action is completed before its deadline, the corresponding deadlines for the following tasks are recalculated, but the maximum timeframes are still respected.

For more information on:

- Substantial modification for sponsor users, *refer to the video of Module 10*: How to submit a substantial modification in the CTIS Sponsor workspace.
- *How to evaluate a substantial modification, refer to the Step-by-step guide of Module 08:* How to evaluate a Substantial Modification clinical trial application.

Substantial Modification CTA



**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.*

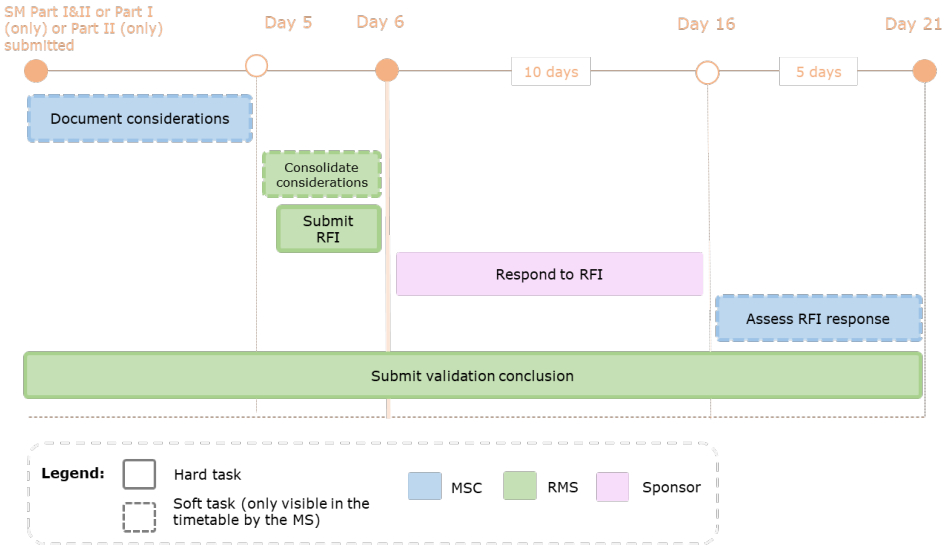
[8] European Commission, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, EU Official Journal L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol1/reg_2014_536/reg_2014_536_en.pdf

Substantial modification CTA: Validation

Actors involved: **Member States** **Sponsors**

CT Regulation[9] establishes that the **validation phase** for a substantial modification should take **up to 6 days**. This timeline can be further **extended by a maximum addition of 15 days if an RFI is submitted** (this deadline comprises an additional time for the sponsor to reply (10 days) and MSC to assess RFI responses (5 days). Sponsors need to check the deadlines given by the MSC for responding the RFIs in the system, as MSCs can determine a shorter period for sponsors to respond to the RFIs. In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application (see image and table below for further reference).

Substantial modification CTA: Validation



Note: In case of Substantial Modifications CTAs limited to Part II only, all tasks will be performed by the MSC.

Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
MSC	Document considerations	Soft task	Day 5 (day 0 + 5 days): Up to 5 days from the submission of a substantial modification from the sponsor (having two consecutive working days and not falling on a non-working day).
RMS	Consolidate considerations	Soft task	Day 6 (day 5 + 1 day): Up to 1 day from the 'Document consideration' task (not falling on a non-working day).
RMS	Submit RFI (if applicable)	Soft task	Day 6 (day 5 + 1 day): Up to 1 day from the 'Document consideration' task (not falling on a non-working day).
Sponsor	Respond to RFI (if applicable)	N/A	Day 16 (day 6 + 10 days): Up to 10 days from the submission of the RFI.
MSC	Assess RFI response (if applicable)	Soft task	Day 21 (day 6 + 10 days + 5 days): Up to 5 days from the date when the sponsor responded to an RFI, up to day 21 (having two consecutive working days and nor falling on a non-working day)
RMS	Submit validation conclusion	**Hard task**	Day 6 or day 21 if an RFI is submitted: Up to 1 day from day 5 (not falling on a non-working day). Day 21 if an RFI is submitted.

[9] European Commission, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, EU Official Journal L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol1/reg_2014_536/reg_2014_536_en.pdf

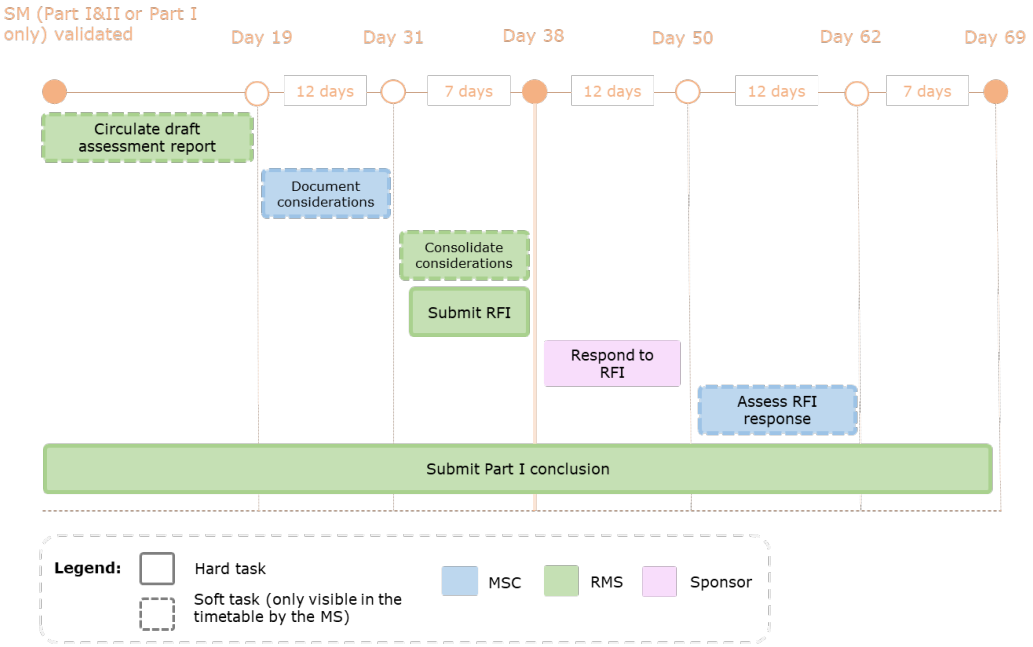
Substantial modification CTA: Assessment of Part I only or Part I and II

Actors involved: **Member States** **Sponsors**

The **assessment of Part I** of a substantial modification can take **up to 38 days**, or **up to 69 days if Requests for Information (RFIs) are raised.** In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application (see image and table below for further reference).

If the RMS does not complete the task 'Submit Part I conclusion' by the due date, Part I will remain labelled as with 'No conclusion', and the overall application will remain 'Under evaluation'.

Substantial modification CTA: Assessment of Part I only or Part I and II



Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
RMS	Circulate draft assessment report	Soft task	Day 19 (day 0 + 19 days): Up to 19 days from the validation of the substantial modification (having two consecutive working days and not falling on a non-working day).
MSC	Document considerations	Soft task	Day 31 (day 19 + 12 days): Up to 12 days from the circulation of the draft assessment report (having two consecutive working days and not falling on a non-working day).
RMS	Consolidate considerations	Soft task	Day 38 (day 19 + 12 days + 7 days): Up to 7 days from the document consideration task (counted in a staggered approach as stated and not falling on a non-working day).
RMS	Submit RFI (if applicable)	Soft task	Day 38 (day 19 + 12 days + 7 days): Up to 7 days from the document consideration task (counted in a staggered approach as stated and not falling on a non-working day).
Sponsor	Respond to RFI (if applicable)	N/A	Day 50 (day 38 + 12 days): Up to 12 days from the submission of the RFI.
MSC	Assess RFI Response (if applicable)	Soft task	Day 62 (day 38 + 12 days + 12 days): Up to 12 days from the RFI response (having two consecutive working days and not falling on a non-working day).
RMS	Submit Part I conclusion	**Hard task**	Day 69 (day 38 + 12 days + 12 days + 7 days): Up to 7 days from the assessment of the RFI response (not falling on a non-working day).

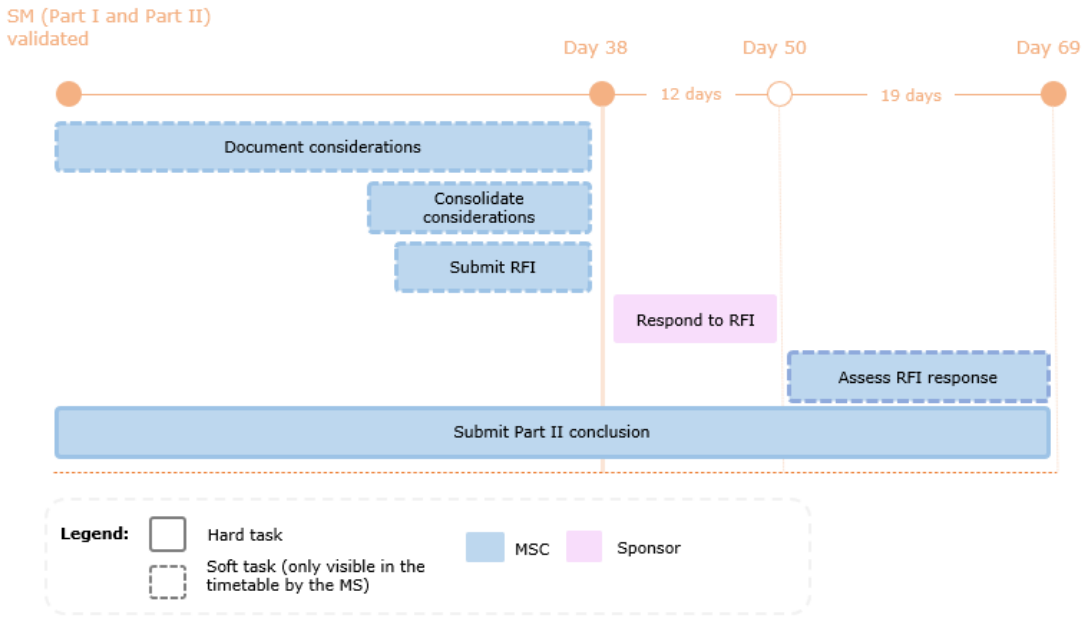
Substantial modification CTA: Assessment of Part II

Actors involved: **Member States** **Sponsors**

The **assessment of Part II** can run in parallel to the assessment of Part I and can take **up to 38 days, and up to 69 days if RFIs are submitted** to the sponsor (12 days for the sponsor to respond and additional 19 days for the MSCs to assess the RFI). In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application (see image and table below for further reference).

If the MSC does not complete the task 'Submit Part II conclusion', Part II of the application will remain as with 'No conclusion'. Nonetheless, the application will proceed to the Decision phase.

Substantial modification CTA: Assessment of Part II



Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
MSC	Document considerations	Soft task	Day 38 (day 0 + 38 days): Up to 38 days from the validation of the substantial modification (having two consecutive working days and not falling on a non-working day).
MSC	Consolidate considerations	Soft task	Day 38 (day 0 + 38 days): Up to 38 days from the validation of the substantial modification (having two consecutive working days and not falling on a non-working day).
MSC	Submit RFI (if applicable)	Soft task	Day 38 (day 0 + 38 days): Up to 38 days from the validation of the substantial modification (having two consecutive working days and not falling on a non-working day).
Sponsor	Respond to RFI (if applicable)	N/A	Day 50 (day 38 + 12 days): Up to 12 days from the submission of the RFI.
MSC	Assess RFI Response (if applicable)	Soft task	Day 69 (day 50 + 19 days): Up to 19 days from the date when the sponsor responded to the RFI (having two consecutive working days and not falling on a non-working day).
MSC	Submit Part I conclusion	**Hard task**	Day 38 or day 69 if an RFI is submitted (Day 0 + 38 days + 12 days + 19 days). Having two consecutive working days and not falling on a non-working day.

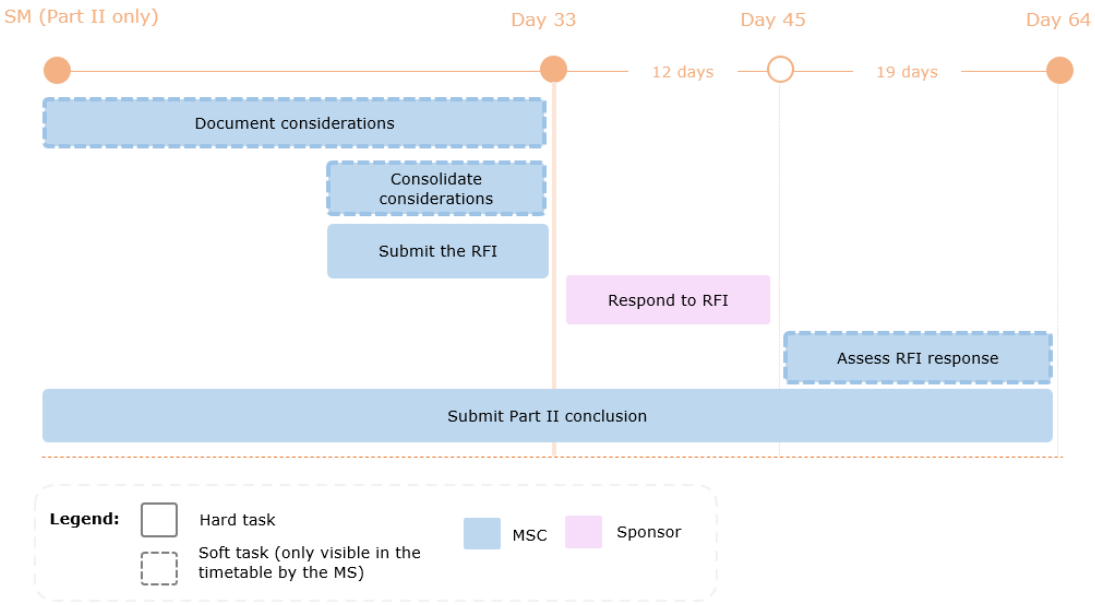
Substantial modification CTA: Assessment of Part II only

Actors involved: **Member States** **Sponsors**

The **assessment of Part II** of a substantial modification can take **up to 33 days, or up to 64 days if Requests for Information (RFIs) are raised** (see image and table below for further reference).

If the MSC does not complete the task 'Submit Part II conclusion', Part II of the application will remain as with 'No conclusion'. Nonetheless, the application will proceed to the Decision phase.

Substantial modification CTA: Assessment of Part II only



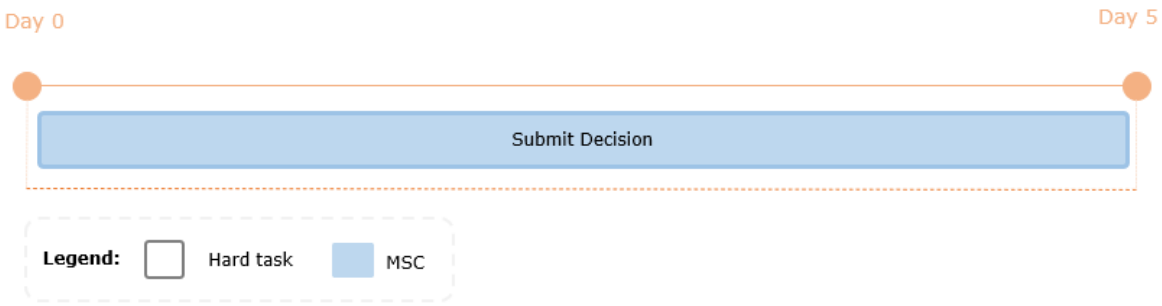
Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
MSC	Document considerations	Soft task	Day 33 (day 0 + 33 days): Up to 33 days from the validation of the substantial modification (having two consecutive working days and not falling on a non-working day).
MSC	Consolidate considerations	Soft task	Day 33 (day 0 + 33 days): Up to 33 days from the validation of the substantial modification (having two consecutive working days and not falling on a non-working day).
MSC	Submit the RFI (if applicable)	Soft task	Day 33 (day 0 + 33 days): Up to 33 days from the validation of the substantial modification (having two consecutive working days and not falling on a non-working day).
Sponsor	RFI Response (if applicable)	N/A	Day 45 (day 33 + 12 days): Up to 12 days from the submission of the RFI.
MSC	Assess RFI Response (if applicable)	Soft task	Day 64 (day 33 + 12 days + 19 days): Up to 19 days from the RFI response (having two consecutive working days and not falling on a non-working day).
MSC	Submit Part II conclusion	**Hard task**	Day 64 (day 33 + 12 days + 19 days): Up to 19 days from the RFI response (having two consecutive working days and not falling on a non-working day).

Substantial modification CTA: Decision

Actors involved: **Member States** **Sponsors**

The **Decision** phase of a substantial modification can take **up to 5 days** (see image and table below for further reference).

Substantial modification CTA: Decision



Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
MSC	Submit Decision*	**Hard task**	Day 5 (day 0 + 5 days): Up to 5 days from the Submission of Part II conclusion (having two consecutive working days and not falling on a non-working day). If no conclusion has been submitted, the task is still triggered.

*The above due date calculation is for Initial, SM PI&II and PI only.
For the decision of SM PII only the due date is Day 38 or day 69 in case of RFI and the timelines will **not** be shortened if the previous task in the evaluation process, Submit part II conclusion, is completed earlier.

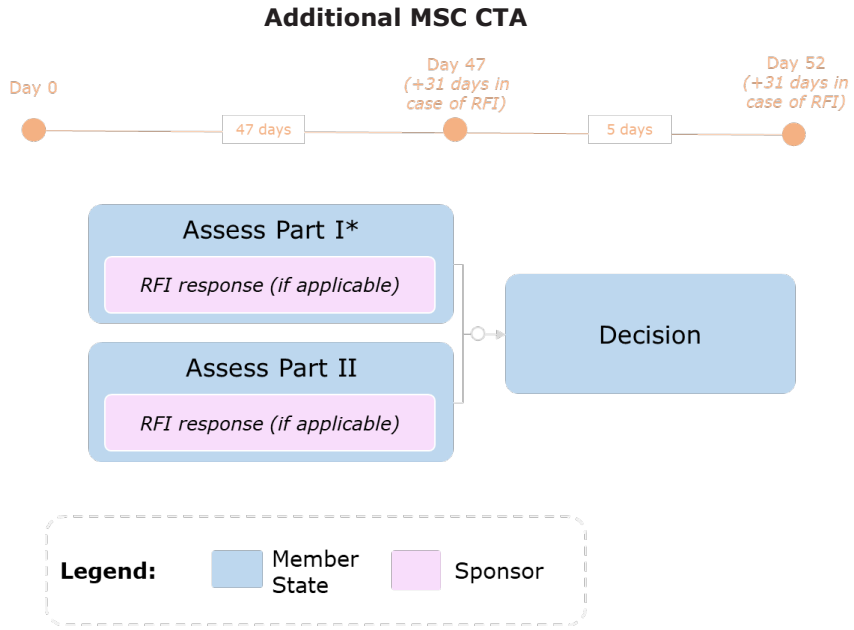
Additional MSC clinical trial application – Timelines

Actors involved: **Member States** **Sponsors**

An Additional Member State Concerned Clinical Trial Application (Add MSC CTA) is an application for extending a previously authorised Clinical Trial (CT) to the territory of another Member State(s). Such process involves Assessment Part I considerations, Assessment Part II and Decision (see image below for further reference).

The dates shown in the figure above **correspond to the maximum deadlines foreseen for each task/action**. However, the system includes a **dynamic workflow** by which, if a task/action is completed before its deadline, the corresponding deadlines for the following tasks are recalculated, but the maximum timeframes are still respected.

For more information on Add MSC CTA, refer to the Step-by-step guide of Module 08: How to evaluate an Additional Member State Concerned clinical trial application.



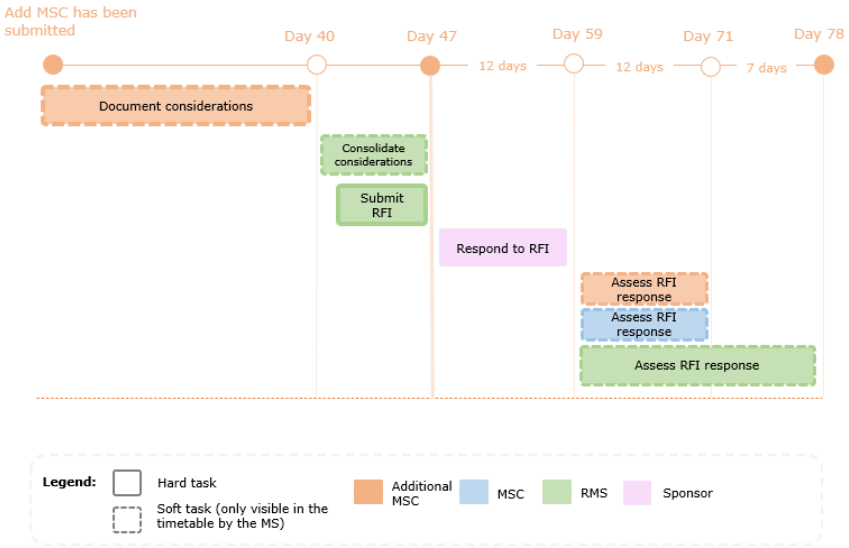
**Step in the process that may occur depending on the CTA submitted. For an Add MSC CTA users may raise considerations for Part I, but the conclusion cannot be modified.*

Additional MSC CTA: Assessment of Part I

Actors involved: **Member States** **Sponsors**

The **assessment of Part I** of an Additional Member State Concerned can take **up to 47 days, or up to 78 days if Requests for Information (RFIs) are raised.** In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application (see image and table below for further reference).

Additional MSC CTA: Assessment Part I



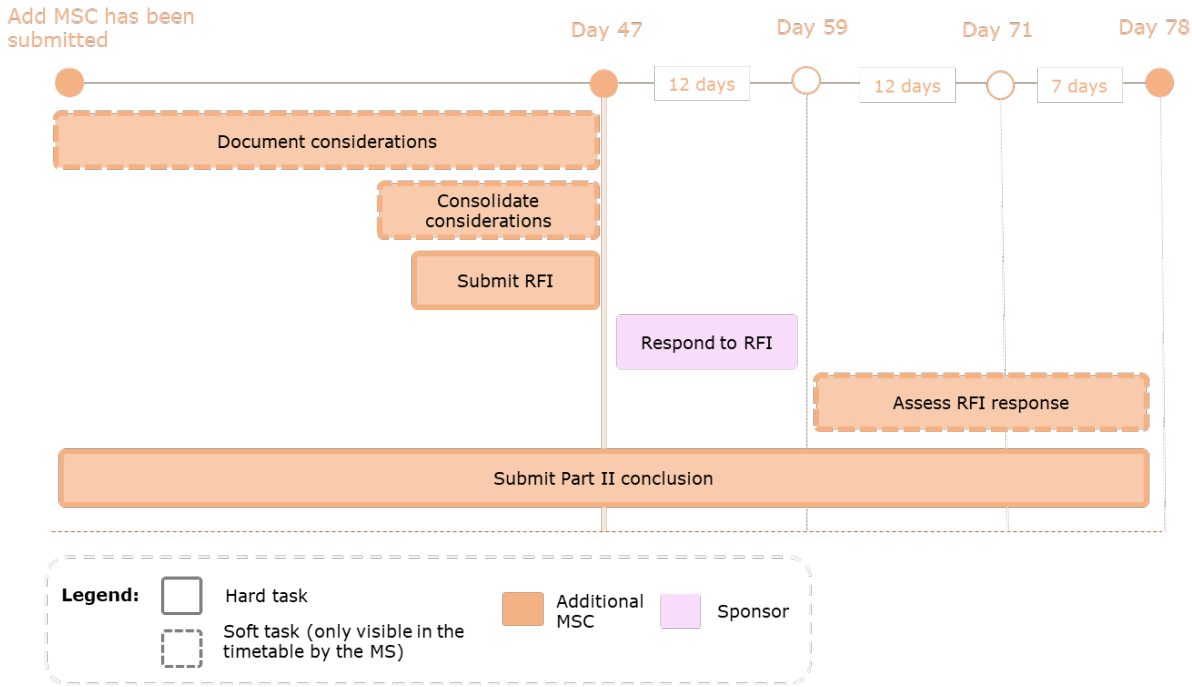
Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
Additional MSC	Document considerations	Soft task	Day 40 (day 0 + 40 days): Up to 40 days from submission (having two consecutive working days and not falling on a non-working day).
RMS	Consolidate considerations	Soft task	Day 47 (day 0 + 47 days): Up to 47 days from submission (having two consecutive working days and not falling on a non-working day).
RMS	Submit RFI (if applicable)	Soft task	Day 47 (day 0 + 47 days): Up to 47 days from submission (having two consecutive working days and not falling on a non-working day).
Sponsor	RFI Response (if applicable)	N/A	Day 59 (day 47 + 12 days): Up to 12 days from the submission of the RFI.
All MSCs	Assess RFI response (if applicable)	Soft task	Day 71 (day 47 + 12 days +12 days): Up to 12 days from the RFI response (having two consecutive working days and not falling on a non-working day).
RMS	Assess RFI response (if applicable)	Soft task	Day 78 (day 47 + 12 days +12 days + 7 days): Up to 19 days from the RFI response (having two consecutive working days and not falling on a non-working day).

Additional MSC CTA: Assessment of Part II

Actors involved: **Member States** **Sponsors**

The **assessment of Part II** of a substantial modification can take **up to 47 days, or up to 78 days if Requests for Information (RFIs) are raised**. In case the sponsor does not respond to an RFI before the due date, it will cause the lapse of the application (see image and table below for further reference).

Additional MSC CTA: Assessment Part II



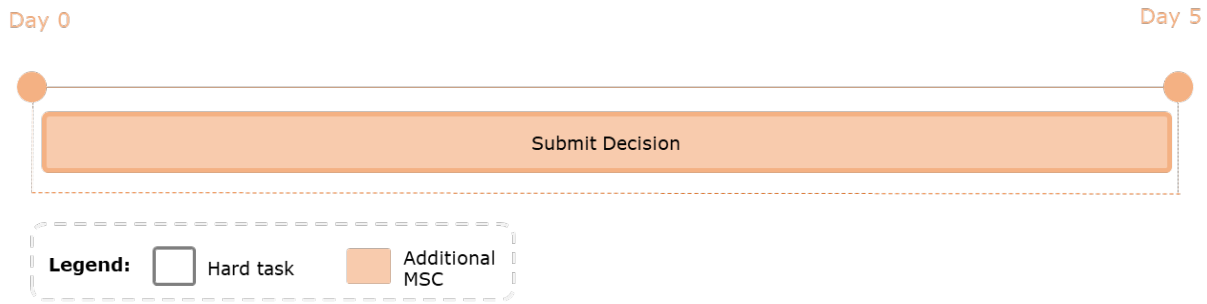
Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
Additional MSC	Document considerations	Soft task	Day 47 (day 0 + 47 days): Up to 47 days from submission (having two consecutive working days and not falling on a non-working day).
Additional MSC	Consolidate considerations	Soft task	Day 47 (day 0 + 47 days): Up to 47 days from submission (having two consecutive working days and not falling on a non-working day).
Additional MSC	Submit RFI (if applicable)	**Hard task**	Day 47 (day 0 + 47 days): Up to 47 days from submission (having two consecutive working days and not falling on a non-working day).
Sponsor	RFI Response (if applicable)	N/A	Day 59 (day 47 + 12 days): Up to 12 days from the submission of the RFI.
Additional MSC	Assess RFI response (if applicable)	Soft task	Day 78 Day 78 (day 47 + 12 days +12 days + 7 days): Up to 19 days from the RFI response (having two consecutive working days and not falling on a non-working day).
Additional MSC	Submit Part II conclusion	**Hard task**	Day 78 Day 78 (day 47 + 12 days +12 days + 7 days): Up to 19 days from the RFI response (having two consecutive working days and not falling on a non-working day).

Additional MSC CTA: Decision

Actors involved: **Member States** **Sponsors**

The **Decision** phase of an additional MSC CTA can take **up to 5 days** (see image and table below for further reference). For this type of application, the timeline of the task 'Submit Decision' is not shortened if the previous hard task is completed earlier (in this case, the 'Submit Part II conclusion'), as it would happen in the cases of the Initial application and Substantial Modification application.

Additional MSC CTA: Decision



Responsible	Action	Hard or soft task	Deadline for action *(dynamic workflow)*
Additional MSC	Submit Decision	**Hard task**	Day 5 (day 0 + 5 days): Up to 5 days from the Submission of Part II conclusion (having two consecutive working days and not falling on a non-working day). If no conclusion has been submitted, the task is still triggered. *

* The timeline is not shortened, in case the 'Submit Part II conclusion' is completed earlier than its respective due date. The due date for the 'Submit Decision' in an Additional MSC application will be on the Day 52 (47 + 5) or 83 (78 + 5) in case RFIs are raised during assessment phase and will not change regardless an earlier completion of previous tasks during the assessment.

Timetable section in CTIS

The 'Timetable' section allows users to **monitor the progress of the assessment of a particular CTA**, by displaying the actual completion dates of each phase of the assessment, and the expected completion date of the remaining ones. To view this feature, users need to perform a CT or a CTA search and then go to the summary page. Sponsors and Member states can view the timetables of CTAs which their organisation manages.

The Clinical Trials Information System (CTIS) requires Member States to undertake hard tasks (mandatory) and soft tasks (non-mandatory), and sponsors to perform actions. Both tasks and actions are reflected in the 'Timetable' section of the system. However, sponsors are not able to see the soft tasks of Member States.

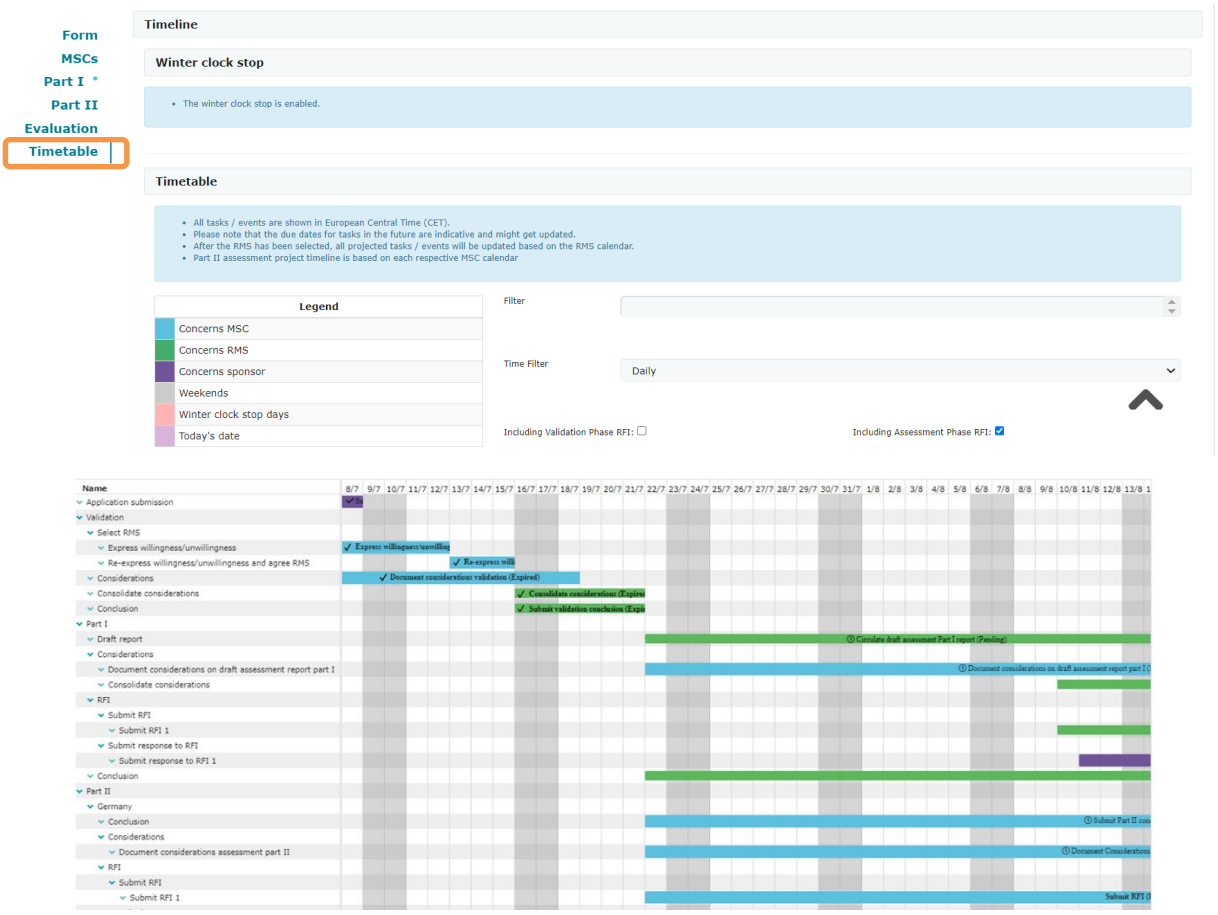


Figure 1. Member states' timetable

In case a new task/action is created by the sponsor or Member state, the system will automatically include it in the timetable:

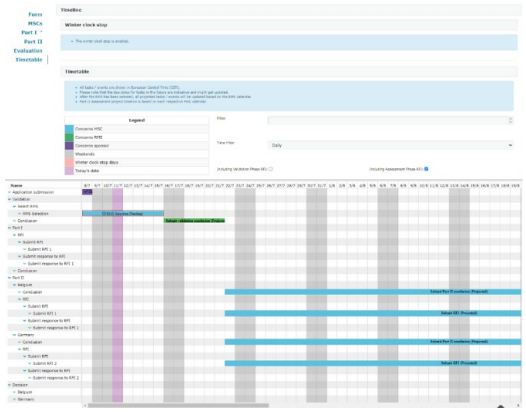


Figure 2. Sponsor's timetable

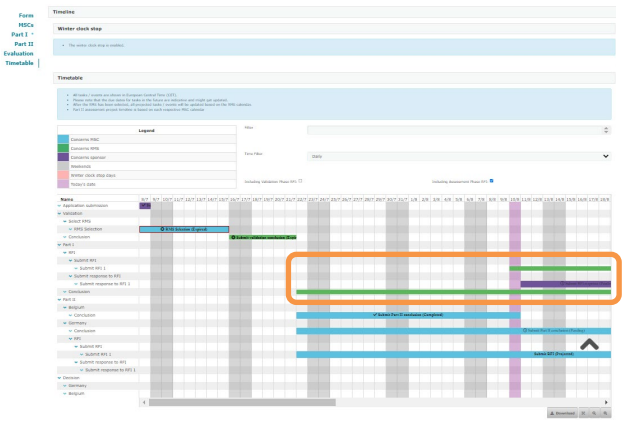


Figure 3. Sponsor's timetable with RFI

Dynamic workflow

The 'Timetable' reflects the CTIS dynamic workflow by keeping updated the current and projected due dates.

A projected due date is an estimated calculation of when a task/action will take place based on the maximum deadlines set out in the CT Regulation[10]. This means, for example, that users can view from the beginning which is the maximum due date of the decision. It is indicated in the functionality with the label '(Projected)'.

Once a task or action is done, the 'completed' and 'expired' tasks/actions are updated and indicated with the corresponding label, and **the future tasks/actions due dates are automatically adjusted,** maintaining the maximum deadlines.

Also, new tasks/actions are triggered (with their new due dates adjusted) and they can have an impact on any of the actors involved. For this reason, users are advised to consult, on a regular basis, the tasks/actions due dates and the timetable, in order not to miss any mandatory step that could lead to the lapse of the CTA.

For example, in the image below it is shown that the task 'Submit decision' (orange box) is projected for week 50. But, after the completion of the task 'Submit Part I' (blue box) the 'Submit decision' can be completed from week 38, but also it still needs to be completed within 5 days.

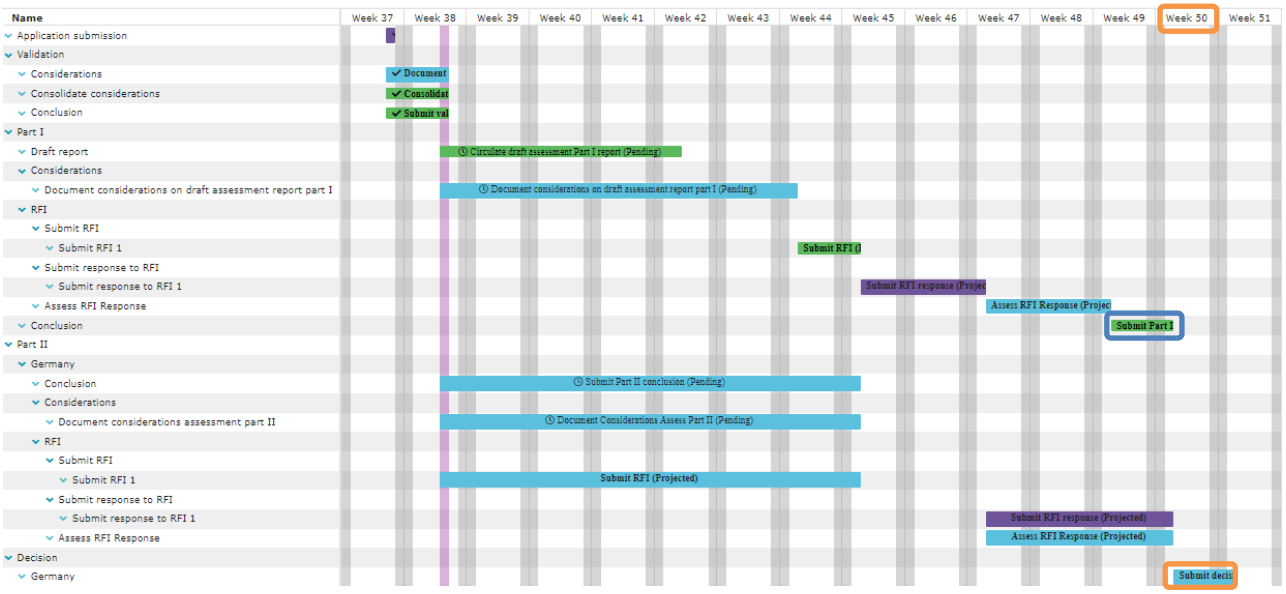


Figure 4. 'Submit decision' task projected for week 50.

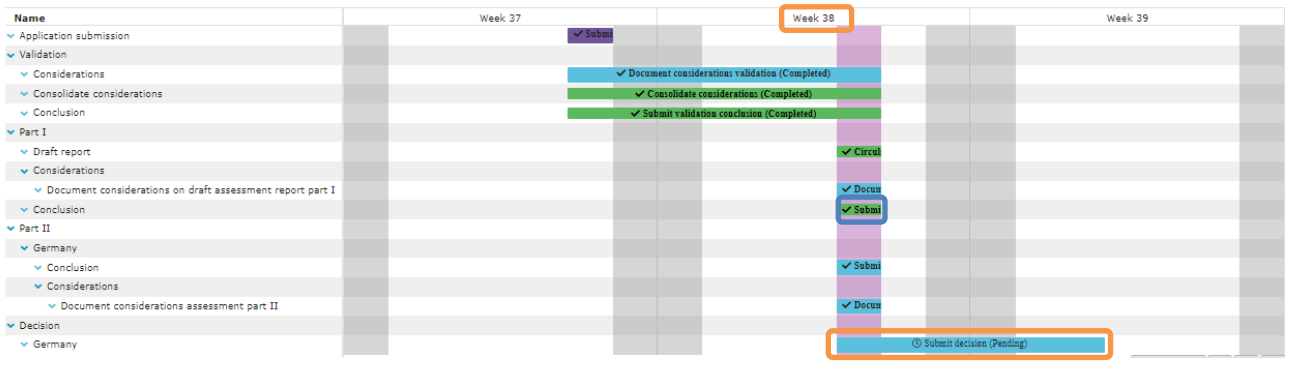
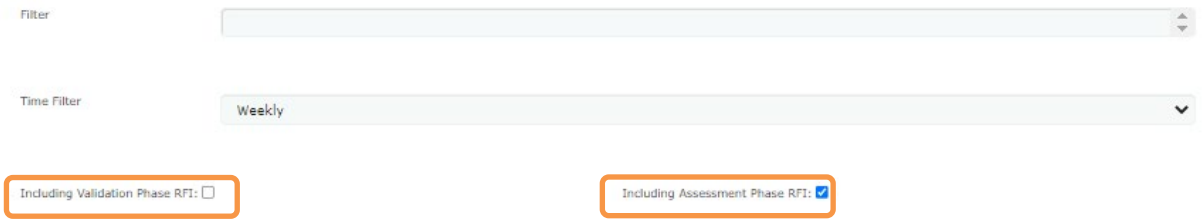


Figure 5. 'Submit decision' task projected for week 38.

[10] European Commission, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, EU Official Journal L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol1/reg_2014_536/reg_2014_536_en.pdf

Projected timelines including RFIs

The 'Timetable' functionality also allows users to consult projected timelines with or without RFIs submitted for each phase. To view the projected RFIs' impact on the due dates, users can click on the tick boxes for each phase, as shown in the image below:



In the example in the image below, the timelines are shown without the RFI projected due dates. In this scenario the 'Submit Part I' due date is on week 37.

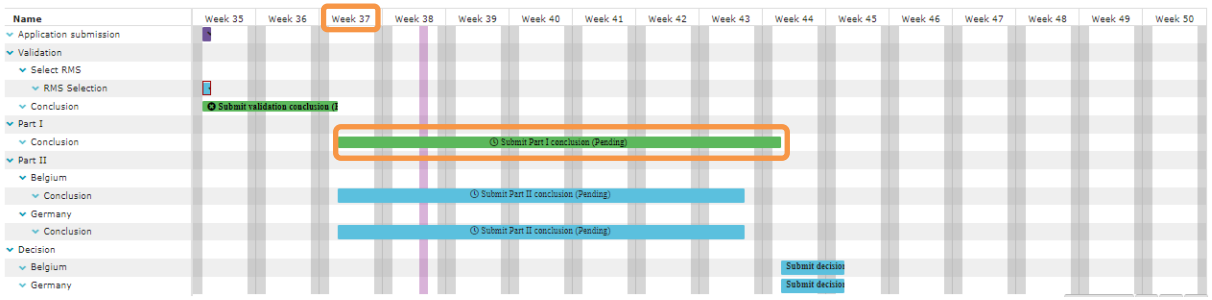


Figure 6. Projected timelines without RFIs.

If the projected timelines for the RFI of the assessment phase are included, the 'Submit decision' projected due date is on week 48. The timelines are extended when the first RFI is submitted, they are not extended subsequently if more RFIs are submitted.

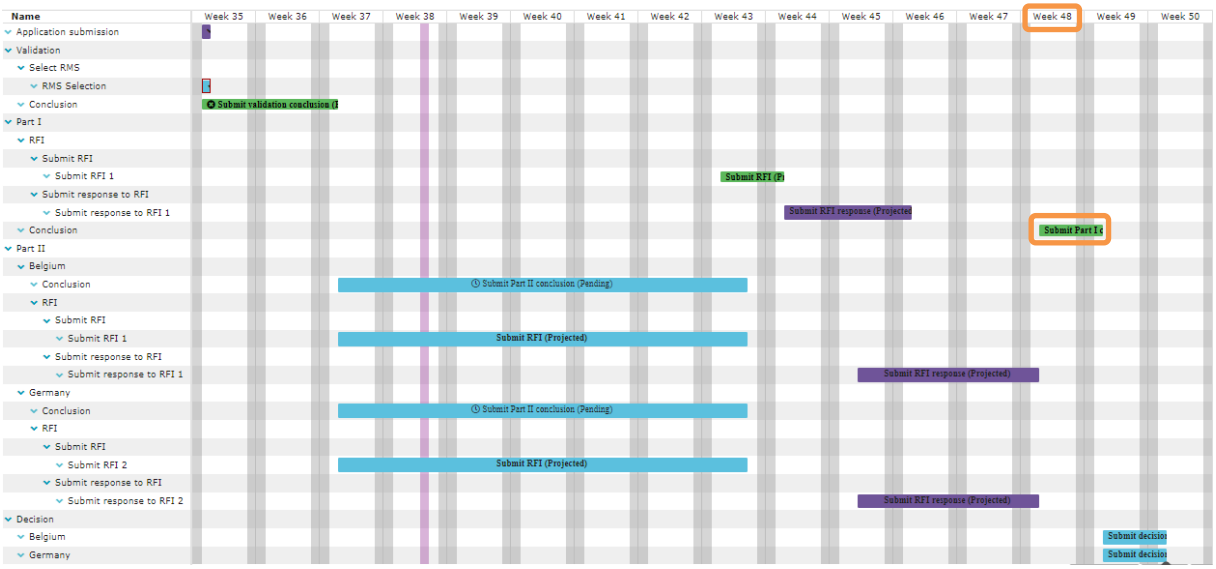
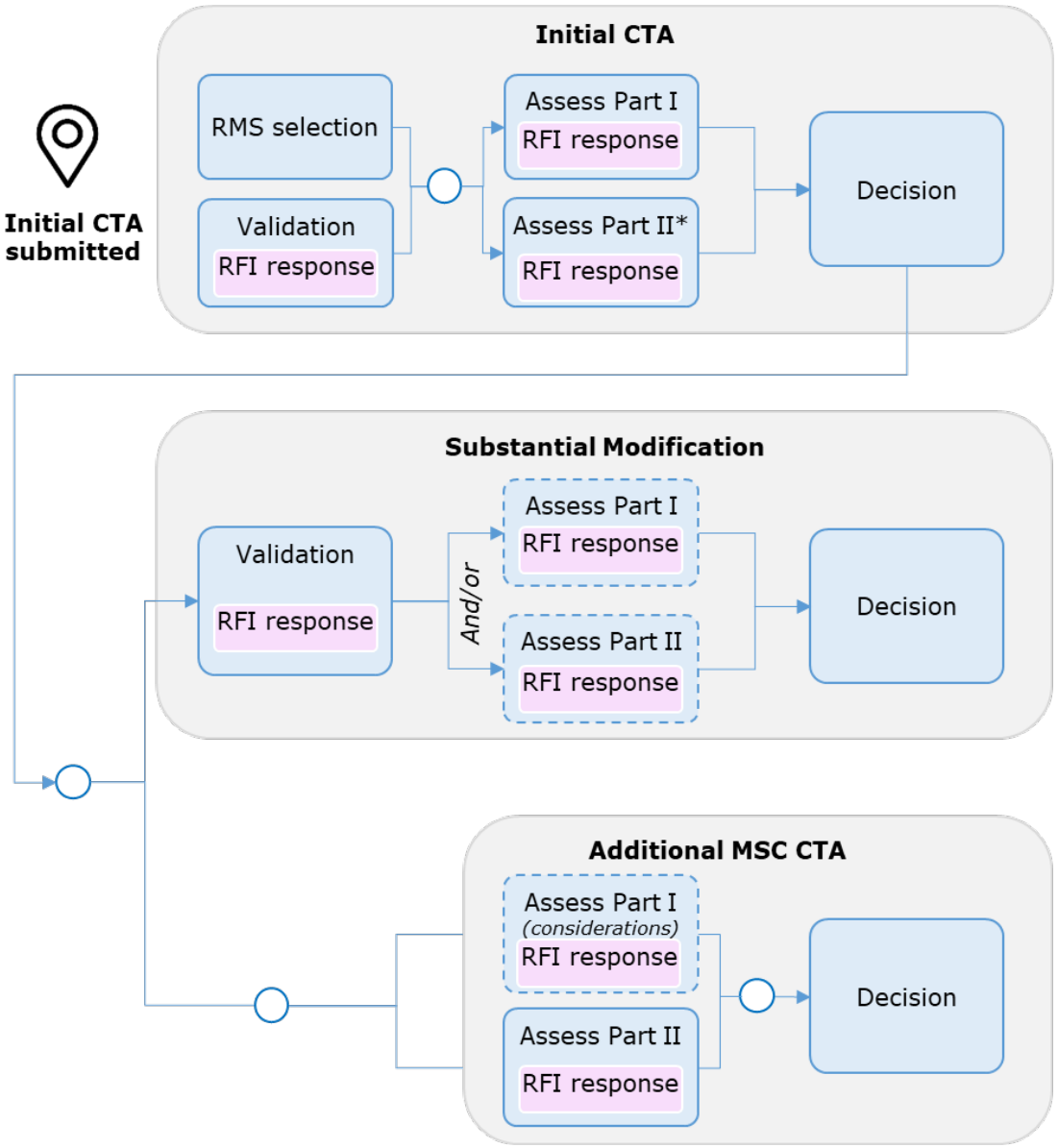


Figure 7. Projected timelines with RFIs.

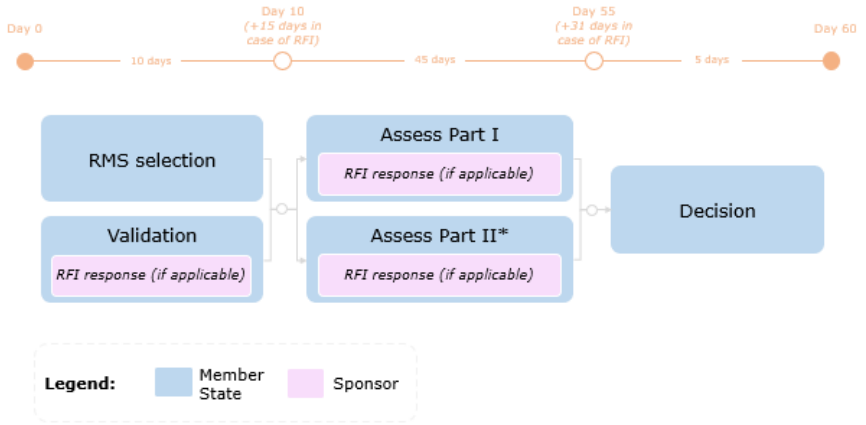
Annex

Clinical trial application types



*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.

Initial clinical trial application



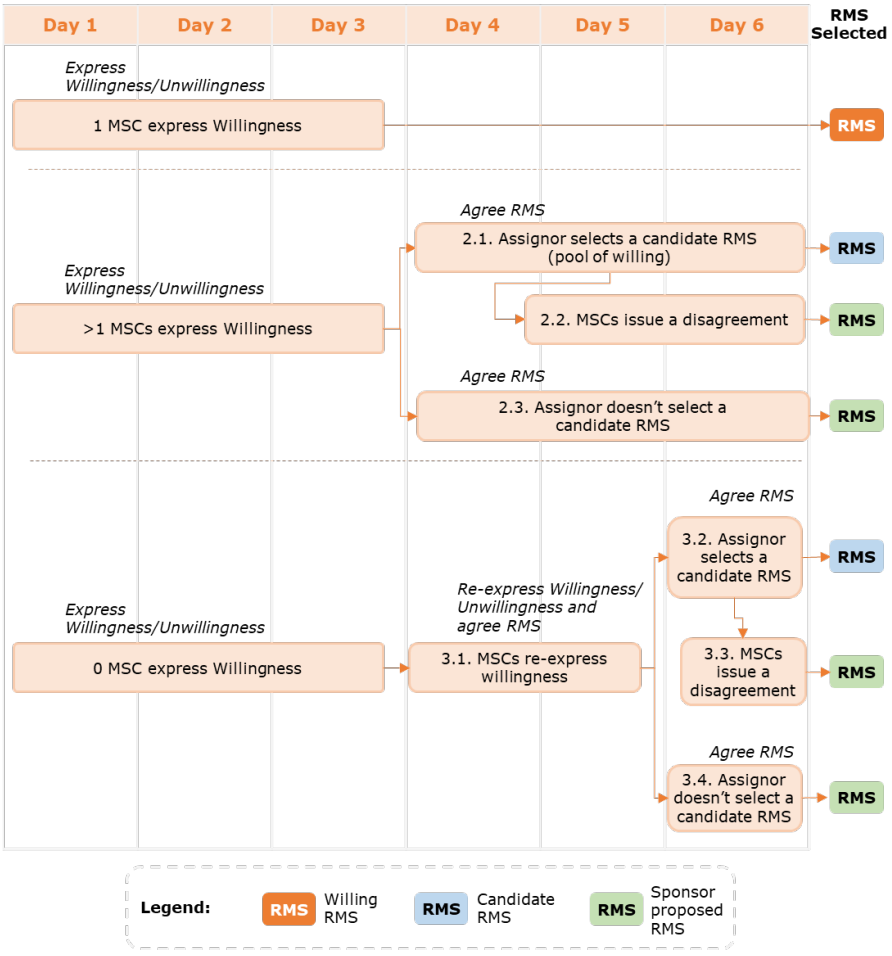
* In case of applications limited to Part I, the sponsor has two years from the notification of the conclusion of Part I to submit an application to Part II.

Initial CTA: RMS selection

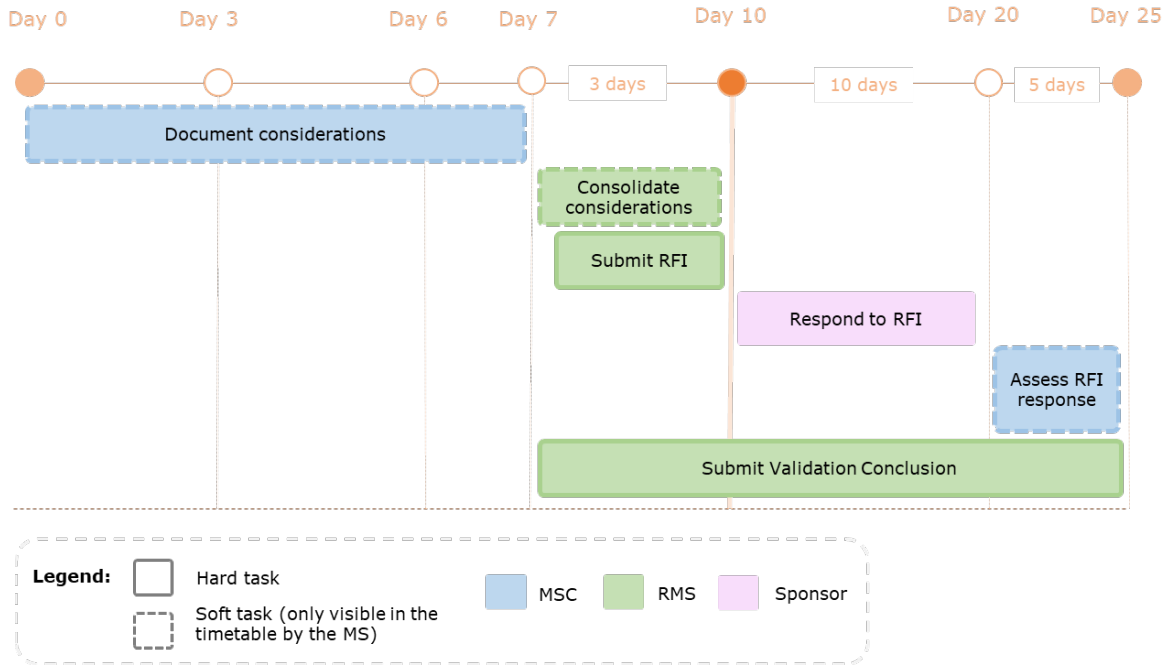
RMS selection Mononational clinical trials

The MSC is appointed RMS

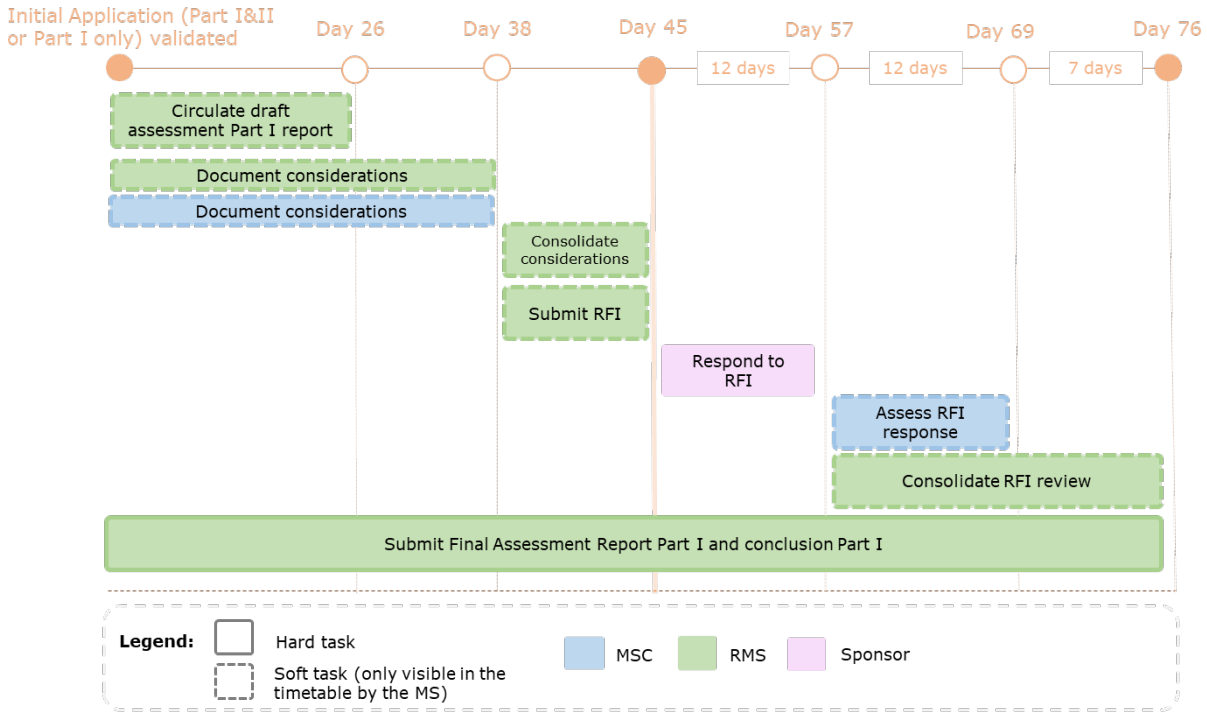
RMS selection Multinational clinical trials



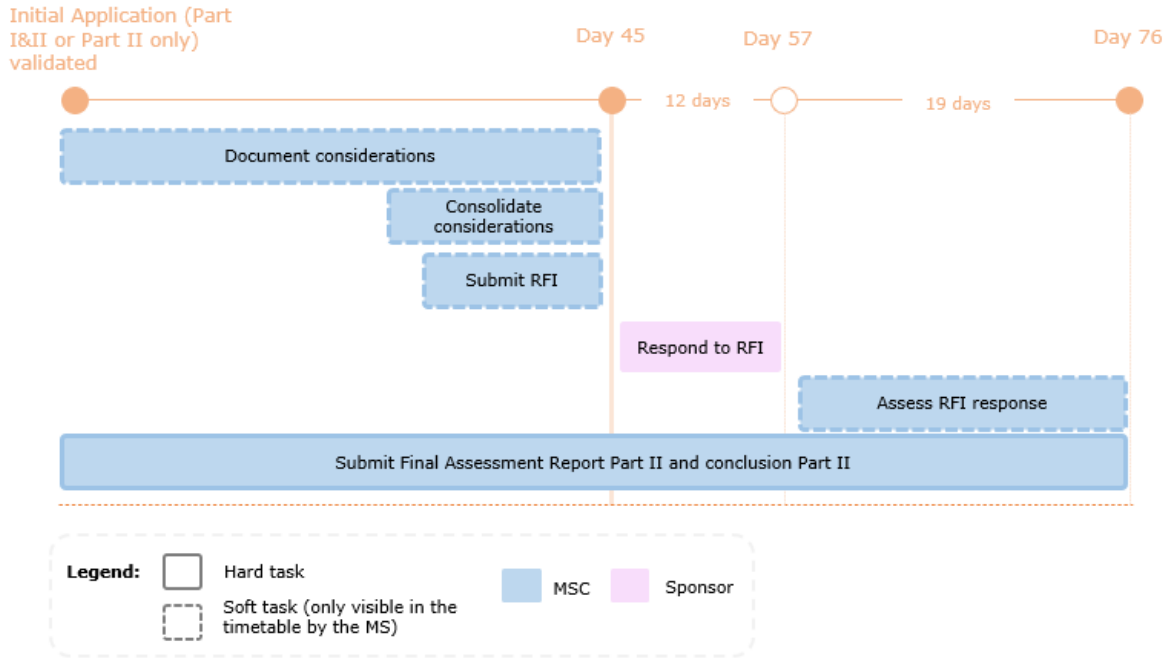
Initial CTA: Validation



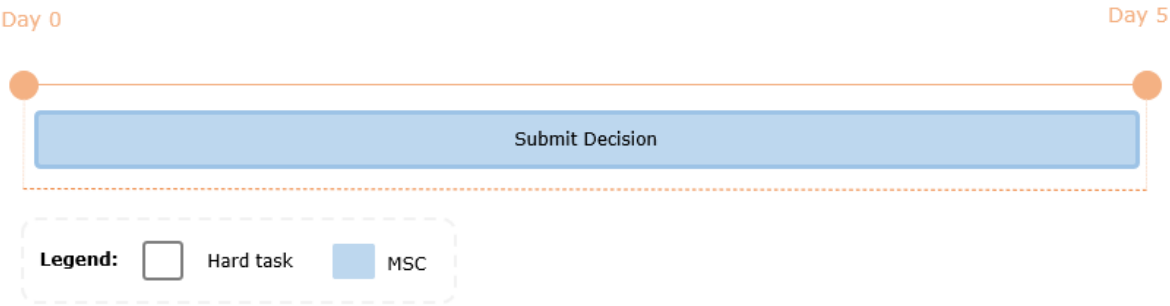
Initial CTA: Assessment of Part I



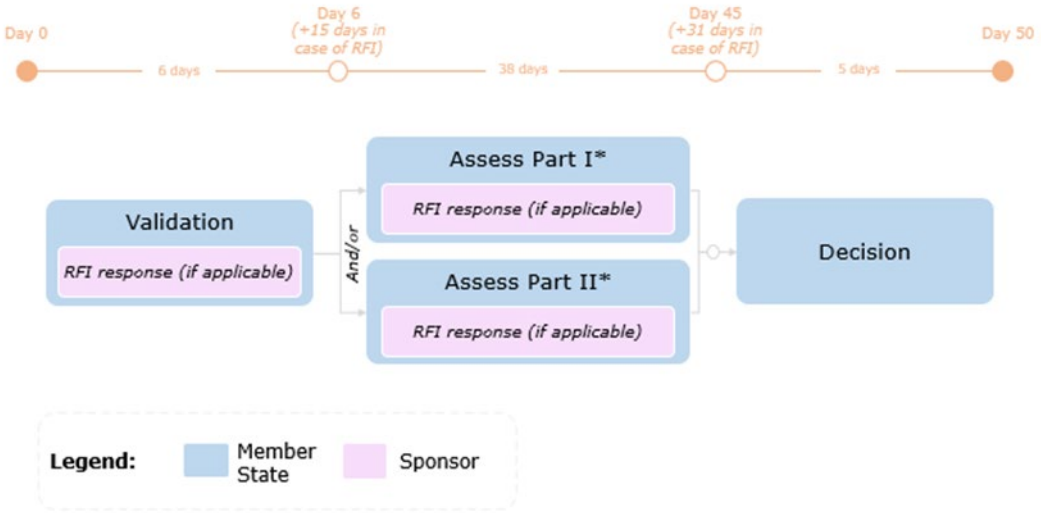
Initial CTA: Assessment of Part II



Initial CTA: Decision

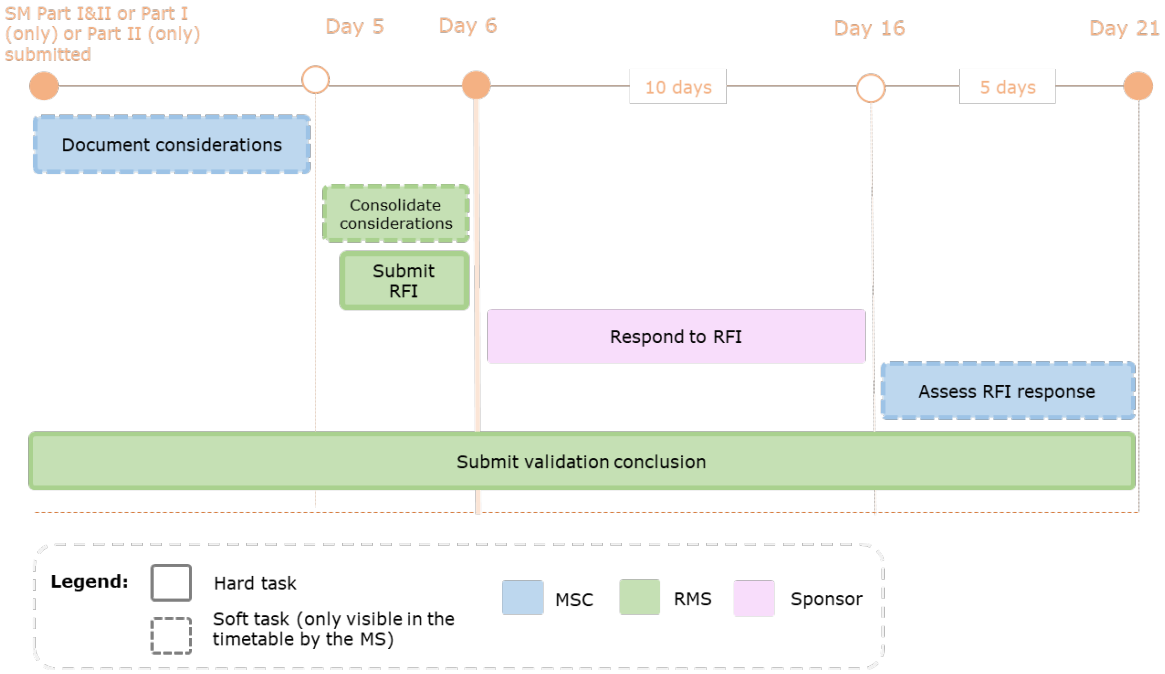


Substantial modification clinical trial application

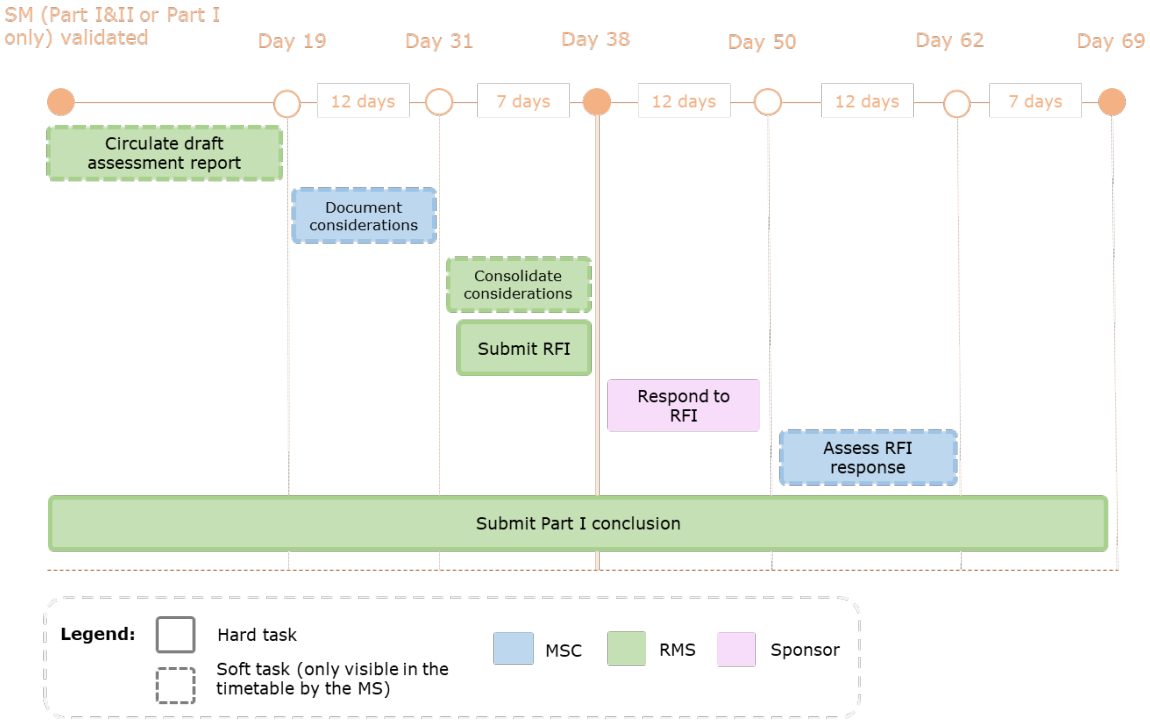


**Step in the process that may occur depending on the CTA submitted. An SM CTA can include Part I and Part II, Part I only or Part II only.*

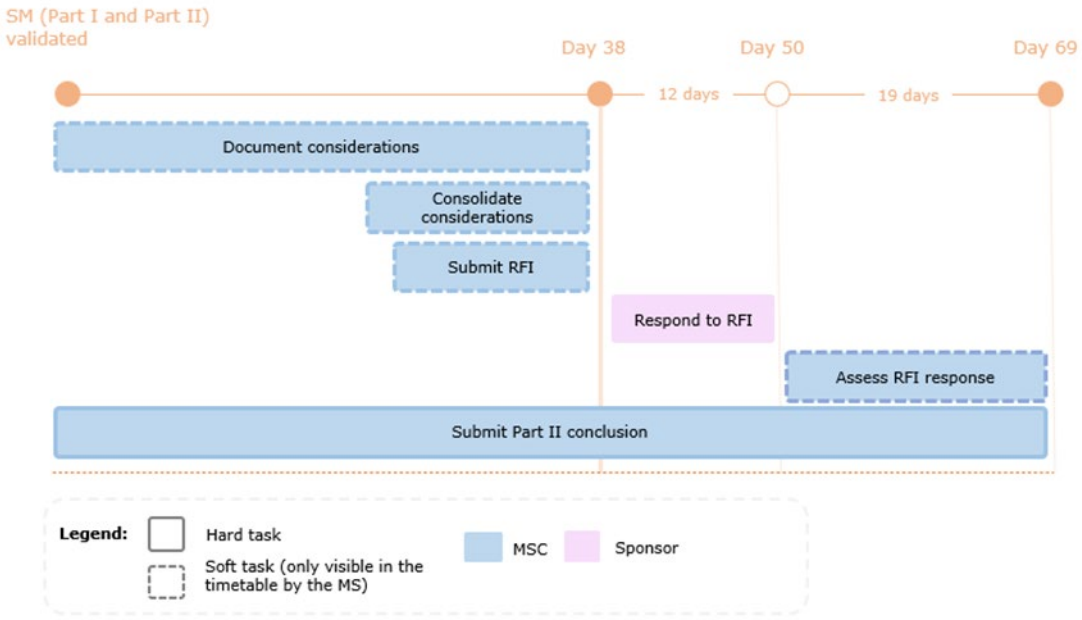
Substantial modification CTA: Validation



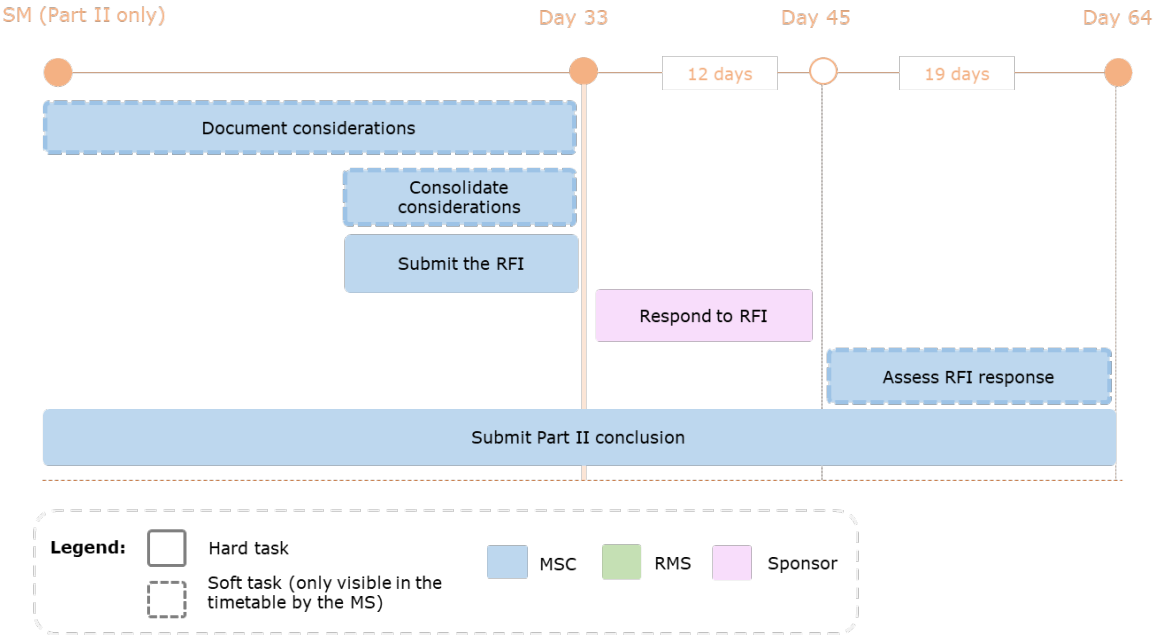
Substantial modification CTA: Assessment of Part I only or Part I and II



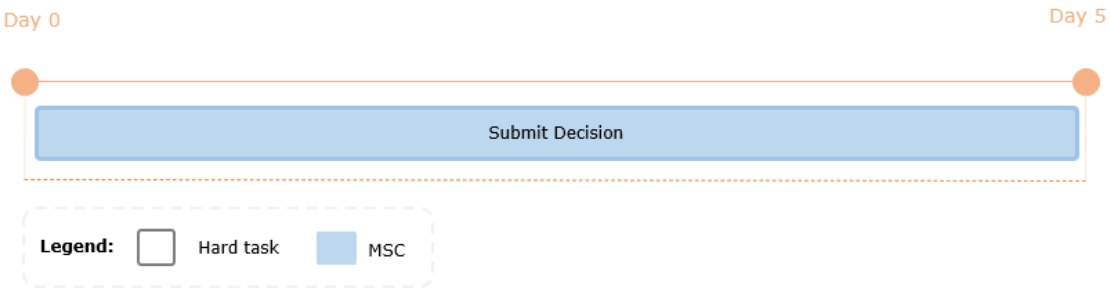
Substantial modification CTA: Assessment of Part II



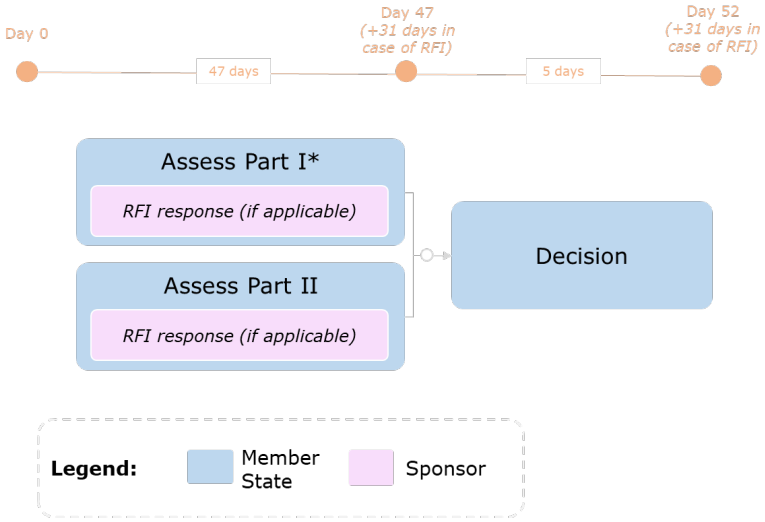
Substantial modification CTA: Assessment of Part II only



Substantial modification CTA: Decision

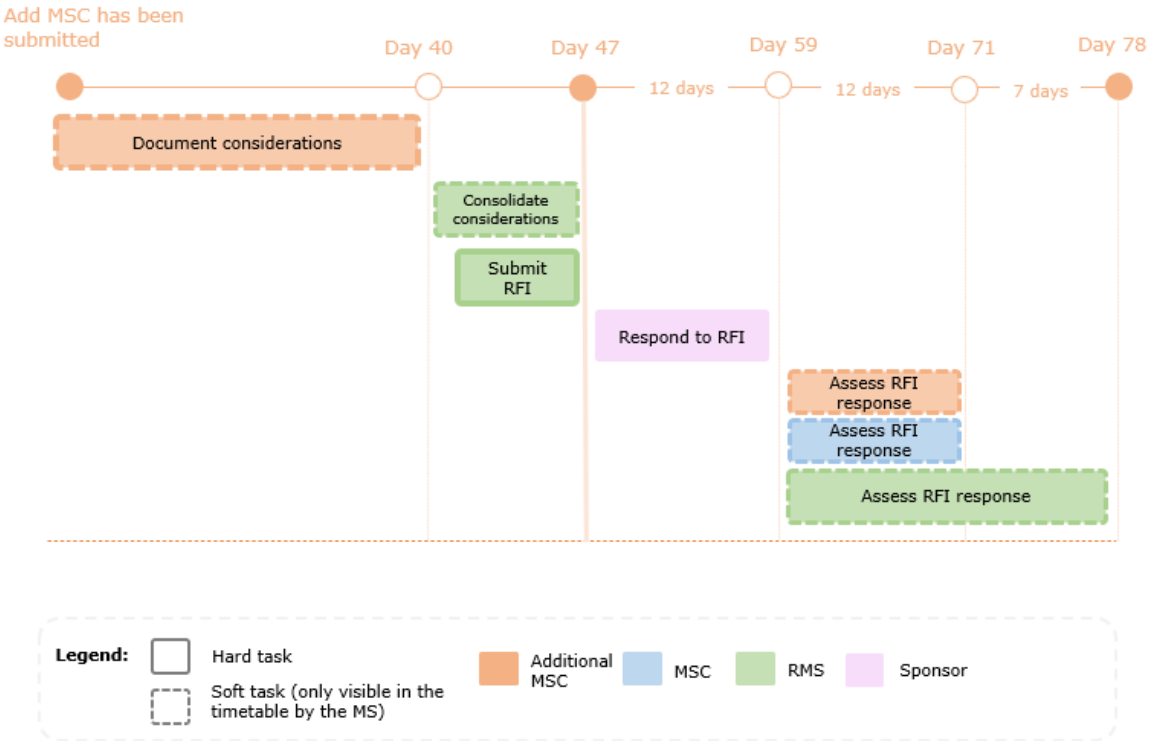


Additional MSC clinical trial application

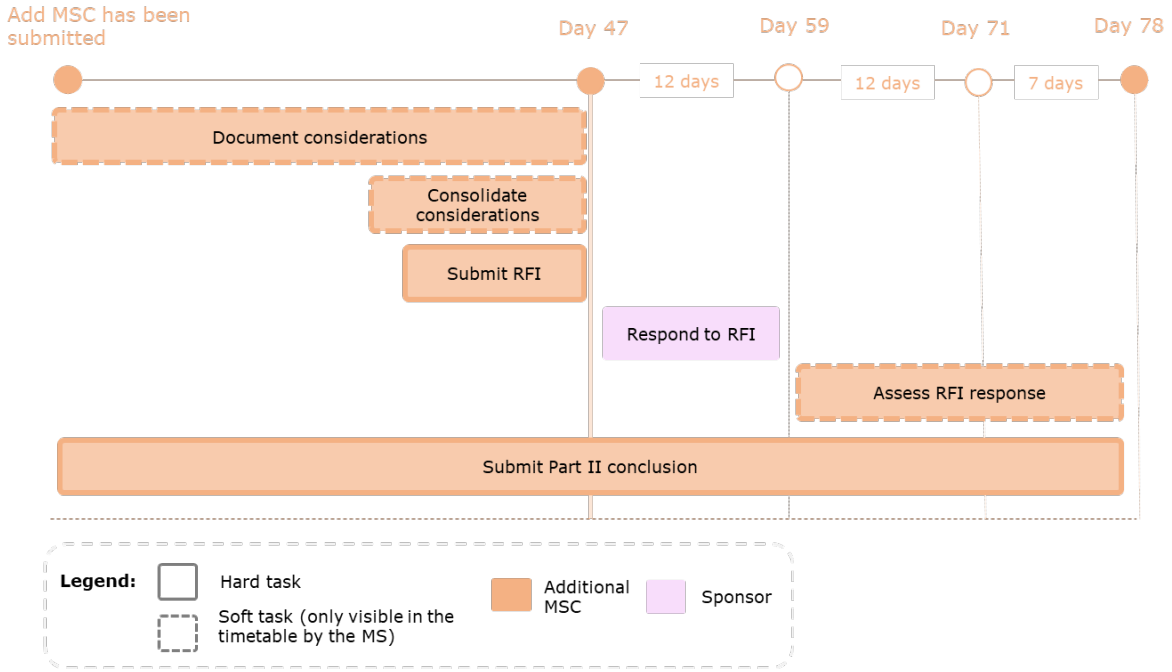


**Step in the process that may occur depending on the CTA submitted. An SM CTA can include Part I and Part II, Part I only or Part II only.*

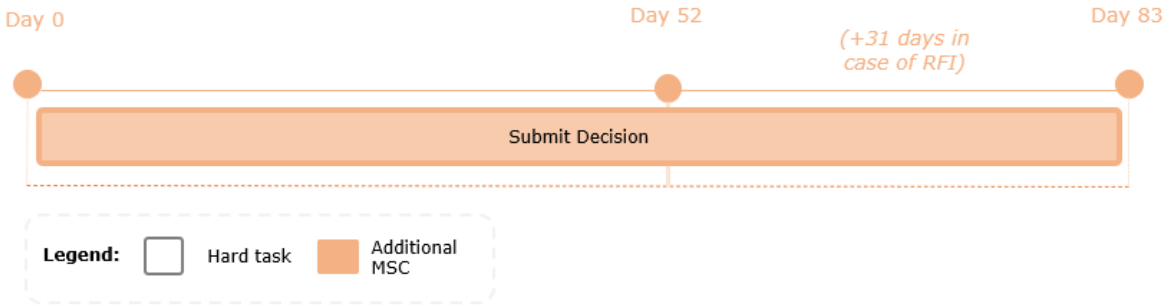
Additional MSC CTA: Assessment of Part I



Additional MSC CTA: Assessment of Part II



Additional MSC CTA: Decision



Examples of timelines and calculation the due dates of tasks

Below, some examples of due dates calculations are presented.

Example 01: A multi-national trial that was submitted on 17/07 (Day 0). There is a public holiday on 21/07, before the RMS is agreed (longest calendar applies).

- Task 'Express Willingness/Unwillingness' might take up to three days from the submission date. Due date of the task is on 20/07 (Day 03 of the timeline).
- Task 'Agree on RMS' might take up to six days after the submission date. The task is released after the task 'Express Willingness/Unwillingness' is completed. The timeline continues and the 4th day is on 21/07. In the graph below, Day 6 is repeated three times, as the rule 'Two consecutive working days' applies (page 7), extending the timeline until the day that the rule is fulfilled. This task was released after the completion of the previous task and the rule 'Two consecutive working days' will be violated without the additional days.
- Task 'Submit validation RFI' (or 'Submit Validation Conclusion' if RFI is not submitted)

might take up to 10 days from the submission date. Continuing adding days on the timeline, the 7th day of the timeline falls on Wed 26. In this case, the rule 'Two consecutive working days' is fulfilled on the 8th day already. But still, the 10th day (due date) is repeated three times, until it falls on a working day. It cannot fall on weekend.

- Action 'Submit RFI response' is expected to be completed by the 20th day since the trial submission date (considering that all tasks are performed on their due dates and not earlier). The timeline continues from where it was left, therefore Day 20 falls on 10/08.
- Task 'Submit validation conclusion' might take up to 25 days from the trial submission date. Earlier completion of the related soft tasks (i.e. submit RFI, assess RFI response) or sponsor's actions **will not** shorten the maximum timeline of the (hard) task 'Submit validation conclusion'. Continuing the established timeline, Day 25 falls on 15/08.

Day	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su
Month	17/07	18/07	19/07	20/07	21/07	22/07	23/07	24/07	25/07	26/07	27/07	28/07	29/07	30/07
Day #	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 6	Day 6	Day 7	Day 8	Day 9	Day 10	Day 10
Task / Action	CTA Submis sion			Express Willing-ness	Public Holiday				Agree on RMS	Document Validation Consider.				

Day	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su
Month	31/07	01/08	02/08	03/08	04/08	05/08	06/08	07/08	08/08	09/08	10/08	11/08	12/08	13/08
Day #	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23
Task / Action	Submit Valid. RFI or Conclusion										Submit RFI response (sponsor)			

Day	Mo	Tu	We	Th
Month	14/08	15/08	16/08	17/08
Day #	Day 24	Day 25	Day 26	Day 27
Task / Action		Submit Validation Conclusion		

Due dates of tasks
Weekend days
Public Holiday

Example 02: Continuing the previous example, the Part I assessment phase is broken down.

- The timeline of the tasks and actions that comprise the Part I assessment phase starts from the Validation conclusion task completion.
- Due to the rule 'Working day due date', the timeline of the tasks 'Circulate DAR' & 'Document considerations' is extended, as it happened with the previous example.
- The projected (maximum) due date for sponsor's action 'Respond to RFI' is Day 57. If sponsor responds earlier than the due date (i.e. on Day 54, instead on Day 57), the due date of the MSCs' task 'Assess an RFI response' will be recalculated and based on the rules, presented on table of page 17, the due date will change from Day 69 to Day 64. If another RFI is submitted, due dates might be recalculated. The due dates of soft tasks might be subjected to changes, based on the rules listed in table of page 17.
- The due date of the MSCs' (hard) task will not change. According to the same rules, the due date of the 'Submit Part I conclusion' task is not affected by earlier completion of the related soft tasks or sponsor's actions. It remains on Day 76.

Day	Mo	Tu	We	…	Sa	Su	Mo	…	Fr	Sa	Su	Mo	Tu	…
Month	15/08	16/08	17/08	…	09/09	10/09	11/09	…	22/09	23/09	24/09	25/09	26/09	…
Day #	Day 0	Day 1	Day 2	Day …	Day 25	Day 26	Day 26	Day …	Day 37	Day 38	Day 38	Day 38	Day 39	Day …
Task / Action	Submit Valid. Concl.			→			Circulate DAR	→				Document considerations		→

Day	Su	Mo	…	We	…	Mo	…	Mon	…	Mo	…	Su	Mo
Month	01/10	02/10	…	11/10	…	16/10	…	23/10	…	30/10	…	05/11	06/11
Day #	Day 44	Day 45	Day …	Day 54	Day …	Day 57	Day …	Day 64	Day …	Day 69	Day …	Day 75	Day 76
Task / Action		Consolid. Consider. & submit RFI	→	Respond to RFI (sponsor) earlier	→	Respond to RFI (sponsor)	→	Assess an RFI response earlier	→	Assess an RFI response	→		Submit Part I Conclu-sion

Due dates of tasks

Weekend days

Actual completion of task (earlier)

Example 03: Winter clock stop and calculation of due dates

- Three clinical trial applications (CTA) are submitted before, or during Winter Clock Stop. In the graph below, the due date of the first task of the MSCs (Express Willingness/Unwillingness has the Day 03 from application submission date as its due date) is indicated with yellow.
- No days of the timeline are consumed during Winter clock Stop period.

Day	Th	Fr	Sa	Su	Mo	...	Su	Mo	Tu	We	Th
Month	21/12	22/12	23/12	24/12	25/12	...	07/01	08/01	09/01	10/01	11/01
Day #			WCS*	WCS*	WCS*	WCS*	WCS*				
Task / Action	CTA1 submission	Day 01					End of WCS*	Day 02	Day 03		
		CTA 2 submission					End of WCS*	Day 01	Day 02	Day 03	
					CTA 3 submission		End of WCS*	Day 01	Day 02	Day 03	

* Winter Clock Stop

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www.ema.europa.eu/contact

Clinical Trials Information System (CTIS).

CTIS Evaluation Timelines.