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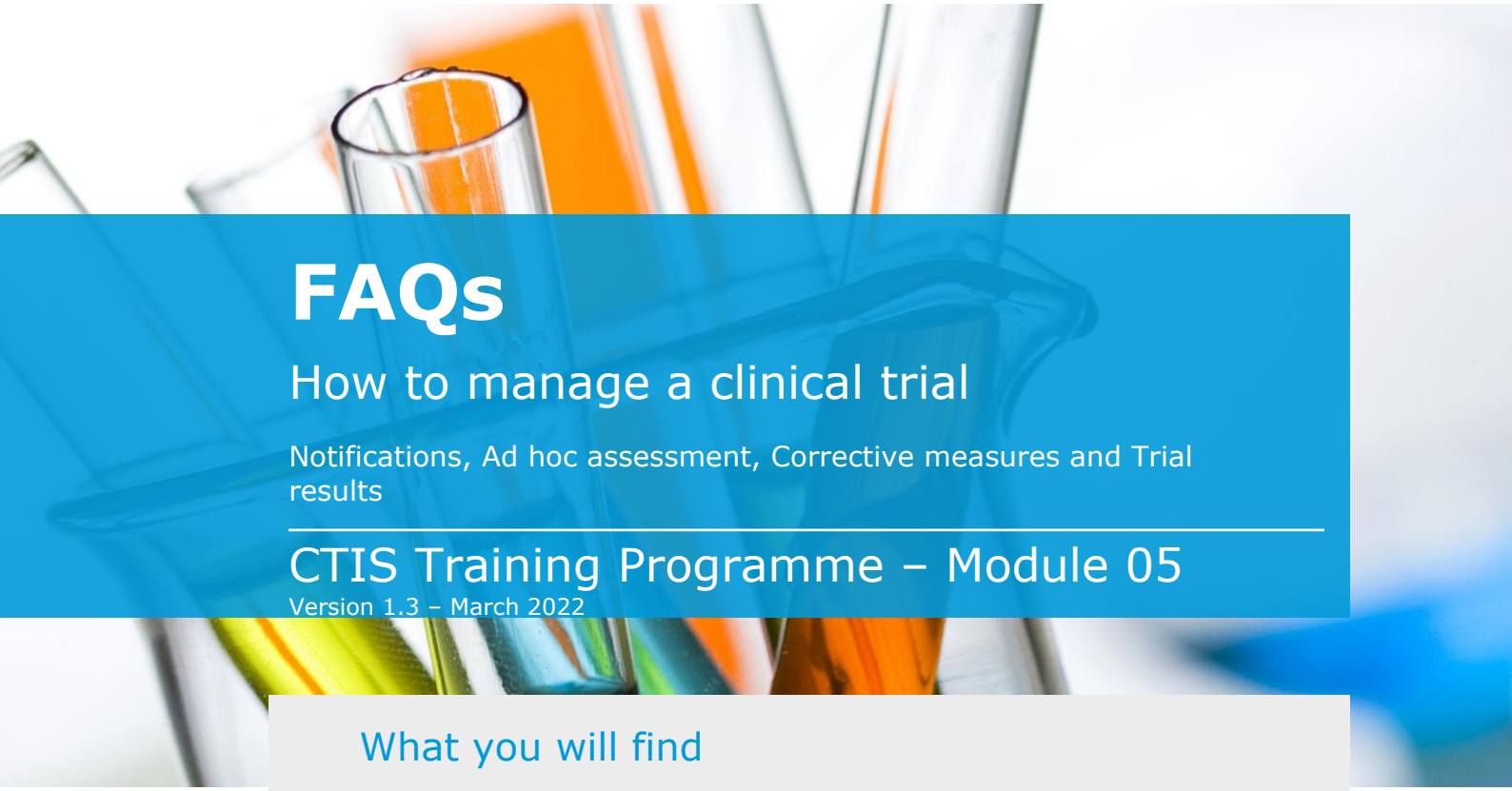

FAQs

How to manage a clinical trial

Notifications, Ad hoc assessment, Corrective measures and Trial results

CTIS Training Programme – Module 05

Version 1.3 – March 2022

What you will find

- Answers to questions regarding Notifications.
- Answers to questions regarding Requests for information (RFIs) raised as part of an Ad hoc assessment and Corrective measures.
- Answers to questions related to the submission of Trial results.

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

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FAQs

In this document, we list common questions regarding Module 5: Manage a CT: Notifications, Ad hoc assessment, Corrective measures and Trial results. They are categorised into questions about notifications; questions about requests for information (RFIs) raised as part of an ad hoc assessment; questions about RFIs raised before a corrective measure is applied by a Member State Concerned (MSC); and questions about Trial results' submission. The specific learning objectives of this module are:

1. Remember the responsibilities of the sponsors from the submission of a Clinical Trial Application (CTA) until the submission of the Clinical Trial (CT) summary of results[1].

2. Understand the use of Notifications.

3. Understand the processes of Ad Hoc assessment and corrective measures and how to respond to requests for information related to them.

4. Understand how to prepare and submit CT results.

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] Questions about the responsibilities of the sponsors related to how to submit a CT and Annual safety reporting will be addressed dedicated modules.

1. Notifications

1.1. What is a Notification?

A notification is a functionality that allows the sponsor to notify each Member State Concerned (MSC) about relevant events occurred while the trial is being conducted which imply obligations from the MSC side (e.g. start trial, start recruitment, etc.). To be able to submit a notification the trial needs to have been previously authorised.

1.2. What types of Notifications may the sponsor create during the clinical trial (CT) life cycle?

The sponsor may submit five different types of notifications in CTIS. While most of the trial and recruitment periods notifications need to be reported in all trials (e.g. if the sponsor does not notify about the start of the recruitment, the CT will expire), the rest of notifications are only mandatory in certain circumstances, such as when events occur that were not foreseen in the protocol. Either way, it is the sponsor's obligation to notify all relevant events to the MSC. In case of events not foreseen, the sponsor shall also notify to the MSC if measures have been applied. The different types of notifications are:

- **Trial and recruitment periods:** Allow the sponsor to inform the MSC about different events related to the CT life cycle, such as: start, restart and end of the trial, start and restart of recruitment, temporary halt, end of trial in EU/EEA and global end of the trial. These types of notifications must be made within 15 days from the start of the event (article 36-38 of the CT Regulation[2]).

- **Unexpected event:** Allows the sponsor to inform the MSC about any unexpected event that might influence the benefit-risk balance of the medicinal product, or that would lead to changes in the administration of a medicinal product or in overall conduct of a clinical trial (e.g. a significant hazard to the patient population). Such notifications must be made without undue delay but no later than 15 days from the date the sponsor became aware of the event (article 53 of the CT Regulation[3]).

- **Urgent safety measure:** Allows the sponsor to inform where an unexpected event is likely to seriously affect the benefit-risk balance and the urgent safety measures which have been taken to protect the subjects. The sponsor must notify the MSC of such events without undue delay but no later than 7 days from the date on which the measures were taken (article 54 of the CT Regulation[4]).

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[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
[4] Idem

- **Serious breach:** Allows the sponsor to inform about a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial. These notifications must be made without undue delay but no later than 7 days from the date on which the sponsor became aware of the breach (article 52 of the CT Regulation[5]). *For more information, refer to the following documents: Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol and Appendix III b – Information to be submitted with a notification of a serious breach.*

- **Third-Country Inspectorate Inspection:** Allows the sponsor to submit all inspection reports of third-country authorities concerning the CT (article 78 of the CT Regulation[6]).

1.3. What types of Trial and recruitment periods notifications are there?

Trial and recruitment periods notifications enable sponsors to inform MSC of critical moments occurred during the execution of a CT. They can be classified into notifications that need to be submitted for every CT and those that are only needed in certain circumstances. For more information, see articles 36-38 of the CT Regulation[7].

Notifications that need to be submitted for every CT:

- **Start trial:** the first act of recruitment of a potential subject for a specific CT, unless defined differently in the protocol.

- **Start recruitment:** the first visit of the first subject. The date could be the same one as for start trial.

- **End recruitment:** act of not recruiting subjects anymore in an MSC.

- **End trial:** last visit of the last subject, or a later point in time as defined in the protocol.

Notifications that need to be submitted only when the sponsor needs to interrupt a CT on specific grounds with a view to resuming it afterwards:

- **Temporary halt:** An interruption not provided in the protocol of the conduct of a CT with the intention of the sponsor to resume it.

- **Restart trial:** The act of restarting the trial, after a temporary halt or after a suspension of the CT as part of a corrective measure by an MSC.

- **Restart recruitment:** The act of restarting the recruitment of subjects. The trial

[5] Idem
[6] Idem
[7] Idem

must have been restarted to be able to restart the recruitment.

1.4. How is the 'start of a clinical trial' defined?

Unless defined differently in the protocol, the date of start of the CT is the date when the recruitment of subjects is opened in an MSC. The first act of recruitment shall be identified by the sponsor in the recruitment strategy. It could be, for example, the date of initiation of the CT in the first site or the date when the first trial-specific advertisement is published. In some cases, the sponsor may define in the protocol the start of the trial differently than the first act of recruitment. In any case, the CT can neither start earlier than the authorisation date, nor later than the first visit of the first subject. *For more information, please refer to Question 10.1 of the European Commission's Q&A document to the CT Regulation*[8]*.*

1.5. What should be considered as the date of the first visit of the first subject?

As provided in the European Commission's Q&A document of the CT Regulation (question 10.2)[9], the date of the first visit of the first subject should be the date on which the first subject or the person that has been designated as the legal representative signs the first informed consent to participate in activities that are protocol-directed interventions.

1.6. What happens if the sponsor does not start the recruitment of subjects within 2 years from the CT authorisation?

The recruitment of subjects shall start within two years from the CT authorisation. If the start recruitment notification is not submitted within that period, the trial will end, unless the sponsor submits a Substantial Modification (SM)[10] for an extension of this period beyond two years that is authorised by the MSC.

1.7. What is a Temporary Halt?

It is an interruption not provided in the protocol of the conduct of a CT with the intention by the sponsor of resuming it. There are two types of temporary halt notifications, depending on

[8] European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 2.4, July 2020. Page 93 question 10.1. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[9] European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 2.4, July 2020. Page 93 question 10.2. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[10] To know more about a substantial modification application, please refer to How to submit a CT module.

whether they are related to a matter of Subject safety and/or benefit-risk balance, or to other reasons. In some cases, an SM may be needed to be submitted and authorized in order to restart a trial after a temporary halt. *For more information, see question 1.8 below or refer to Question 10.4 of the European Commission's Q&A document to the CT Regulation*[11].

1.8. How is it possible to restart a trial after a Temporary Halt?

If the halt was not related to reasons regarding subject safety/benefit-risk balance, the sponsor can restart the trial automatically. The sponsor should restart the trial within two years since the halt and notify the MSC within 15 days of the restart of the CT.

To restart a CT which was halted in an MSC for reasons of subject safety/benefit-risk balance, the sponsor needs to submit a substantial modification application and have it authorized by the MSC. The sponsor shall provide a justification for the restart, including conclusions of the analysis, the mitigation measures if applicable, and an updated benefit-risk assessment.

When creating a substantial modification application, the sponsor needs to select 'restart trial' as the justifying reason. Afterwards, in order for the user to submit the restart trial notification, the substantial modification previously authorised needs to be linked to the notification in the restart form (only authorised SMs with reason 'Restart trial' will be displayed in order that the user can link them to the notification).

1.9. How is it possible to restart a trial with no impact on subject safety/ benefit-risk balance that has not been resumed within 2 years after the temporary halt?

If the halt was not related to reasons of subject safety/benefit-risk balance, it is possible to restart the trial within two years from the halt. In addition, a 15-day period is available for the sponsor to notify the MSC of the restart. It is it also possible to extend the date of the restart of a trial beyond 2 years from the halt if a substantial modification is submitted for authorisation before the two years since the temporary halt date.

1.10. What happens if a CT is not resumed within 2 years after a temporary halt and no substantial modification is submitted?

If the trial is not restarted within two years or within the extension period requested through

[11] European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 2.4, July 2020. Page 94 question 10.4. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

a substantial modification, the trial will be deemed as ended.

1.11. What is the 'end of trial EEA and global'?

The end of a CT is the last visit of the last subject, or as defined in the protocol. The sponsor shall notify each MSC in the European Economic Area (EEA) of the end of a CT in that MSC territory, within 15 days from the end date. The end of trial in EEA refers to the date of the end of trial in the last EEA MSC where the CT was conducted; while end of trial Global is the date of the end of trial in the last country where the CT was conducted.

1.12. What happens in case of early termination?

Early termination means the premature end of a CT due to any reason, before the conditions specified in the protocol are accomplished. However, when the protocol specifies circumstances that would determine an early termination of the CT, should such circumstance(s) occur, the sponsor needs to also notify an early termination of the CT, clarifying the reasons to the MSCs. The sponsor shall notify each MSC of the early termination, the reasons and the follow-up measures (if applicable), within 15 days of the early termination, when:

- The reasons do not affect the benefit-risk balance (e.g. low recruitment, shortage of drug supply, end of development).
- That treatment options for subjects still participating in the CT will not be compromised or no subject has been included.

When the CT is ended based on an impact on benefit-risk balance, the early termination should be notified without undue delay but not later than 15 days, including the reasons for such action and specifying the follow-up measures.

In all cases, except when no subject was included in the CT, a summary of results with the relevant available information is expected within one year of the early termination of the CT. The summary should include post-trial follow-up data, where applicable. The date of the early termination shall be deemed to be the date of the end of the CT. *For more information, refer to the European Commission's Q&A document of the CT Regulation, question 10.10*[12]*.*

[12] European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 2.4, July 2020. Page 96 question 10.10. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

1.13. When can an unexpected event lead to an urgent safety measure?

Where unexpected events require an urgent modification of a CT, it is possible for the sponsor to take an urgent safety measure without awaiting prior authorisation by the MSC. The sponsor shall notify the measure without undue delay but no later than 7 days. If such measure constitutes a temporary halt of the CT, it shall be notified within 15 days.

1.14. How can users save, edit and cancel a draft notification?

When populating the pop-up form of a notification, the sponsor is allowed to save it as a draft before submitting it. The following buttons are displayed:

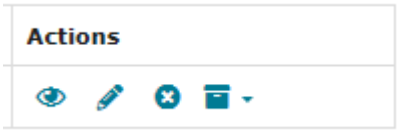
Until the sponsor clicks on the 'Submit' button, the notification remains as a draft and is only visible to him/her. After saving the notification as a draft, only two options are available: to view and to edit, as shown in the image below.

To edit the draft, the sponsor must click on the pencil icon  . A pop-up will display the information that the user filled out when creating the draft notification. This allows the sponsor to make the changes needed, including if there is an impact on subject safety and/or benefit-risk balance. Finally, the user needs to click on the 'Save' button, as shown before. To delete the draft notification, the user shall click on the 'Cancel' button.

1.15. How can users update and withdraw a notification?

After a notification has been submitted, the sponsor can update it, for instance, to correct errors, provide additional information or supplementary documentation. To do so the user needs to access the 'Notifications' sub-tab within the summary CT page, in the section where the notification was created.

In case of Trial and recruitment periods notifications, the user needs to access to the notification's history of a country, by clicking on its name in the countries list. Other notifications (e.g. serious breaches, unexpected events, etc.) will be listed under the countries list. For each notification listed, the following options will be available: view, update and withdraw. The icons appear as shown below:



In order to update the notification, the pencil icon must be clicked. Afterwards, a pop-up will display the information populated when creating the notification. This allows the sponsor to make the changes needed, including if there is an impact on subject safety and/or benefit-risk balance. Finally, the user needs to click on the 'Upload' button. After uploading it, a button to list the previous versions of it will become available .

To withdraw a notification, the sponsor needs click on the withdraw icon . Afterwards, a pop-up will display where the sponsor needs to provide a justification. Afterwards, the only available action will be to view the withdrawn notification, as shown in the image below:

1.16. When are Trial and recruitment periods notifications published on the public website?

Information related to the following notifications are published in the public view as soon as they are submitted through CTIS:

- Start, restart and end of trial including early termination
- Start, restart and end of recruitment
- Temporary halts (for reasons not related to subject safety)

In the case of temporary halts related to subject safety, the publication will be made after the MSC has submitted the corresponding assessment.

When an update for these types of notifications is submitted, the update is immediately reflected in the public website.

1.17. When are other types of notification published on the public website?

In case of unexpected events, serious breaches, urgent safety measures and third-country

inspectorate reports, the publication will be made after the MSC has submitted the corresponding assessment. Also, a report of the event shall be published when the assessment has been completed. When an update for this type of notifications is submitted, the changes are immediately reflected in the public website.

1.18. How can users withdraw a notification from the public website?

Once the notifications start, restart and end of trial and recruitment have been published, if they are withdrawn by the sponsor, they shall be automatically removed from the public website.

Other types of notifications like an unexpected event, serious breach, urgent safety measure, third-country inspectorate report, early termination and temporary halt must be removed from the public website before the sponsor can withdraw them. To remove these notifications from the public website, the sponsor should submit a request to EMA's Service Desk for an amend procedure. The amend procedure is carried out by the EMA admin, for the selected CT.

For notifications that have been withdrawn, a note will be published stating that the notification was published by mistake and removed on a given date.

2. Request for Information (RFI) raised as part of an ad hoc assessment

2.1. What is an ad hoc assessment?

The process that enables the Member State to discuss and assess information related to a submitted notification, a suspected unexpected serious adverse reaction (SUSAR), investigational medicinal product (IMP) or any other information relevant to the supervision of a trial. During this process, the Member State can request additional information from the sponsor and consult with the other Member States.

2.2. Which actors are involved in an ad hoc assessment?

The Member States of the European Union, who will be represented by National Competent Authorities (NCAs) and Ethics Committee in CTIS, and the Sponsors in case requests for information (RFIs) are raised.

- **Member States:** They are able to create, update and complete an ad hoc

assessment. They can also search, view, or download an ad hoc assessment that has been already completed. The assessing Member State is the MS that starts the ad hoc assessment and the discussion with the other MS, and that can raise an RFI to the sponsor.

- **Sponsors:** They participate in the process in case the MSs raise a request for information.

2.3. What are the reasons for creating an ad hoc assessment?

The ad hoc assessment process enables the Member State to assess information based on different reasons, depending on if it is related to a notification, an investigational medicinal product, or any other information relevant to the supervision of the trial.

The notifications that can trigger an ad hoc assessment are:

- **Temporary halt:** Article 2 (28) of the Clinical Trials Regulation[13] (CT Regulation) defines the temporary halt of a clinical trial as an interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it. It can be related to subject safety and/or benefit-risk balance or not.
- **Serious breach:** Notification to inform of a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the CT. These notifications must be made no later than 7 days from the date on which the sponsor became aware of the breach (Article 52 of the CT Regulation[14]).
- **Unexpected event:** Notification of an incident that might influence the benefit-risk assessment of the medical product or that would lead to changes in the administration of a medical product or the overall conduct of a CT (e.g. a significant hazard to the patient population). These notifications must be made no later than 15 days from the date the sponsor became aware of the event (Article 53 of the CT Regulation[15]).
- **Urgent safety measure:** Notification of an unexpected event that is likely to affect the benefit-risk balance of a CT significantly, and the appropriate urgent safety measures to protect the subjects that have been taken by the sponsor and/or the investigator. The sponsor shall notify the Member State Concerned (MSC) accordingly and within 7 days from the date on which the measures were taken (Article 54 of the CT Regulation[16]).

The other aspects of the CT that can trigger an ad hoc assessment are:

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[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 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
[14] Idem
[15] Idem
[16] Idem

- **SUSAR related:** A suspected unexpected serious adverse reaction is an untoward and unintended response to a study drug, that is fatal or life-threatening.
- **Investigational Medical Products (IMP) class and mode action**: It can trigger an ad hoc assessment if a safety issue is affecting medicinal products with a similar mode of action. The mode action is capture in the uploaded documents, e.g. Protocol.
- **Other:** Relevant information to the supervision of a trial.

2.4. What is an RFI raised as part of an ad hoc assessment?

It is a request for information submitted by an MS to the sponsor in the context of an ad hoc assessment. Ad Hoc assessment RFIs and their corresponding responses are not subject to the publication rules established by the CT Regulation.

2.5. How is an RFI raised as part of an ad hoc assessment received?

The sponsor receives a notice related to the RFI as part of an ad Hoc assessment. To navigate to the RFI, the sponsor shall click on the received notice. A pop-up will be displayed.

2.6. Where can users view and respond to an RFI raised as part of an ad hoc assessment?

The sponsor has three ways to search and respond to this type of RFIs:

- **Listed in the 'RFI' tab:** the user needs to filter the received RFIs that appear on the list by searching for example by the CT number.
- **Listed in the 'Notices & alerts' tab:** the user may use the basic search to search by CT number, use relevant filters such as 'source type' (Ad hoc assessment), or use the advanced search to apply multiple parameters (e.g. source type, RMS, reception date, etc.).
- **Listed in the 'Ad Hoc assessment' sub-tab under the CT page:** The user will find there all Ad hoc assessment listed that may exist for a given CT. By accessing each of them, the sponsor will be able to display the RFIs raised as part of them.

For each option, a pop up allows the sponsor to respond to the information requested after clicking on the RFI.

In case of an ad hoc assessment RFI related to a notification, the response submitted by the sponsor does not automatically update the notification. If the notification requires to be updated, this will be done through a separate action. *For more information, refer to question 1.15.*

2.7. Where can users view the ad hoc assessments and the RFI related to them?

The sponsor may access the Ad hoc assessment listed, regarding a particular CT, in the 'Ad Hoc assessment' sub-tab under the CT page. For each Ad hoc assessment, the sponsor may display the RFIs that may have been raised and view the responses or act if needed.

3. Request for Information (RFI) – i.e. opinion – before a corrective measure is applied

3.1. What is a corrective measure?

The corrective measure is a process defined in the Article 77 of the CT Regulation[17], that allows the Member State Concerned (MSC) to request a modification of a Clinical Trial (CT) or to modify its status if the MSC considers that the requirements of the Clinical Trials Regulation (CT Regulation) are no longer met. MSCs may apply measures such as the request for modification of the CT, the revocation of an authorisation, or the suspension of the CT. The CT Regulation foresees that the MSC shall request the sponsor's opinion before applying the corrective measure, except where immediate action is required.

3.2. Which users are involved in a corrective measure?

Throughout the corrective measure process, the Reporting Member State (RMS), the MSCs, and sponsors are involved. However, each of them has a different role:

- **RMS & MSCs:** The corrective measure is a supervision activity that should be taken individually by each MSC. Both the RMS and MSCs can create and submit corrective measures in their territory regardless of their role. Throughout the document, only the term 'MSC' will be used to refer to both. As part of the process MSCs can consult

[17] 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

each other and assess the opinion of the sponsor. They may also consult the rest of MSCs before taking any corrective measure.

- **Sponsors:** Sponsors participate in the process only in case their opinion is requested, as part of the process, by the MSC.

3.3. What types of corrective measures are there?

A corrective measure is an instrument of supervision available to MSC to ensure compliance of clinical trials with the requirements set out in the CT Regulation[18]. The corrective measures can be organised in types according to the measures that can be taken by the MSC in case of non-compliance. The following types can be chosen in CTIS in line with the CT Regulation:

- **Suspend:** If the MSC creates a corrective measure of the 'Suspend' type and submits it, the CT status changes to suspended (only for that MSC).
- **Revoke:** If the MSC creates a corrective measure of the 'Revoke' type and submits it, the CT status changes to revoked (only for that MSC).
- **Require modification:** If the MSC creates a corrective measure of the 'Require modification' type and submits it, the sponsor is notified that a substantial modification is required in the application. This type has no impact on the trial status (only for that MSC).
- **Suspend & Require modification**: If the MSC creates a corrective measure of the 'Suspend & Require modification' type and submits it, the status of the clinical trial will be changed to suspended. The sponsor needs to submit a substantial modification to address the changes required by the MSC (only for that MSC).

  The required substantial modification needs to be evaluated by the MSC(s) that relates to (e.g. if it is a Part I substantial modification, it needs to be evaluated by all MSCs). *For more information on the substantial modification CTA refer to Module 06: How to evaluate a CT application*.

The system also allows users to select the type 'No further action needed', which allows MSCs to cancel draft corrective measures. For example, an MSC can consider that the corrective measure is no longer needed, after consulting other MSCs or requesting the sponsor's opinion on the draft corrective measure.

3.4. What is an RFI raised before a corrective measure?

As a general rule, before the MSC takes any corrective measures, it must ask the sponsor for

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

its opinion through an RFI, except where immediate action is required. That opinion shall be delivered by the sponsor within 7 days.

RFIs to request the sponsor's opinion on an intended corrective measures and their corresponding responses are not subject to the publication rules established in the CT Regulation. Only an applied corrective measure is subject to the publication rules of the CT Regulation.

3.5. How is an RFI raised before applying a corrective measure?

The sponsor receives an alert for any RFI raised as part of a corrective measure under the 'Notices & Alerts' tab.

3.6. How can users view and respond to an RFI raised as part of a corrective measure?

To locate and respond to this type of RFI, the sponsor needs to go to the 'RFI' tab, where the sponsor will be able filter the RFIs by parameters such as source type ('Corrective measures') or EUCT number. In addition, the user may also use the basic or the advanced search functionality. When clicking on the RFI, a pop-up allows the sponsor to deliver the opinion requested and attach any relevant documents.

3.7. How can users view the Corrective measures already applied?

The sponsor has two ways to search for the Corrective measures already applied:

- **Listed in the 'Notices & alerts' tab:** the user may use the basic search to search by CT number, use relevant filters such as 'source type' (Corrective measure), or use the advanced search to apply multiple parameters (e.g. source type, RMS, reception date, etc.).

- **Listed in the 'Corrective measures' sub-tab within the CT page:** The user will find there any Corrective measure applied to a given clinical trial. Remember that only Corrective measures submitted will be displayed. An MSC may have requested an opinion to the sponsor, but not have applied any corrective measure yet.

3.8. What happens if the sponsor does not respond to the request for opinion?

If the sponsor does not respond to the request for opinion within the expected 7 days timeline; the functionality in CTIS will be enabled for the MSC to apply the corrective measure or not, as applicable.

3.9. What happens if the MSC is not satisfied with the response provided by the sponsor?

In case the MSC is not satisfied with the response provided by the sponsor, the MSC may re-submit a request for opinion to the sponsor through the corrective measure form.

4. Trial results

4.1. How many types of trial results exist?

Regardless of the outcome of a CT, the sponsor shall submit a summary of the results of the CT. The content of that summary is set out in Annex IV of the CT Regulation[19]. It shall be accompanied by a summary written in a manner that is understandable to laypersons, the content of which is set out in Annex V of the CT regulation[20]. This summary is known as summary of CT results for laypersons.

In addition to the summary of the results, where the CT was intended to be used for obtaining marketing authorisation for the investigational medicinal product, the applicant for marketing authorisation shall also submit the clinical study report[21].

4.2. When does the sponsor need to submit the trial results?

Within one year from the end of a CT (in all EEA MSC or Global if applicable and justified), and within six months in case of paediatric trials, the sponsor shall submit a summary of the results and a summary for laypersons.

[19] 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
[20] Idem
[21] For more information, please refer to module 13: Clinical study results submissions.

4.3. What is a paediatric trial?

A trial that involves minors aged from 0 to 17 years.

4.4. What happens if the sponsor does not submit the summary of results within 12 or 6 months from the end of the CT?

Where it is not possible to submit the summary of the results within the defined timelines for scientific reasons, for example when the CT is still ongoing in third countries and data from that part of the trial are not available, which would make a statistical analysis not relevant, the sponsor should justify this in the protocol and specify when the results are going to be submitted. The expected end of trial date is indicated when submitting the CTA.

4.5. When does the sponsor need to submit an intermediate analysis summary of results?

If the CT protocol provides for an intermediate data analysis date prior to the end of the CT and the results are available, a summary shall be submitted within one year of the intermediate data analysis date.

4.6. When are the trial results published on the public website?

Publication of summary of results, layperson summary of results and, when applicable, intermediate data analysis will vary in CTIS depending on the trial category.

- **For category 1 trials,** i.e. phase I human pharmacology, BE/BA trials, biosimilar trials, the trial results can be published as soon as they are submitted, or sponsors have the option to apply for a deferral to delay the publication date for submission of results to CTIS.

  The due date for the submission to CTIS of the intermediate data analysis is 12 months since the intermediate data analysis date.

  The due date for the submission to CTIS of the summary of results and layperson summary is 12 months since the end of the trial in the EU/EEA, or 6 months since the end of trial in EU/EEA for trials conducted in paediatric population.

- **Intermediate data analysis** are published as soon as they are submitted, or within 12 months from the end of trial in the EEA (this corresponds to the date when the results are due to be submitted to CTIS) or the publication can be deferred up to 30 months after the end of trial in the EU/EEA.

- **Summary of results and layperson summary** are published as soon as they are submitted, or within 12 months from the end of trial in the EEA (this corresponds to the date when the results are due to be submitted to CTIS) or the publication can be deferred up to 30 months after the end of trial in the EU/EEA.

  For category 2 and 3 trials, i.e. phase II, III and IV trials publication of the summary of results, the layperson summary and the intermediate data analysis cannot be deferred in CTIS and therefore these documents are published as soon as they are submitted.

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Clinical Trials Information System (CTIS).

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