Learning Objectives

• Understand all the deadlines and timers applicable across the evaluation of a clinical trial application.
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Record of updated versions

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

<table>
<thead>
<tr>
<th>Version</th>
<th>Version description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>Additional clarification on server time and Winter clock (pages 6 &amp; 7).</td>
<td>January 2023</td>
</tr>
<tr>
<td>1.1</td>
<td>Small fix regarding Winter clock (page 7).</td>
<td>October 2022</td>
</tr>
</tbody>
</table>
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.

Once Member States or sponsors perform a task or action in CTIS, such activity will have an implication on 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 Regulation¹ (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 is detailed the timelines for Member States and sponsors in all types of applications within the evaluation of a clinical trial.

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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.
T**imelines overview**

In order to have a complete overview of the timelines, it is important to take into account the following aspects:

- **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.

- **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, 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      | RMS selected   | Longest calendar⁵             | -                         | -                         |
    | Validate Application                   | Application      | Validation     | RMS⁴                         | RMS (for Substantial modification Part I/II or Part I only) | -                         |
    |                                       | submitted        | concluded      |                               | MSC (SM for Part II only) |                          |
    | Assess Part I                         | Application      | Part I         | RMS calendar                 | RMS calendar              | RMS calendar             |
    |                                       | validated        | concluded      |                               |                           |                          |
    | Assess Part II                        | Application      | Part II        | Each MSC calendar            | Each MSC calendar          | Each MSC calendar        |
    |                                       | validated        | concluded      |                               |                           |                          |
    | Submit Decision                       | Application      | Decision on the application | Each MSC calendar | Each MSC calendar | Each MSC calendar |
    |                                       | Part I Concluded |                                             |                              |                           |                          |
    |                                       | Part II Concluded|                                             |                              |                           |                          |

  - **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:**

    - **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.

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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).
CTIS Evaluation Timelines

- **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 case:

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

* 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.
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.

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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).

- 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:

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<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action (dynamic workflow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC</td>
<td>Express willingness/unwillingness</td>
<td>Hard task</td>
<td>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)</td>
</tr>
<tr>
<td>MSC</td>
<td>Agree RMS</td>
<td>Hard task</td>
<td>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)</td>
</tr>
<tr>
<td>MSC</td>
<td>Re-express willingness and Agree RMS</td>
<td>Hard task</td>
<td>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)</td>
</tr>
</tbody>
</table>

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 Diagram](image)

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.

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<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action <em>(dynamic workflow)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC</td>
<td>Document Considerations</td>
<td>Soft task</td>
<td>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. <strong>In case of multinational trials:</strong> 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. <strong>In case of mono-national trials:</strong> Day 7 is calculated as Day 0 + 7 days, not falling on a non-working day and keeping the two consecutive working days rule.</td>
</tr>
<tr>
<td>RMS</td>
<td>Consolidate Considerations</td>
<td>Soft task</td>
<td>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. <strong>In case of multinational trials:</strong> 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). <strong>In case of mono-national trials:</strong> Day 10 is calculated as Day 7 + 3 days, not falling on a non-working day.</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit RFI (if applicable)</td>
<td>Soft task</td>
<td>Day 10 (day 7 + 3 days): Up to day 10 from the application submission, once an accepted, adapted, or merged consideration has been shared. <strong>In case of multinational trials:</strong> 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). <strong>In case of mono-national trials:</strong> Day 10 is calculated as Day 7 + 3 days, not falling on a non-working day.</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Respond to RFI (if applicable)</td>
<td>N/A</td>
<td>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).</td>
</tr>
<tr>
<td>MSC</td>
<td>Assess RFI response (if applicable)</td>
<td>Soft task</td>
<td>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.</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit Validation Conclusion</td>
<td>Hard task</td>
<td>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.</td>
</tr>
</tbody>
</table>
Initial CTA: Assessment of Part I

**Actors involved:**

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.

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**Initial CTA: Assessment Part I**

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action (dynamic workflow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMS</td>
<td>Circulate Draft Assessment Report (DAR)</td>
<td>Soft task</td>
<td>Day 26 (day 0 + 26 days): Up to 26 days from the Validation of the initial CTA.</td>
</tr>
<tr>
<td>RMS &amp; MSC</td>
<td>Document considerations</td>
<td>Soft task</td>
<td>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.</td>
</tr>
<tr>
<td>RMS</td>
<td>Consolidate considerations</td>
<td>Soft task</td>
<td>Day 45 (day 38 + 7 days): Up to 7 days after the considerations are shared.</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit the RFI (if applicable)</td>
<td>Soft task</td>
<td>Day 45 (day 38 + 7 days): Up to 45 days from the validation of the Initial CTA.</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Respond to RFI (if applicable)</td>
<td>N/A</td>
<td>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.</td>
</tr>
<tr>
<td>RMS &amp; MSC</td>
<td>Assess an RFI response (if applicable)</td>
<td>Soft task</td>
<td>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.</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit Final Assessment Report (FAR) Part I and conclusion Part I</td>
<td>Hard task</td>
<td>Day 45 or day 76: Up to 45 days or 76 days (if RFIs are raised), from the Validation of the initial CTA.</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action <em>(dynamic workflow)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC</td>
<td>Document considerations (application documents)</td>
<td>Soft task</td>
<td>Day 45: Up to 45 days from the Validation of the initial CTA.</td>
</tr>
<tr>
<td>MSC</td>
<td>Consolidate considerations</td>
<td>Soft task</td>
<td>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.</td>
</tr>
<tr>
<td>MSC</td>
<td>Submit RFI (if applicable)</td>
<td>Soft task</td>
<td>Day 45: Up to 45 days from the validation of the Initial CTA. This task will be performed after the considerations have been consolidated.</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Respond to RFI (if applicable)</td>
<td>N/A</td>
<td>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.</td>
</tr>
<tr>
<td>MSC</td>
<td>Assess RFI response (if applicable)</td>
<td>Soft task</td>
<td>Day 76 (day 57 + 19 days): Up to 19 days after the response is sent by the sponsor.</td>
</tr>
<tr>
<td>MSC</td>
<td>Submit Final Assessment Report Part II and conclusion Part II</td>
<td>Hard task</td>
<td>Day 45 or day 76: Up to 45 days or 76 days (if RFIs are raised), from the Validation of the initial CTA.</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action (dynamic workflow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC</td>
<td>Submit decision</td>
<td><strong>Hard task</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>
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](https://youtube.com/watch?v=example).
- 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](https://example.com).

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**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.*

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Substantial modification CTA: Validation

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

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action (dynamic workflow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC</td>
<td>Document considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>RMS</td>
<td>Consolidate considerations</td>
<td>Soft task</td>
<td>Day 6 (day 5 + 1 day): Up to 1 day from the 'Document consideration' task (not falling on a non-working day).</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit RFI (if applicable)</td>
<td>Soft task</td>
<td>Day 6 (day 5 + 1 day): Up to 1 day from the 'Document consideration' task (not falling on a non-working day).</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Respond to RFI (if applicable)</td>
<td>N/A</td>
<td>Day 16 (day 6 + 10 days): Up to 10 days from the submission of the RFI.</td>
</tr>
<tr>
<td>MSC</td>
<td>Assess RFI response (if applicable)</td>
<td>Soft task</td>
<td>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 not falling on a non-working day)</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit validation conclusion</td>
<td>Hard task</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action (dynamic workflow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMS</td>
<td>Circulate draft assessment report</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>MSC</td>
<td>Document considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>RMS</td>
<td>Consolidate considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit RFI (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Respond to RFI (if applicable)</td>
<td>N/A</td>
<td>Day 50 (day 38 + 12 days): Up to 12 days from the submission of the RFI.</td>
</tr>
<tr>
<td>MSC</td>
<td>Assess RFI Response (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit Part I conclusion</td>
<td>Hard task</td>
<td>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).</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action (dynamic workflow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC</td>
<td>Document considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>MSC</td>
<td>Consolidate considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>MSC</td>
<td>Submit RFI (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Respond to RFI (if applicable)</td>
<td>N/A</td>
<td>Day 50 (day 38 + 12 days): Up to 12 days from the submission of the RFI.</td>
</tr>
<tr>
<td>MSC</td>
<td>Assess RFI Response (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>MSC</td>
<td>Submit Part I conclusion</td>
<td>Hard task</td>
<td>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.</td>
</tr>
</tbody>
</table>
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 'No conclusion'. Nonetheless, the application will proceed to the Decision phase.

Substantial modification CTA: Assessment of Part II only

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action (dynamic workflow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC</td>
<td>Document considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>MSC</td>
<td>Consolidate considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>MSC</td>
<td>Submit the RFI (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>Sponsor</td>
<td>RFI Response (if applicable)</td>
<td>N/A</td>
<td>Day 45 (day 33 + 12 days): Up to 12 days from the submission of the RFI.</td>
</tr>
<tr>
<td>MSC</td>
<td>Assess RFI Response (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>MSC</td>
<td>Submit Part II conclusion</td>
<td><strong>Hard task</strong></td>
<td>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).</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action (<em>dynamic workflow</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSC</td>
<td>Submit Decision</td>
<td><strong>Hard task</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

Legend: [ ] Hard task  [ ] MSC
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

**A.ctors 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

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action <em>(dynamic workflow)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional MSC</td>
<td>Document considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>RMS</td>
<td>Consolidate considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>RMS</td>
<td>Submit RFI (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>Sponsor</td>
<td>RFI Response (if applicable)</td>
<td>N/A</td>
<td>Day 59 (day 47 + 12 days): Up to 12 days from the submission of the RFI.</td>
</tr>
<tr>
<td>All MSCs</td>
<td>Assess RFI response (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>RMS</td>
<td>Assess RFI response (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
</tbody>
</table>
### 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

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action <em>(dynamic workflow)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional MSC</td>
<td>Document considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>Additional MSC</td>
<td>Consolidate considerations</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>Additional MSC</td>
<td>Submit RFI (if applicable)</td>
<td>Hard task</td>
<td>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).</td>
</tr>
<tr>
<td>Sponsor</td>
<td>RFI Response (if applicable)</td>
<td>N/A</td>
<td>Day 59 (day 47 + 12 days): Up to 12 days from the submission of the RFI.</td>
</tr>
<tr>
<td>Additional MSC</td>
<td>Assess RFI response (if applicable)</td>
<td>Soft task</td>
<td>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).</td>
</tr>
<tr>
<td>Additional MSC</td>
<td>Submit Part II conclusion</td>
<td>Hard task</td>
<td>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).</td>
</tr>
</tbody>
</table>
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).

**Additional MSC CTA: Decision**

<table>
<thead>
<tr>
<th>Responsible</th>
<th>Action</th>
<th>Hard or soft task</th>
<th>Deadline for action <em>(dynamic workflow)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional MSC</td>
<td>Submit Decision</td>
<td><strong>Hard task</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

Legend: [Hard task] [Additional MSC]
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.

![Timetable example](image)

_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:

![Timetable example](image)

_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\textsuperscript{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 \textbf{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.

\textbf{Figure 4. 'Submit decision' task projected for week 50.}

\textbf{Figure 5. 'Submit decision' task projected for week 38.}

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.

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.
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.

Legend:
- Member State task
- Sponsor actions
- Step in the process that may occur depending on the CTA submitted. A SM CTA can include Part I and Part II, Part I only or Part II only. For an Add MSC CTA users may rise considerations.
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**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>RMS Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Express Willingness/Unwillingness</td>
<td>Express Willingness/Unwillingness</td>
<td>Express Willingness/Unwillingness</td>
<td>Express Willingness/Unwillingness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 MSC express Willingness</td>
<td>&gt;1 MSCs express Willingness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend:
- RMS: Willing RMS
- RMS: Candidate RMS
- RMS: Sponsor proposed RMS
**Initial CTA: Assessment of Part II**

- **Initial Application (Part I & II or Part II only) validated**
- Document considerations
- Consolidate considerations
- Submit RFI
- Respond to RFI
- Assess RFI response
- Submit Final Assessment Report Part II and conclusion Part II

**Legend:**
- Hard task
- Soft task (only visible in the timetable by the MS)
- MSC
- Sponsor

---

**Initial CTA: Decision**

- **Day 0**
- **Day 5**
- Submit Decision

**Legend:**
- Hard task
- MSC

---

**Substantial modification clinical trial application**

- **Day 0** (6 days)
- **Day 6 (+11 days in case of RFI)**
- **Day 45 (+21 days in case of RFI)**
- **Day 50** (5 days)

- **Validation**
  - RFI response (if applicable)
- **Assess Part I**
  - RFI response (if applicable)
- **Assess Part II**
  - RFI response (if applicable)
- **Decision**

**Legend:**
- Member State
- Sponsor

---

*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**

- **Day 5**: Document considerations
- **Day 6**: Consolidate considerations, Submit RFI
- **Day 16**: Respond to RFI
- **Day 21**: Assess RFI response

**Legend:**
- Hard task
- Soft task (only visible in the timetable by the MS)
- MSC
- RMS
- Sponsor

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

- **Day 19**: Circulate draft assessment report
- **Day 31**: Document considerations
- **Day 38**: Consolidate considerations, Submit RFI
- **Day 50**: Respond to RFI
- **Day 62**: Assess RFI response
- **Day 69**: Submit Part I conclusion

**Legend:**
- Hard task
- Soft task (only visible in the timetable by the MS)
- MSC
- RMS
- Sponsor
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**

- **Day 47**: Document considerations
- **Day 59**: Consolidate considerations
- **Day 59**: Submit RFI
  - **Day 59**: Respond to RFI
- **Day 71**: Assess RFI response
- **Day 78**: Submit Part II conclusion

**Additional MSC CTA: Decision**

- **Day 0**
- **Day 52**: Submit Decision
  - (+31 days in case of RFI)

**Legend:**
- Hard task
- Soft task (only visible in the timetable by the MSC)
- Additional MSC
- Sponsor

---

**CTIS Evaluation Timelines**

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