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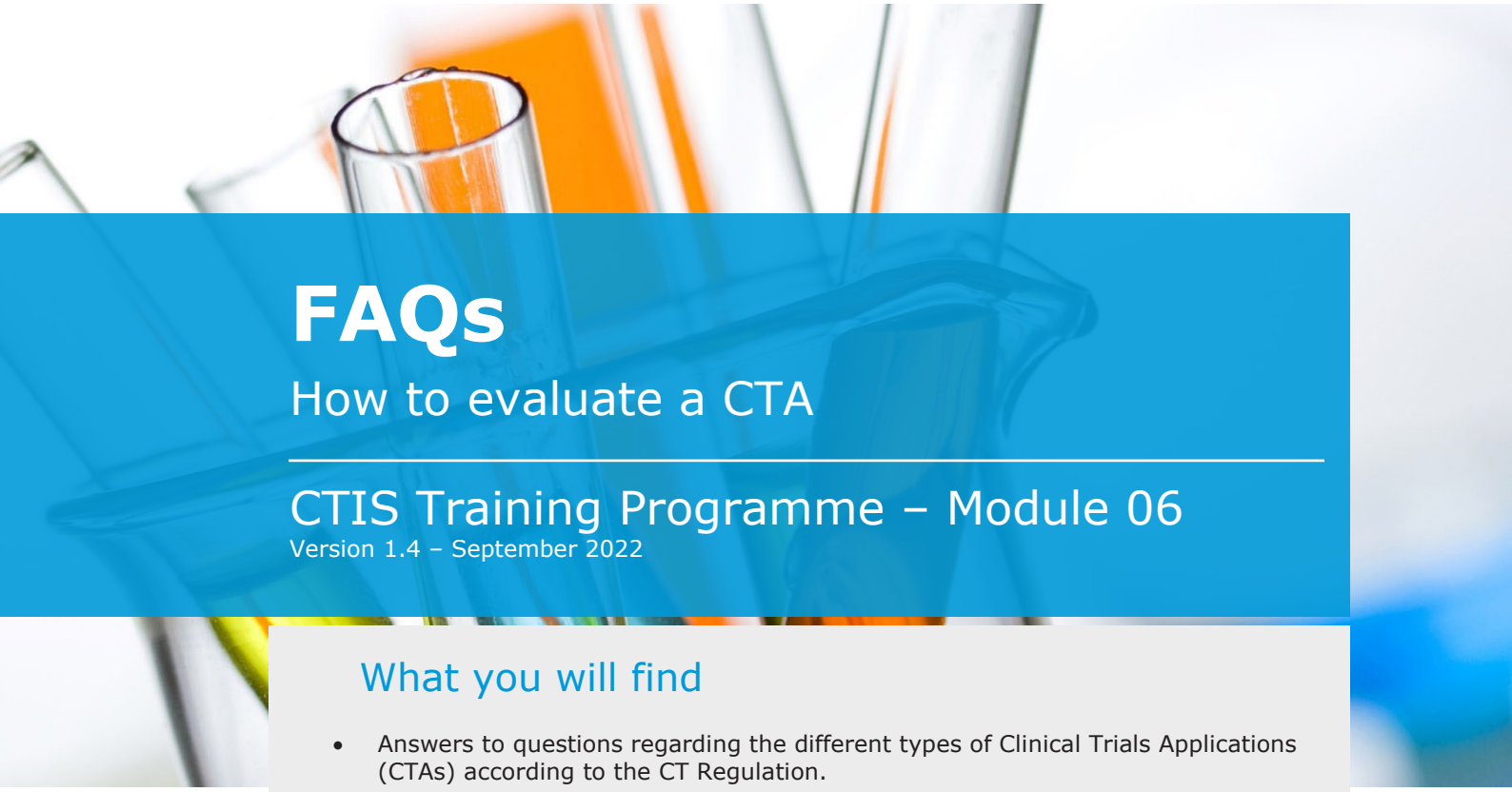

FAQs

How to evaluate a CTA

CTIS Training Programme – Module 06

Version 1.4 – September 2022

What you will find

- Answers to questions regarding the different types of Clinical Trials Applications (CTAs) according to the CT Regulation.
- Answers to questions regarding the different phases in the evaluation of an application and how to monitor the progress.
- Answers to questions related to the first steps in the evaluation of an initial CTA (RMS selection and validation).

Record of updated versions

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

Version	Version description	Date
1.4	**New questions:** 4.9. How can users upload a document not for publication? 4.10. How can users raise a consideration for an application section/document not included in the drop-down list?	September 2022
1.3	**New questions:** 4.8. Is it mandatory to submit an RFI in the context of an application validation?	February 2022
1.2	Training material version published at CTIS go-live	January 2022

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FAQs

In this document, we list common questions regarding Module 06: Evaluate a Clinical Trial Application (CTA). They are categorised into general questions about clinical trials application; questions about the evaluation phase; questions about the RMS selection; questions about the validation phase of an initial CTA; and questions about roles and permissions. The specific learning objectives of this module are:

1. Understand the different types of Clinical Trial Applications (CTAs).

2. Understand the evaluation process of an initial CTA and the common aspects of the different types of CTAs.

3. Understand the RMS selection process for a multinational Initial CTA.

4. Understand the validation phase for 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. Clinical Trial Applications (CTAs)

1.1. What is a 'clinical trial' in the context of the Clinical Trial Regulation (EU) No 536/2014[1]?

According to Article 2(2) (2) of the CT Regulation[2], a Clinical Trial (CT) is a clinical study which fulfils any of the following conditions:

- The assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within the normal clinical practice of the Member State Concerned (MSC).
- The decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study.
- The diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

1.2. What is a CTA according to the CT Regulation?

Under the meaning of the CT Regulation3, a CTA is a A request (made by the sponsors) for the authorisation (by the Member States concerned), to perform an action related to clinical trials conducted in the EU. These actions can include a request to start a clinical trial, the extension of a clinical trial to another MSC territory and subjects, or to perform an important modification to an already started CT.

1.3. What types of CTAs are there?

The CT Regulation[4] provides for three different types of application dossiers: an Initial Application (Article 5); a Substantial Modification (SM) (Article 2(2) (13); and a subsequent Addition of an MSC (Article 14).

Depending on the number of Member States (MS) they concern, CTAs can be:

- **Mononational:** CTAs which concern only one Member State. These applications aim at receiving the authorisation to conduct a CT in the territory of a Member State.

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

[2] Idem

[3] Idem

[4] Idem

- **Multinational:** CTAs which concern more than one Member State. These applications aim at receiving the authorisation to conduct a CT in the territories of several Member States.

1.4. What is an Initial CTA according to the CT Regulation[5]?

An Initial CTA provides comprehensive information about the trial to be conducted and the investigational medicinal product(s) to be used, enabling the authorities of the MSC to evaluate the acceptability of conducting the trial. The elements to be included in the application dossier for an Initial CTA are defined in Annex I of the CT Regulation[6].

1.5. What is a Substantial Modification (SM)?

Under the scope of the CT Regulation[7], an SM is any change to any aspect of a CT, which is made after the notification of a decision on a previously submitted application and which is likely to either:

- Have a substantial impact on the safety or rights of the subjects; or
- On the reliability and robustness of the data generated in the CT.

In all cases, a modification is regarded as 'substantial' when one or both of the above criteria are met. In principle, it is the responsibility of the sponsor to judge whether a modification is to be regarded as 'substantial' or not. This judgement is to be made on a case-by-case basis considering the above criteria. Examples of SMs are found in Annex III of the European Commission's Q&A[8] document to the CT Regulation[9].

If none of the above criteria is met, and the sponsor wants to make a change that is not likely to have a substantial impact on the safety or rights of the subjects or the reliability and robustness of the data generated in the CT; a non-Substantial Modification (non-SM) can be made. A non-SM is not considered as an application and is therefore not the subject to the evaluation by the Member States. Examples of non-SM include the correction of typographical errors, the update of contact details, etc.

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

[6] Idem

[7] Idem

[8] European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 4, July 2021. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

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

In case of doubt about whether a change should be deemed as an SM or not, the sponsor shall consult the MSC.

1.6. What is an application for a subsequent addition of an MSC?

A subsequent addition of an MSC is an application for extending a previously authorised CT to another Member State. This request can only be submitted after at least one Member State has issued a positive decision regarding the initial authorisation of the CT. Article 14 of the CT Regulation foresees a period of 52 days for the evaluation of the application to add an MSC.

1.7. Is the deletion of an MSC considered an SM?

The deletion of an MSC is not recognised by the CT Regulation and is not considered as an SM. In this case, various scenarios are possible: the sponsor can decide to withdraw an application for a CT in an MSC at any time from the reporting date (date on which the conclusion of Part I is submitted) until the decision is made, or to terminate early an ongoing trial in one of the MSCs for justified reasons. In both cases, if the CT is ongoing in other MSC, the sponsor should judge the potential impact on the overall sample size of the CT and submit an SM to the other MSC, if necessary (e.g. to add more sites in the MSC). *Please refer to Question 3.9 of the European Commission's Q&A document to the CT Regulation*[10] *for more information.*

1.8. Can a subsequent addition of an MSC be submitted whilst another one is ongoing?

Yes. However, it is strongly recommended to combine the addition of MSCs into one single application[11].

1.9. How can the user search for a specific application?

Users can search for specific CTAs using the search functionality in the 'Clinical Trials' tab, either by entering the EU CT number (basic search option) or by populating several parameters in the two advanced search options (trials advanced search, and application advanced search).

[10] European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 4, July 2021. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf.
[11] Idem. Page 34 question 2.12.

In the application advanced search, users can fill in fields such as the application status, the title of the trial, the sponsor who submitted the application, the product name, etc. Once the search is launched, the user will retrieve, in the results summary page, a list of CTs which contain application(s) that match the entered search parameters, such as the application type (i.e. initial, substantial modification, or additional MSC), or the status of the application (e.g. lapsed, authorised, withdrawn, not authorised, etc.). Users need then to select the CT with the relevant associated application. Once on the CT summary page, users need to scroll down to the 'Application and Non-substantial Modification' section and select the ID of the application to access its details.

2. Evaluation of a CTA

2.1. What are the general principles for authorising a CTA?

As provided for in Article 3 of the CT Regulation[12], a CT may only be conducted, and therefore authorised by Member States, if the following conditions apply:

- The rights, safety, dignity, and well-being of subjects are protected and prevail over all other interests.
- The CT is designed to generate reliable and robust data.

To show compliance with these principles, sponsors need to provide specific documentation to the MSC in an initial application submitted through CTIS. The MSC can evaluate the documentation to ensure that these principles are met.

2.2. What are the phases of the evaluation of a CTA?

The evaluation process is divided into three main phases: validation, assessment, and secision. The assessment phase is, in turn, divided into two parts (part I and part II) with specific documentation in each of them.

- **Validation:** Consists in a review by the MSC of the completion of the documentation and information provided in the application dossier submitted by the sponsor applicant, as set out in Article 25 and in Annex I of the CT Regulation[13]. It aims to assure that the CT falls under the scope of the CT Regulation[14], and that the

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

application dossier documentation is complete. An application can only be valid if it is in the scope of the CT Regulation[15] and complete, as defined previously.

- **Assessment:** Consists in a review by MSC of specific content provided by the sponsor in the application dossier and concludes with an assessment report for each application part.

    - **Part I:** Consists in a joint review by the MSCs of the scientific and medicinal product documentation, as defined in Article 6 of the CT Regulation[16] (e.g. completeness and adequateness of the investigator's brochure, compliance with labelling requirements, protocol, etc.). This review is coordinated by the Reporting Member State (RMS)[17].

    - **Part II:** Consists in the individual assessment by each MSC of the aspects covered in Article 7 of the CT Regulation[18], including the requirements for informed consent, the arrangements for recruiting and compensating the patients, the data protection rules, etc.

- **Decision:** Consists in the outcome of the assessment of the CTA by each MSC. The decision may be authorisation, authorisation subject to conditions, or rejection. *Please refer to Article 8 of the CT Regulation[19] for more information.*

2.3. Which phases include the different types of applications?

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

- **Initial CTA:** Includes the whole process of evaluation: validation, assessment (part I and part II), and decision. It should be noted that in an initial CTA the assessment of Part I and Part II can occur in parallel, or at different times in case of a partial initial application as described in article 11 of the CT Regulation[20].

- **Substantial Modification (SM):** Includes the whole process of evaluation: validation, assessment (part I and part II), and decision. Please note that some SM may concern part I only, part II only, or both, depending on the scope of the modification.

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

[16] Idem

[17] See section 3 for more information on the RMS.

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

[19] Idem

[20] Idem

- **Addition of an MSC:** Generally includes an assessment of the part II and 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 decision made on this part of the application.

2.4. Where can the users monitor the process of evaluation of a CTA?

Users can view the process of evaluation of a given CTA by accessing the 'Timetable' feature. The Timetable allows users to monitor the progress of the evaluation of a particular CTA, by displaying the actual completion dates of the past evaluation phases, and the expected completion date of the remaining ones.

The Timetable can be found in the 'Timetable' section inside a CTA. Once on the CTA page, select the heading 'Timetable' from the navigation panel on the left side of the screen, as shown in the picture below.

3. Selection of the Reporting Member State (RMS)

3.1. Who is the RMS?

The MSC that has a leading role during the trial lifecycle and performs several tasks including: leading the assessment (or creating the draft assessment report), raising and consolidating considerations during the validation and the part I assessment phase, and issuing conclusions on part I.

In the case of multinational trials, the RMS is proposed by the sponsor at the submission of the application dossier and is assigned following the expressions of willingness or

unwillingness by the MSC. In a mononational trial, the RMS is the one proposed by the sponsor since there is only one MSC.

3.2. Who is the MSC?

A Member State of the European Economic Area (EEA) where an application for authorisation of a CT or a Substantial Modification (SM) has been submitted.

3.3. What is the purpose of the RMS selection process?

The purpose of the RMS selection in the context of multinational trials is to establish the MSC that will have a leading role during the trial lifecycle and perform tasks including consolidation of considerations, raising RFI to the sponsor during the evaluation process, and issuing conclusions on part I.

3.4. What is a consideration?

An observation raised by an MSC regarding the documentation provided for the evaluation of a CT. These considerations must be shared with the RMS before they can be used as part of an RFI to be submitted to the sponsor for clarification. Considerations enable MSC to cooperate in the evaluation of the information provided in a CT, in accordance with Article 6(3) and (5) of the CT Regulation[21].

3.5. How long does the RMS selection process take?

The RMS selection process is triggered as soon as the application dossier for a multinational trial is submitted by the sponsor. This process runs in parallel to the Validation phase. However, an RMS needs to be selected to be able to complete the validation phase, as the RMS is responsible for compiling the considerations made by the MSC and submit the validation conclusion. The selection of the RMS should occur within 6 days from the submission of the application dossier by the sponsor, in line with Article 5(1) of the CT Regulation[22]. The RMS must be selected before the submission of the validation conclusions.

It is important to note that only calendar days are counted and the due dates displayed are calculated based on a set of rules from Regulation 1182/71:

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

[22] Idem

- The task due date cannot fall on a weekend or bank holidays. It will automatically be moved to the following calendar day.
- At least a period of two consecutive working days shall be foreseen for completing a task.
- The tasks timer will be paused during the period from the 23rd December until the 7th January.

3.6. Who is the proposed RMS?

The proposed RMS is the MSC that the sponsor proposes to be the leader for its CTA. The proposed RMS is communicated when submitting the application dossier. In mononational trials, this proposed RMS corresponds to the MSC to which the application is submitted. In multinational trials, the sponsor proposes an RMS at the time of submission of an application. However, all MSC must be given a chance to express their willingness or unwillingness to become the RMS and the RMS is assigned by the system taking into account the outcome of the discussion.

3.7. What happens if only one MSC has expressed willingness?

If only one MSC expresses willingness (including the proposed RMS), that willing MSC will become the RMS. *Please refer to Article 5 (1) of the CT Regulation[23] for more information.*

3.8. What happens if an MSC does not express its willingness/unwillingness to become the RMS?

MSC have until day 3 after the initial CTA has been submitted for a multinational CT to express their willingness or unwillingness to become the RMS. In case an MSC, including the proposed RMS, does not take any action by the end of day 3, it will be deemed by the system as unwilling to become the RMS. MSC can express their preference (willingness or unwillingness) only once, and they are not able to withdraw or change their expression.

In case there is no agreement on the RMS by the end of day 3 since the application submission, either due to a tie in willingness or unwillingness by the MSCs, the assignor will be in change of selecting a candidate RMS by day 5. If no disagreement is issued, the candidate RMS proposed by the assignor will become the RMS by day 6.

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

3.9. What happens if the proposed RMS is not willing to be the RMS?

The proposed RMS has the chance to express its willingness/unwillingness to become the RMS. It will need to provide a justification with the reasons why it is not willing to be the RMS. The reason and the internal discussion held amongst the MSC along the RMS selection process will not be shared with the sponsors.

In case of no action, the system considers that the proposed RMS is unwilling. In any case, if the CT involves only one MSC (mononational CTs), the proposed will be the RMS.

3.10. What happens if more than one MSC is willing to be the RMS?

If there is more than one MSC willing to be the RMS (including the proposed RMS), the MSC with the lowest workshare out of those willing to be the RMS will become the assignor. Once the assignor has been appointed by the system, the MSCs will discuss who should become RMS. After the discussion, the assignor will select a candidate RMS from the pool of MSC willing. If there is a disagreement regarding the candidate RMS, the proposed RMS will automatically become the RMS. If no disagreement is issued, the candidate RMS proposed by the assignor will become the RMS. Also, in case no action is taken by the assignor, the proposed RMS (by the sponsor) will become the RMS.

3.11. Who is the assignor in the process of RMS selection?

The assignor is the MSC in charge of selecting a candidate RMS for approval by MSC in case there is no agreement on the RMS by the end of day 3 since the application submission, either due to a tie in willingness or a tie in unwillingness by the MSC. The assignor will be the MSC with the lowest workshare among the willing MSCs (the workshare is the result dividing the number of multinational clinical trials where the Member State acts as RMS by the total number of multinational trials where the Member State participates).

In the case that more than one MSC is willing to become the RMS, the assignor will select a candidate RMS from the pool of MSC willing.

In the case that no MSC is willing to become the RMS, the RMS will be the proposed RMS (by the sponsor).

3.12. Does the assignor have to give reasons when selecting one MSC as RMS?

No, the assignor does not have to provide reasons when selecting a candidate RMS from the list of willing MSCs. However, MSCs are encouraged to use the discussion area to reach an agreement before the assignor selects a candidate RMS.

3.13. What is the candidate RMS?

The candidate RMS is the MSC selected by the assignor (after discussion among the MSC) if more than one or no MSCs are willing to become the RMS by day 3. The candidate RMS will be selected for approval by MSC. If any MSC disagrees with the candidate RMS selection, the proposed RMS will be appointed as the RMS.

3.14. What is the difference between the 'proposed RMS' and the 'candidate RMS'?

The proposed RMS is the MSC proposed by the sponsor at the time of submission of the CTA to become the RMS during the trial life cycle. The candidate RMS is selected by the assignor MSC if there is more than one or no MSC willing to become the RMS by the end of day 3, considering the discussion among the MSC.

3.15. What happens if any MSC disagrees with the proposal of the candidate RMS?

If any MSC disagrees with the proposal of the candidate RMS made by the assignor, the RMS proposed by the sponsor will be automatically appointed.

3.16. Who can disagree to the candidate RMS selected by the assignor?

All MSC can express their disagreement with the candidate RMS, except for the assignor, out of consistency grounds. The MSC who disagrees with the candidate RMS needs to provide a justification for this.

3.17. What happens if no MSC is willing to be the RMS?

If no MSC (including the proposed RMS) is willing to be the RMS by the end of day 3 after the application has been submitted, all MSC are invited to re-express willingness or unwillingness until day 5. Then the assignor will select a candidate RMS from the pool of those willing by day 5 or after all the MSC have re-expressed their willingness/unwillingness. In case of disagreement with the candidate selected by the assignor, the proposed RMS will become the RMS. If no disagreement is issued, the candidate RMS proposed by the assignor will become the RMS. Also, in case no action is taken by the assignor, the proposed RMS (by the sponsor) will become the RMS.

Note that the system only displays the willingness or unwillingness at the end of days 3 and 6, so in case an MSC wants to record the response in the system between days 3 and 6, this should be noted in the discussion forum under the 'Re-express willingness/unwillingness and agree RMS' task.

3.18. Can the RMS of a specific clinical trial be changed?

The RMS of a specific CT (and its related applications) cannot be changed. Articles 14(2) and 17(1) of the CT Regulation[24] specify that the RMS for the authorisation of an initial CTA will remain the RMS for any subsequent application.

3.19. Which actors are involved in the RMS selection process? What are their activities?

- **Sponsors:** Propose an MSC as the RMS when they submit the application dossier for a CT.
- **MSC:** Express willingness/unwillingness to become RMS, participate in the discussion on who should become the RMS, and (if applicable) issue disagreement with the candidate RMS selection. Among the MSC, the assignor will be in charge of selecting the candidate RMS. It is important to note that depending on how each Member State decides to assign roles among the users, National Competent Authorities (NCAs) and Ethics Committees (ECs) will be able to participate in the RMS selection.

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

3.20. Is it mandatory for sponsors to select a proposed RMS?

Yes, when submitting a clinical trial application, sponsors should specify their proposed RMS from the list of MSCs.

3.21. Are the RMS selection due dates calculated considering working days or calendar days?

The system calculates the due dates based on calendar days. However, the task due date cannot fall on a weekend or bank holidays, if this is the case it will automatically be moved to the following working day, and at least a period of two consecutive working days shall be foreseen for completing a task.

The tasks timer will be paused during the period from the 23rd December until the 7th January

3.22. In case of re-submissions of the CTA, is the RMS from the original trial also the RMS for the new re-submission?

If a multinational application is re-submitted the RMS selection process will be triggered again. In the case of mononational applications, the RMS will be the MSC of that application.

4. Validation phase

4.1. What is the purpose of the validation phase?

The validation phase aims to assure that the CT falls under the scope of the CT Regulation[25], and that the application dossier documentation is complete. It determines if the documentation and information set out in Annex I and II of the CT Regulation has been provided by the sponsor and if the CTA can move to the assessment phase.

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

4.2. When does the validation phase of an initial CTA start?

The validation starts as soon as the application dossier is submitted. In an initial CTA, MSC can start documenting the considerations about the application dossier before the RMS is selected. In multinational CTAs, the process of RMS selection will occur in parallel and will finish on day 6 (at the latest) from the submission of the application dossier. However, the RMS needs to be selected for completing the validation phase, as the RMS is in charge of consolidating the considerations, raising RFIs if applicable, and submitting the validation conclusion.

4.3. How long can the evaluation of an initial CTA take?

The CT Regulation[26] establishes strict timelines for the evaluation of CTAs. For initial CTAs, the validation phase starts when the application dossier is submitted. Article 5 of the CT Regulation 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)).

4.4. How long can the validation process of a substantial modification CTA take?

MSC may communicate to the RMS any considerations relevant to the validation of the application of an SM within 5 days from the submission of the application dossier. Within 6 days from the submission of the application dossier, the RMS shall validate the CTA taking into account considerations expressed by the other MSC, and notify the sponsor.

4.5. Which steps does the validation phase include?

The validation phase includes the following tasks:

- **Document considerations:** MSCs evaluate if the dossier is complete and accurate and if the trial falls within the scope of the CT Regulation, and may provide their considerations.
- **Consolidate considerations:** The RMS reviews and consolidates all the considerations shared by the MSCs.
- **Submit an RFI:** If necessary, the consolidated considerations will be sent to the sponsor, in the form of RFIs, requesting for additional information. This step is not

[26] Idem

mandatory. The RMS will determine if additional information is needed to evaluate the CTA and reach a final validation conclusion.

- **Assess an RFI response:** MSCs assess the response of the sponsor and discuss among them, and with the RMS, if the additional information is sufficient to proceed with the submission of the validation conclusion. This step is only mandatory where an RFI has been submitted.

- **Submit validation conclusions:** The CTA is validated once the RMS indicates that the dossier is accurate and complete (or not) and that the CT falls within the scope of CT Regulation (or not).

4.6. Can MSCs start documenting considerations before the RMS is appointed?

Yes. In an initial CTA, MSCs (including National Competent Authorities and Ethics Committees) can start reviewing the application and documenting considerations on the application dossier in parallel to the process for RMS selection. It should be noted that the RMS needs to be appointed by the end of day 6 from the application submission to be able to consolidate the considerations, submit an RFI (if applicable), and provide a validation conclusion.

4.7. Who can view the considerations?

The considerations can be seen by all MSCs once they are shared.

4.8. Is it mandatory to submit an RFI in the context of an application validation?

No. The RMS will determine if additional information is needed to evaluate a CTA and reach a final validation conclusion. In case the RMS decides that the RFI is not necessary, the validation process may proceed once the users have consolidated and shared the considerations.

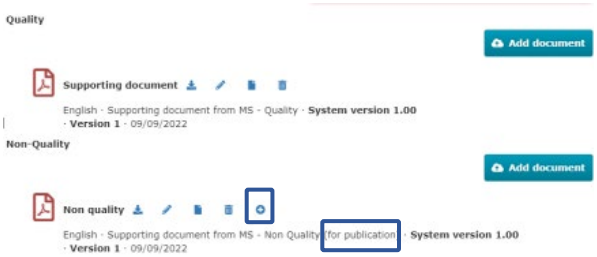
4.9. How can users upload a document not for publication?

In most cases, documents uploaded in CTIS are by default for publication (e.g. assessment reports, documents providing when raising an RFI, etc.), therefore users should not include Commercial confidential information (CCI) and personal data. This will be indicated in the document upload pop-up window with the legend 'The above documents will be published'.

For certain CTA sections, documents are never published (e.g. IMPD - Quality) and it is indicated in the pop-up window with the legend 'This document will not be publicly accessible'.

In cases when documents are uploaded for publication, and users need to upload a document with the redacted data from the original (personal data or CCI), they need to submit a version 'not for publication'.

To do so, users can click on the 'Add' button (+) that appears in the document section after uploading the first version of the document intended for publication (only available in CTIS sections where the documents to be uploaded are published).

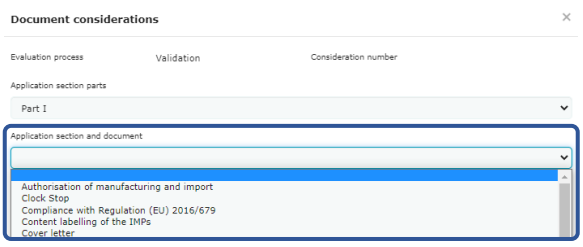


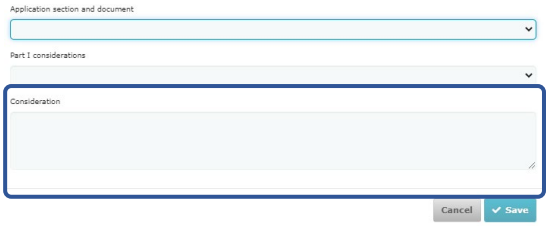
This button is a cross-system functionality available in some sections of the CTA, where applicable, in the form when creating an RFI and in other sections related to the life-cycle of a CT.

4.10. How can users raise a consideration for an application section/document not included in the drop-down list?

If MSCs users need to raise a consideration for an application section or document that is not included in the 'Application section and document' drop-down list, users may select a value that fits the most to the content of the consideration and describe the relevant area related to this consideration in the 'Consideration' field, along with any other details that will help sponsor users to respond to the corresponding RFI.

For example, if MSCs users need to ask sponsor users for clarifications during the CTA validation phase for the submitted document 'Agreement from another sponsor', they can raise a consideration, select the value 'Sponsor details' in the drop-down list 'Application section and document' and describe the matter related to the aforementioned document in the free text field 'Consideration'.





4.11. Which actors are involved in the validation phase?

- **Sponsors:** Submit the application dossier and answer any RFIs submitted by the RMS.
- **MSCs:** Document their considerations and assess any response to RFIs (if applicable).
- **RMS:** Consolidates the considerations, sends an RFI (if applicable), and provides the validation conclusion regarding the CTA.

5. Roles and permissions

5.1. What user roles are involved in the evaluation of a clinical trial application?

Below you can see the distribution of roles by type of activity:

- **Submit validation conclusion; Submit RFI validation; Share considerations/consolidated considerations excl. IMPD-Q:** Validator Submitter Full rights (Part I and Part II); Validator Part II submitter.
- **Share considerations/consolidated considerations IMPD-Q:** Validator Submitter Full rights (Part I and Part II).
- **Create/Delete considerations IMPD-Q; Create/Delete consolidated considerations IMPD-Q:** Validator Submitter/Preparer Full rights (Part I and Part II).
- **Create/Delete consolidated considerations excl. IMPD-Q**: Validator Submitter/Preparer Full rights (Part I and Part II); Validator Part II Preparer/Submitter.
- **Create/Delete considerations excl. IMPD-Q:** Validator Submitter/Preparer Full rights (Part I and Part II); Validator Preparer restricted rights (Part I excl. IMPD and Part II); Validator Part II Preparer/Submitter.
- **Submit RMS selection; Agree RMS:** Decision Maker Submitter.

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FAQs: How to evaluate a clinical trial application.