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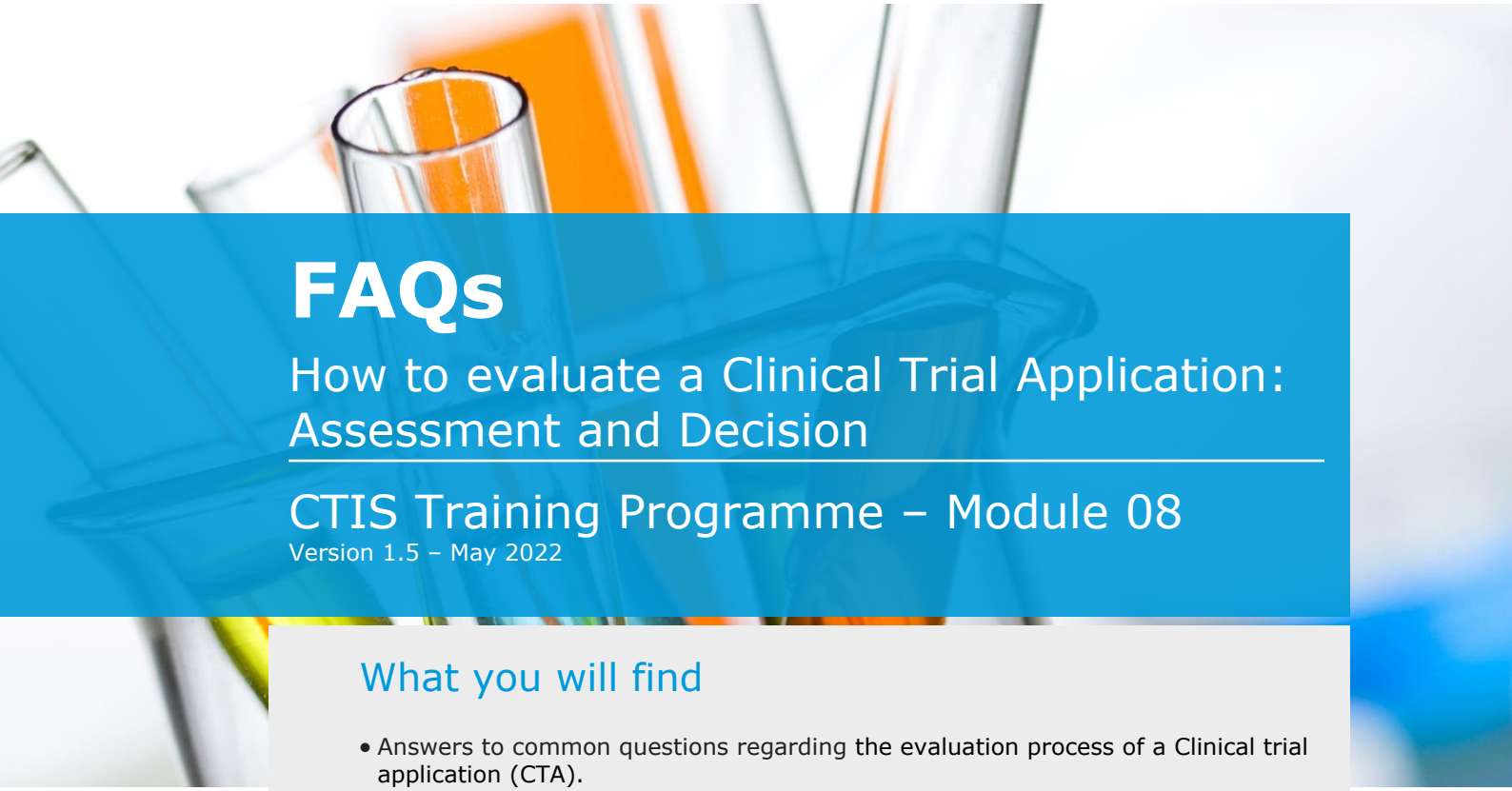

FAQs

How to evaluate a Clinical Trial Application: Assessment and Decision

CTIS Training Programme – Module 08

Version 1.5 – May 2022

What you will find

- Answers to common questions regarding the evaluation process of a Clinical trial application (CTA).
- Answers to common questions regarding the assessment of Part I and Part II of the evaluation process.
- Answers to common questions regarding the Decision on the authorisation of a CTA.

Record of updated versions

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

Version	Version description	Date
1.5	**Updated questions:** 2.2. When does the assessment of Part I begin and end? 3.2. When does the assessment of Part II begin and end?	May 2022
1.4	**Updated questions:** 4.9. What are the possible outcomes of a tacit Decision?	May 2022
1.3	**New questions added:** 2.17. Which documents does the RMS need to provide in the Final Assessment Report (FAR)? 4.3. What tasks must be performed during the Decision phase? 4.6. Is there any standard European form that must be filled out when submitting a decision?	March 2022

Table of Contents

1. Evaluation of a CTA 7

1.1. What are the phases and the timelines for evaluating an Initial CTA? 7

1.2. What is the purpose of each phase in the evaluation of an Initial CTA? 7

1.3. What are the phases for evaluating a Substantial Modification and the Addition of a Member State Concerned? 8

1.4. How can users know that a new application has been submitted? 9

1.5. What information will users find on the CTA page? 9

1.6. How can users know which MSCs are involved in a CTA, and who is the proposed RMS? 10

1.7. How can MS users monitor the tasks that they need to perform regarding a CTA? 10

2. Part I 10

2.1. What aspects of an Initial CTA do MSCs assess in Part I? 10

2.2. When does the assessment of Part I begin and end? 11

2.3. Which documents does the application dossier include for Part I of an Initial CTA? 11

2.4. Can Initial applications be limited to Part I only? 12

2.5. What is the role of the RMS in the assessment of Part I? 12

2.6. What tasks can be performed during the Assessment phase of Part I? 12

2.7. Is it mandatory for the RMS to circulate the Draft Assessment Report? 13

2.8. Which parts integrate the Draft Assessment Report? 13

2.9. When should the Draft Assessment Report be circulated? 13

2.10. What happens if a task is completed before the maximum deadline foreseen in the CT Regulation? 14

2.11. What types of considerations can the MSC document for Part I? 14

2.12. Who can raise a Request for Information (RFI) to the sponsor in Part I? 14

2.13. What is the deadline for raising an RFI? 14

2.14. What happens if the sponsor does not respond to an RFI? 15

2.15. How many days do the RMS and MSC have to assess the sponsor response to an RFI submitted during Part I? 15

2.16. How can MSCs communicate with each other during the assessment of Part I? 15

2.17. Which documents does the RMS need to provide in the Final Assessment Report (FAR)? 15

2.18. What happens if the RMS does not submit a conclusion for Part I? 15

2.19. How can the RMS extend the period for consultation with experts? 16
2.20. Which roles are involved in the assessment of Part I? 16
3. Part II 17
3.1. What aspects of the CTA do MSCs assess in Part II? 17
3.2. When does the assessment of Part II begin and end? 17
3.3. Which documents do the application dossier include for Part II of an Initial CTA? 18
3.4. What happens if the sponsor does not submit Part II? 18
3.5. What is the difference between the assessment of Part I and Part II? 19
3.6. What tasks can be performed during the assessment of Part II? 19
3.7. Why is there no task associated with the Draft Assessment Report of Part II in the system? 20
3.8. Are there different types of considerations that the MSC can document for Part II? .20
3.9. How many days do MSCs have to assess a response to an RFI submitted during Part II? 20
3.10. How can MSC users communicate with others during the assessment of Part II? 20
3.11. What happens if the MSC does not submit the Part II conclusion? 20
3.12. Which roles are involved in the assessment of Part II? 21
4. Decision....21
4.1. What is the objective of the Decision phase? 21
4.2. Are there any preconditions to submit a decision regarding a CTA? 21
4.3. What tasks must be performed during the Decision phase? 21
4.4. What are the possible outcomes of the Decision? 22
4.5. Must the MSC provide a justification for their Decision? 22
4.6. Is there any standard European form that must be filled out when submitting a decision? 22
4.7. By when must the Decision be submitted? 22
4.8. What happens if an MSC does not submit the Decision by the deadline? 23
4.9. What are the possible outcomes of a tacit Decision? 23
4.10. Can MSCs revert their Decision outcome? 24
4.11. Can MSCs decide not to authorise a trial? 24
4.12. How a CTA decision can be changed from 'Authorised with conditions' to 'Authorised'? 24

4.13. After the receipt of the decision on the clinical trial, does the sponsor have the option to appeal against the decision?.....25

4.14. Does a sponsor have to await positive decisions from all Member States concerned before starting the trial in any of the Member States concerned?.....25

4.15. Will the assessment report on Part I and II be made public at the time of decision? 25

4.16. Which roles are involved in the Decision?.....26

FAQs

In this document, we list common questions regarding *Module 8: How to evaluate a CTA: Assessment and Decision.* They are categorised into general questions about the evaluation process of a Clinical trial application (CTA), and specific questions about the assessment of Part I, Part II, and the Decision phase of a CTA. The specific learning objectives of this module are:

1. Remember the phases and associated timelines for evaluating an Initial Clinical trial application (CTA).

2. Understand the process and the user roles involved in the assessment of Part I of an Initial CTA as a Reporting Member State (RMS) and as a Member State Concerned (MSC).

3. Understand the process and the user roles involved in the assessment of Part II of an Initial CTA as an MSC.

4. Understand the process and the user roles involved in the Decision regarding the authorisation of an Initial CTA.

5. Remember the workload management functionalities in CTIS that allow users to monitor their tasks during the evaluation of an Initial CTA.

We encourage you to read these questions and answers carefully. If you have any questions which are not covered in this document, please contact us at CT.Training@ema.europa.eu so that we can update this document accordingly. This document will be progressively enriched with the input of the experts involved in the validation of the training material, the Master Trainers disseminating the materials, and the end-users.

1. Evaluation of a CTA

1.1. What are the phases and the timelines for evaluating an Initial CTA?

The evaluation process of an Initial CTA is divided into three main phases: Validation[1], Assessment, and Decision. The Assessment phase is divided into two parts (Part I and Part II), which may or may not run in parallel. Each phase has its own timelines and activities to be performed.

The Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (CT Regulation)[2] 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, 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.

1.2. What is the purpose of each phase in the evaluation of an Initial CTA?

Validation: To verify that the CT falls under the scope of the CT Regulation and that the application dossier documentation is complete, as set out in Article 25 and Annex I of the CT Regulation[3]. In the case of Initial applications for multinational trials, the Reporting Member State (RMS) selection occurs in parallel to the validation, as per Article 5 of the CT Regulation. For more information about the validation phase of a CTA and the RMS selection, *please refer to Module 6: How to evaluate a CTA (types of applications, evaluation phases, RMS selection, and Validation)*.

Assessment: To review the specific content provided by the sponsor in the application dossier. For Initial applications, the Assessment phase is divided into two parts: Part I and Part II. It is important to note that these phases can be performed in parallel and can only start after the submission of the validation conclusion by the RMS. The Assessment phase concludes with an assessment report and the submission of the conclusion for both or one of

[1] For specific information about the validation phase of a CTA, please refer to the FAQs document of *Module 6: How to evaluate a CTA (types of applications, evaluation phases, RMS selection and Validation)*.

[2] 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/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

[3] Idem

the assessment parts. The main objective of each part is:

- **Part I:** To review the scientific and medicinal product documentation, as defined in Article 6 of the CT Regulation[4] (e.g. completeness and adequateness of the investigator's brochure, compliance with labelling requirements, protocol, etc.). This review is performed by the MSCs and coordinated by the Reporting Member State (RMS).

- **Part II:** To evaluate the regulatory aspects of the CTA that are of a more national/local nature. To that end, the assessment is performed individually by the MSCs for their own territory. MSCs review the requirements for informed consent, the arrangements for recruiting and compensating the patients, the data protection rules, etc., amongst other documents set out in article 7 of the CT Regulation[5] and the General Data Protection Regulation[6].

Decision: To establish the outcome of the assessment of the CTA for the start of the clinical trial in an MSC territory. The decision is made by each MSC and may result in the authorisation, authorisation subject to conditions, or rejection of the CT. See Article 8 of the CT Regulation [7] for more information.

1.3. What are the phases for evaluating a Substantial Modification and the Addition of a Member State Concerned?

In general, all CTAs go through the previously described evaluation phases. However, there are some specificities to be noted:

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

- **Addition of a Member State Concerned (MSC):** It includes an assessment of Part II and the Decision, since Part I of the application has already been authorised. The additional MSC will have access to Part I of the application and will be able to document considerations, which will reach the RMS. However, the assessment of the additional MSC on Part I will not change the conclusion made on this part of the application.

[4] Idem

[5] Idem

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

[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/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

1.4. How can users know that a new application has been submitted?

Member State users will receive a notice stating that a new application which involves their territory has been submitted. The notice will specify the sponsor submitting the application, the type of application submitted (i.e. Initial application, substantial modification, or additional MSC application), the investigational medicinal product to be tested, and the proposed Reporting Member State (RMS).

1.5. What information will users find on the CTA page?

The CTA page is structured in six sections, which provide all the relevant information regarding a Clinical Trial Application submitted by a sponsor:

- **Form**: Displays information on the application form details including cover letter and the publication dates for data and documents, with deferrals, if applicable.
- **MSC**: Displays information such as the MSCs of the application, the proposed RMS, the countries outside of the EU/EEA where the trial is intended to be conducted, an estimated total population for the trial, etc.
- **Part I**: Displays trial-specific information such as protocol information, trial design, inclusion and exclusion criteria, conditions to be treated, the therapeutic area, product quality information, etc.
- **Part II**: Displays documents of the regulatory nature of the CTA for each of the MSC, including, for example, the informed consent, the subject recruitment arrangements, data protection requirements, etc.
- **Evaluation**: Displays the different phases of the application evaluation to be performed by the MSC. Member State (MS) users need to access this section to perform their evaluation tasks.
- **Timetable**: Displays a visual overview of the evaluation status and progress of the CTA.

In order to access the CTA page, users need to search for a Clinical Trial using the search functionality and click on its EU CT number. They will be directed to the summary sub-tab of the CT, where all CTAs and non-substantial modifications related to that CT are listed at the bottom of the page. The user can open any of the available applications and/or non-substantial modifications by clicking on the ID reference.

1.6. How can users know which MSCs are involved in a CTA, and who is the proposed RMS?

The information about the MSCs involved in a CTA and the proposed RMS is displayed in the notice received by the MS user after an application has been submitted. In addition, this information is available in the evaluation section of the application page in the MSC section.

1.7. How can MS users monitor the tasks that they need to perform regarding a CTA?

Users can monitor the tasks they need to perform regarding a CTA in which they are involved through two functionalities:

- **Tasks tab**: shows the tasks to be completed by the user regarding the assessment of a CTA (e.g. Submit Validation Decision, Document considerations, Assess RFI response, Submit Part I conclusion, etc.). These need to be assigned by the CT administrator, or if the user has the appropriate roles, the user can click on 'Assign to myself'. When clicking on the task, users will be redirected automatically to the section of the application evaluation where the task needs to be performed. The Tasks tab specifically supports the Member States in managing their workload regarding the evaluation of CTAs.

- **Notices and Alerts tab**: shows the messages that inform the user about the new applications submissions, tasks that have been completed or need to be performed, response to RFI, etc. When clicking on the notice or alert, the user will be redirected automatically to the section of the application evaluation where an action has been performed or needs to be performed.

The main difference between both functionalities is that the Tasks tab is specifically designed for helping users to manage their workload regarding the evaluation of CTAs, while in the Notices and Alerts tab users will receive messages relating to any action or event occurred during the life-cycle of a CT (including notifications, ad hoc assessments, etc.).

2. Part I

2.1. What aspects of an Initial CTA do MSCs assess in Part I?

The assessment of Part I consists in the evaluation of scientific documentation related to the trial on the anticipated therapeutic and public health benefits, risks and inconveniences for the subject, manufacturing and import requirements, labelling requirements, and completeness and adequateness of the investigator's brochure *(see Article 6 of the CT*

Regulation for more information on the aspects covered by Part I). This assessment is led by the RMS and conducted jointly with the MSC in the case of multinational trials.

2.2. When does the assessment of Part I begin and end?

For an Initial CTA, the assessment of Part I starts one day after the submission of the validation decision, which can occur up to 10 days since the application submission by the sponsor. The whole assessment process of Part I can take up to 45 days from the submission of the validation decision, or up to 76 days if RFIs are raised during the assessment of Part I. The RMS may also extend the period up to 50 days for consultation with experts.

For a Substantial Modification application, the assessment process begins one day since the end of the validation, which can take up to 6 days. The assessment process can take up to 38 days and can be extended up to 31 days if RFIs are raised during Part I.

For both types of applications, the RMS may also extend the period up to 50 days for consultation with experts (*please refer to question 2.19*).

2.3. Which documents does the application dossier include for Part I of an Initial CTA?

Per Annex I of the CT Regulation (*letters A to J*), Part I of the application dossier can include the following information:

- Introduction and General principles.
- Cover letter.
- EU Application form.
- Protocol.
- Investigator's brochure.
- Documentation relating to compliance with Good manufacturing practice (GMP) for the investigational medicinal product.
- Investigational medicinal product dossier (IMPD).
- Auxiliary medicinal product dossier.
- Scientific advice and Paediatric Investigation Plan (PIP).
- Content of the labelling of the Investigational Medicinal Products (IMP).

2.4. Can Initial applications be limited to Part I only?

Yes. When the sponsor so requests, the application for authorisation of a clinical trial, its assessment, and the conclusion can be limited to the aspects covered by Part I of the assessment report. After the notification of the conclusion for Part I, the sponsor has two years to submit an application for Part II. Failure to do so within this period leads to the application lapse. *(See article 11 of the CT Regulation*[8]*)*.

2.5. What is the role of the RMS in the assessment of Part I?

The RMS leads the evaluation of the application dossier regarding Part I for a multinational Initial CTA or a Substantial Modification, that needs to take into account the considerations of the other MSC involved. The tasks of the RMS include the circulation of the Draft Assessment Report (DAR), the consolidation of all the considerations documented by the MSCs, the preparation and submission of Requests for Information (RFIs) to the sponsor if applicable, and the submission of a Final Assessment Report (FAR) and a conclusion for Part I.

Additionally, the RMS is also an MSC. Hence, the RMS also performs tasks such as documenting considerations for Part I of the application dossier and assessing the response to an RFI (if applicable).

2.6. What tasks can be performed during the Assessment phase of Part I?

The tasks performed during the assessment of Part I for an Initial CTA or a Substantial Modification are:

- Circulate Draft Assessment Report – up to 26 days from the validation of the Initial CTA. Performed by the RMS.
- Document considerations – up to 38 days from the validation of the Initial CTA. Performed by the RMS and MSC.
- Consolidate considerations – up to 7 days after the considerations are shared by the MSC. Performed by the RMS.
- Submit RFI (if applicable) – up to day 45 from the submission of the validation Decision. This task will be performed after the considerations are consolidated. The sponsor has up to 12 days to reply to the RFI. Performed by the RMS.
- Assess RFI response – up to 12 days after the response is sent by the sponsor, for the MSC and 19 for the RMS. Performed by the RMS and the MSC.

[8] Idem

All of the tasks above are non-mandatory (i.e. soft) and are displayed in CTIS in orange colour. However, there is one mandatory task that must be performed during the assessment of Part I (hard task):

- Submit Final Assessment Report Part I and conclusion Part I– up to 45 days or 76 days (if RFIs are raised), from the validation of the Initial CTA. Performed by the RMS.

2.7. Is it mandatory for the RMS to circulate the Draft Assessment Report?

No. The RMS does not need to circulate the Draft Assessment Report (DAR). The process of assessment of Part I will not be stopped if the RMS does not circulate it.

Moreover, even if the RMS chooses to circulate the DAR, it is not compulsory to submit the seven parts that compose it *(please refer to question 2.8)*. In that case, for the task to be considered as completed, the RMS needs to actively click on the 'complete' button displayed on the side of the task.

2.8. Which parts integrate the Draft Assessment Report?

The Draft Assessment Report (DAR) is composed of seven parts that offer a preliminary assessment of Part I of the application dossier. These parts are: the introduction, quality assessment, pre-clinical assessment, clinical assessment, statistical methodological assessment, regulatory assessment, and the conclusion. The RMS can decide which parts to complete and share with the MSCs.

2.9. When should the Draft Assessment Report be circulated?

As stipulated in Article 6 of the CT Regulation[9], the RMS should circulate the DAR by day 26 since the start of the assessment of Part I. Therefore, in CTIS the task 'Circulate Draft Assessment Report' should be completed no later than 26 days from the validation of the Initial CTA.

[9] Idem

2.10. What happens if a task is completed before the maximum deadline foreseen in the CT Regulation?

The system applies a dynamic workflow for the assessment of Part I of an Initial CTA and a Substantial Modification application of Part I. This means that if a task is completed before the deadline, the deadlines for the subsequent tasks are recalculated, maintaining maximum timeframes foreseen for those in the CT Regulation. For example, if the DAR is circulated on day 14 instead of on day 26 after the validation decision, the MSC will still have a maximum of 12 days to document considerations on it (maximum timeframe between the circulation of the DAR and the end of the document considerations task). However, the deadline to complete the task 'document considerations' will be recalculated in the system based on the circulation of the DAR date. Therefore, timelines can be retracted as a result of this dynamic workflow, which aims at enabling a swifter evaluation process.

2.11. What types of considerations can the MSC document for Part I?

The MSC can document five types of considerations following the review of the documentation for Part I of the application dossier: clinical, non-clinical, regulatory, statistical, or quality-related. These five types of considerations cover the scope of Part I of the application dossier, which consists of the scientific documentation of the clinical trial application.

2.12. Who can raise a Request for Information (RFI) to the sponsor in Part I?

Only the RMS can raise an RFI in case that clarifications or questions are deemed necessary prior to the submission of Part I conclusion. However, the RMS must consolidate the considerations documented by the MSCs prior to submitting the RFI.

2.13. What is the deadline for raising an RFI?

The RMS can only raise an RFI after the 'Consolidate consideration' task is complete, and has time until the 'submit FAR' task deadline (day 45 from the submission of the validation decision). This action will extend the deadline for the assessment of Part I by a maximum of 31 days.

2.14. What happens if the sponsor does not respond to an RFI?

If a sponsor does not submit a response to an RFI by the deadline established by the RMS (a maximum of 12 days can be given), the application will lapse.

2.15. How many days do the RMS and MSC have to assess the sponsor response to an RFI submitted during Part I?

MSCs have a maximum of 12 days after the submission of an RFI response by the sponsor to perform a coordinated review of it. The RMS has a maximum of 19 days after the submission of an RFI response to assess it, which comprises the 12 days available for the MSC and 7 extra days for further consolidation after the coordinated review.

2.16. How can MSCs communicate with each other during the assessment of Part I?

MSCs can share their comments on the discussion forum located on the 'Draft Assessment Report' (DAR) tile of the Part I assessment. These comments will also be accessible for the RMS before submitting the Part I conclusion.

2.17. Which documents does the RMS need to provide in the Final Assessment Report (FAR)?

The RMS must submit two documents for the FAR: one regarding the assessment of the quality part of Part I of the application dossier; and another one regarding the assessment of the rest of sections of Part I of the application dossier, excluding quality.

In case of a substantial modification, users need to upload both documents regardless of whether there are any quality parts. For a substantial modification that non-quality information has been modified, authority users are still required to upload a FAR Quality. In this scenario, users can upload an empty document with the proper title.

2.18. What happens if the RMS does not submit a conclusion for Part I?

If the RMS does not complete the task 'Submit Part I conclusion' by day 45 from the validation decision date for an Initial CTA, or by day 38 in case of a Substantial Modification, plus 31 days if an RFI is raised during Part I, Part I will remain labelled as with 'No conclusion', and the overall application will remain 'Under evaluation'.

2.19. How can the RMS extend the period for consultation with experts?

Users can access the Tasks tab and click on the 'Submit Part I Conclusion' task. After the task has been assigned to the user by a CT Coordinator or it has been assigned to himself/herself, the user will find on the right side of the task box a set of icons. The 'Extent' button  will allow the RMS to extend the due date up to 50 days for expert consultation, as it is foreseen in Article 6(7) of the CT Regulation[10]. The extension can be done at different times, until a maximum of 50 days.

An RMS user can extend the period for submitting Part I conclusion if he/she has the appropriate role: Assessor Part I Preparer, Assessor Part I Submitter, Decision Maker Submitter, and/or Decision Maker Supervisor Submitter (*please refer to question 2.20 for more information*).

2.20. Which roles are involved in the assessment of Part I?

There are three roles involved in the assessment of Part I: Assessor Part I preparer full rights, Assessor Part I preparer restricted rights (excluding Quality), and Assessor Part I submitter full rights:

- **Assessor Part I Submitter full rights:** Submit/Share Final assessment report Part I; Create/Delete assessment report IMPD-Q Part I; Create/Delete assessment report excl. IMPD-Q Part I; Create draft assessment report IMPD-Q Part I; Share draft assessment report Part I; Create draft assessment report excl. IMPD-Q Part I; Submit RFI Part I; Share considerations Part I IMPD-Q/excl. IMPD-Q; Create/Delete considerations Part I IMPD-Q; Share consolidated considerations Part I IMPD-Q/excl. IMPD-Q; Create/Delete consolidated considerations Part I IMPD-Q/excl. IMPD-Q; Create/Delete considerations Part I excl. IMPD-Q; Create comments on Part I assessment report; Create/Share comments on assessment of the response to RFI Part I.

- **Assessor Part I Preparer full rights:** Create/Delete assessment report IMPD-Q Part I; Create/Delete assessment report excl. IMPD-Q Part I; Create draft assessment report IMPD-Q Part I; Create draft Part I assessment report excl. IMPD-Q;Create/Delete considerations Part I IMPD-Q; Create/Delete consolidated considerations Part I IMPD-Q/excl. IMPD-Q; Create/Delete considerations Part I excl. IMPD-Q; Create comments on Part I assessment report; Create/Share comments on assessment of the response to RFI Part I.

- **Assessor Part I Preparer restricted rights:** Create/Delete Part I assessment report excl. IMPD-Q; Create/Delete considerations Part I excl. IMPD-Q; Create draft Part I assessment report excl. IMPD-Q; Create comments on Part I assessment report; Create/Share comments on assessment of the response to RFI Part I.

[10] Idem

3. Part II

3.1. What aspects of the CTA do MSCs assess in Part II?

The assessment of Part II consists in the evaluation of the application by each MSC, for their own territory, regarding the following aspects set out in Article 7 of the CT Regulation[11] and the *General Data Protection Regulation*[12]:

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

3.2. When does the assessment of Part II begin and end?

The assessment of Part II of the application dossier can start the day after the submission of the validation Decision. It can run in parallel to the assessment of Part I and may take up to 45 days from the validation Decision and can be extended up to 31 days if RFIs are raised during Part II.

It should be noted that, according to Article 11 of the CT Regulation, it is not compulsory to submit Part II as part of the Initial CTA dossier together with Part I *(please refer to question 2.4 for more information).* The sponsor may decide to submit only Part I and leave Part II for a later stage.

For a Substantial Modification application, the assessment process of Part I begins one day since the end of the validation, which can take up to 6 days. For a Substantial Modification application with Part I and Part II, the assessment can take up to 38 days, but for an

[11] Idem

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

application with only Part II, it can take up to 33 days. In both cases, it can be extended up to 31 days if RFIs are raised.

The assessment of an Additional MSC application begins one day since the end of the validation, it can take up to 47 days, and it can be extended up to 31 days if RFIs are raised.

3.3. Which documents do the application dossier include for Part II of an Initial CTA?

In accordance with Annex I of the CT Regulation[13] (*letters K to R*), Part II of the application dossier of an Initial CTA can include the following documents:

- Recruitment arrangements (information per MSC).
- Subject information, informed consent form, and informed consent procedure (information per MSC).
- Suitability of the Investigator (information per MSC).
- Suitability of the facilities (information per MSC).
- Proof of insurance cover or indemnification (information per MSC).
- Financial and other arrangements (information per MSC).
- Proof that data will be processed in compliance with Union law on Data Protection.

3.4. What happens if the sponsor does not submit Part II?

In accordance with Article 11 of the CT Regulation[14], the sponsor can submit a partial application dossier, including only Part I for the start of the evaluation process. However, the sponsor needs to submit Part II before the MSC can issue a Decision regarding the authorisation of the clinical trial. If the sponsor does not submit Part II after two years from the notification of the conclusion for Part I, the application will be expired *(please refer to question 2.4 for more information).* In the situation an additional MSC CTA is submitted, the new MSC will proceed with the assessment of Part II and Decision, since Part I of the application has been already authorised. The additional MSC will have access to Part I of the application and will be able to document considerations, which will reach the RMS. However, the assessment of the additional MSC on Part I will not change the Decision made on this part of the application.

[13] 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 Journa*l 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

14 Idem

3.5. What is the difference between the assessment of Part I and Part II?

The main difference is that Part I focuses on the assessment of the scientific documentation of the clinical trial intended to be performed, whereas Part II focuses on the assessment of country-specific aspects relating to the recruitment of subjects, data protection requirements, format, and content of the informed consent, and other aspects of a regulatory nature.

For multinational trials, the assessment of Part I is done jointly between the MSC, and a single conclusion is submitted by the RMS. Whereas for Part II, each MSC conducts its own assessment for its territory and submits a Part II conclusion individually. This does not apply to mononational clinical trials, as there is only one MSC involved in the assessment of Part I and II.

3.6. What tasks can be performed during the assessment of Part II?

The tasks to be performed by the MSC during the assessment of Part II are:

- Document considerations (application documents) – up to 45 days from the validation of the Initial CTA.
- Consolidate considerations – up to 45 days after the validation of the Initial CTA. This task will be performed right after the Document considerations task has been completed and prior to submitting an RFI.
- Submit RFI (if applicable) – up to 45 days from the submission of the validation decision. This task will be performed after the considerations are consolidated. The sponsor has up to 12 days to reply to the RFI.
- Assess RFI response (if applicable) – up to 19 days after the response is sent by the sponsor.

All the tasks above are non-mandatory (i.e. soft, and marked in orange colour in CTIS). However, there is one mandatory task that must be performed during the assessment of Part II (hard task):

- Submit Final Assessment Report Part II and conclusion Part II – up to 45 days from the validation of the Initial CTA, and 76 days. in case that RFIs are raised.

3.7. Why is there no task associated with the Draft Assessment Report of Part II in the system?

Since Part II will be individually assessed by each MSC, the DAR is not meant to be circulated with other MSCs. Even though, the MSCs are able to create a DAR to support the exchange of information between the MSC users before raising considerations on the Part II documentation of the application and submitting the FAR.

3.8. Are there different types of considerations that the MSC can document for Part II?

No. Unlike in Part I of the Assessment phase, there are no different types of considerations in Part II.

3.9. How many days do MSCs have to assess a response to an RFI submitted during Part II?

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

3.10. How can MSC users communicate with others during the assessment of Part II?

Users within an MSC can engage in a discussion regarding the conclusion of Part II. This discussion will be performed through a discussion forum that is available in the Evaluation section of an application corresponding to the conclusion of Part II.

3.11. What happens if the MSC does not submit the Part II conclusion?

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 next step in the evaluation phase that is the Decision *(please refer to question 4.8 for more information)*.

3.12. Which roles are involved in the assessment of Part II?

Two roles are involved in the assessment of Part II: Assessor Part II Preparer and Assessor Part II Submitter. Both take part in all the tasks related to the assessment of Part II, except for sending an RFI and submitting the FAR and conclusion of Part II, which can only be performed by the Assessor Part II Submitter.

4. Decision

4.1. What is the objective of the Decision phase?

The Decision phase consists of the notification of the authorisation, the authorisation subject to conditions, or the refusal to conduct a trial in a Member State of the EU or the EEA. Each MSC will submit their own decision for the authorisation (or not) of the start of the conduct of the clinical trial within their territory. The maximum deadline for submitting the Decision is 5 days after the conclusion of the assessment of Part I and Part II.

4.2. Are there any preconditions to submit a decision regarding a CTA?

To submit a Decision, a conclusion regarding Part I and Part II must have been previously issued. Therefore, the Decision phase comes always after the assessment phase for Part I and II has been concluded.

4.3. What tasks must be performed during the Decision phase?

Each MSC must complete one mandatory task in the system as part of the Decision phase of the evaluation of a clinical trial. This task is to authorise (or not) the conduct of the intended clinical trial in their territory.

Additionally, in case a sponsor has applied for a deferral, the RMS/MSC can also defer the publication of their documents or RFI within the period of time stablished by the sponsor's deferral.

4.4. What are the possible outcomes of the Decision?

As per Article 8 of the CT Regulation[15], there are three possible outcomes for the decision:

1. Authorise.

2. **Authorise with conditions:** An authorisation of a clinical trial subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of the decision.

3. **Refuse the authorisation:** as per Article 8(4) of the CT Regulation, an MSC can decide not to authorise a trial if it disagrees with the conclusion of the Reporting Member State for Part I, or on any of the grounds specified in the Regulation:

    - If it considers that the aspects addressed in Part II of the assessment report are not complied with;

    - If an ethics committee has issued a negative opinion in accordance with the law of that MSC.

    - To do so, the MSC can access the 'Intended Disagreements' tile from the 'Evaluation' section.

4.5. Must the MSC provide a justification for their Decision?

Yes, but only in the case of Authorise with conditions MSCs need to provide a justification in form of free text. MSCs additionally can attach documentation to support their Decision in any case.

4.6. Is there any standard European form that must be filled out when submitting a decision?

There is no standard European form available. The creation of the document to be uploaded when submitting a decision on a CTA is up to each Member state.

4.7. By when must the Decision be submitted?

For an Initial CTA or a Substantial Modification application with Part I/ Part I and Part II, each MSC has a maximum of 5 days to submit its decision, from the submission of the conclusion of the assessment of Part I/ Part I and Part II.

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[15] Idem

For a Substantial Modification application with only Part II, each MSC has a maximum of 38 days from the submission of the CTA.

For Additional MSC applications with each MSC has up to day 52 from the submission of the CTA to submit their decision.

4.8. What happens if an MSC does not submit the Decision by the deadline?

If the 'Authorise' task is not completed by the due date, the system will apply a tacit decision taking into account the conclusion of the RMS on Part I or Part II.

4.9. What are the possible outcomes of a tacit Decision?

If the MSC does not submit a Decision by the due date, CTIS will apply a tacit decision, bearing in mind the previous outcome of the assessment of Part I. As a general rule, whenever the conclusion of Part I has been positive (*acceptable or acceptable with conditions*), the application will be authorised. On the contrary, if the conclusion of Part I has been negative, the application will be not authorised, irrespective of the outcome of Part II (except if Part II was not submitted). Finally, if no conclusion was submitted for Part I by the given deadline, the application will be considered as being 'Under evaluation'. See the table below to view all the possible scenarios:

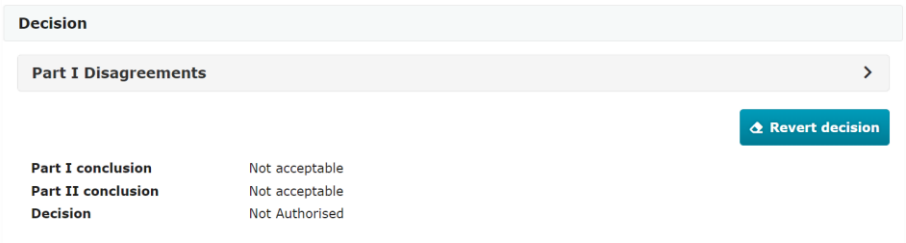
Assessment Part I Conclusion	Assessment Part II Conclusion	Application Status (System Set)
- Acceptable/Acceptable with condition	Acceptable/Acceptable with condition	Authorised
- Acceptable/Acceptable with condition	Not Acceptable	Authorised
- Acceptable/Acceptable with condition	No Conclusion	Authorised
- Not Acceptable	Acceptable/Acceptable with condition	Not Authorised
- Not Acceptable	Not Acceptable	Not Authorised
- Not Acceptable	No Conclusion	Not Authorised
- No Conclusion	Acceptable/Acceptable with condition	Under Evaluation*
- No Conclusion	Not Acceptable	Under Evaluation*
- No Conclusion	No Conclusion	Under Evaluation*
- Acceptable/Acceptable with condition - No Conclusion	None	Lapsed**
- Acceptable/Acceptable with condition - (Disagreed)	None	Not Authorised

*The application will remain under evaluation (without authorisation).

**If the sponsor does not submit Part II after two years from the notification of the conclusion for Part I, the application will be expired (please refer to question 2.4 and 3.5).

4.10. Can MSCs revert their Decision outcome?

Yes. Each MSC can revert the decision outcome after it has been submitted. However, this will be only valid through a legal appeal initiated by the sponsor, and the decision can only be reverted from not authorised to authorised, with or without conditions. To do so, users can access the Evaluation section and click on the 'Revert decision' button in the 'Decision' sub-section.



4.11. Can MSCs decide not to authorise a trial?

As per Article 8(4) of the CT Regulation[16], an MSC can decide not to authorise a trial if it disagrees with the conclusion of the Reporting Member State for Part I, or on any of the grounds specified in the Regulation:

- If it considers that the aspects addressed in Part II of the assessment report are not complied with.
- If an ethics committee has issued a negative opinion in accordance with the law of that MSC.

In this case, though, the MSC will need to provide a justification.

4.12. How a CTA decision can be changed from 'Authorised with conditions' to 'Authorised'?

If a CTA is authorised with conditions, the decision remains until the conditions are fulfilled by the sponsors, for example by submitting a following application, which could be a Substantial Modification. There is no mechanism in CTIS to flag the conditions as being addressed, or to change the decision of the CTA from 'Authorised with conditions' to 'Authorised'.

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

4.13. After the receipt of the decision on the clinical trial, does the sponsor have the option to appeal against the decision?

Yes. The CT Regulation states that Member States shall provide an appeal procedure in respect of a refusal related to[17]:

- Article 8 (Decision on the clinical trial).
- Article 14 (Subsequent addition of a Member State concerned).
- Article 20 (Validation, assessment, and decision regarding a substantial modification of an aspect covered by Part II of the assessment report) and.
- Article 23 (Decision on the substantial modification of aspects covered by Parts I and II of the assessment report).

In this situation, the respective national laws apply for each MSC.

4.14. Does a sponsor have to await positive decisions from all Member States concerned before starting the trial in any of the Member States concerned?

No. The sponsor/investigator can start a clinical trial in an MSC if a positive decision has been issued by at least that MSC. The trial can only start in the MSC that has authorised the trial, even if the assessment is still ongoing in the rest of them.

4.15. Will the assessment report on Part I and II be made public at the time of decision?

The FAR is in principle made public at the time of the Decision, but the moment of publication can be deferred in line with the timelines proposed by the sponsor at the time of the Initial application submission, provided that such deferral is agreed upon by the MSC[18].

[17] European Commission, 'Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT', Version 2.4, July 2020. Page 29 question 2.4 Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[18] Idem. Page 32 question 2.9

4.16. Which roles are involved in the Decision?

For this phase, only users with the Decision maker-submitter can submit the Decision of the MSC.

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Clinical Trials Information System (CTIS).

FAQs: How to evaluate a Clinical Trial Application: Assessment and Decision.