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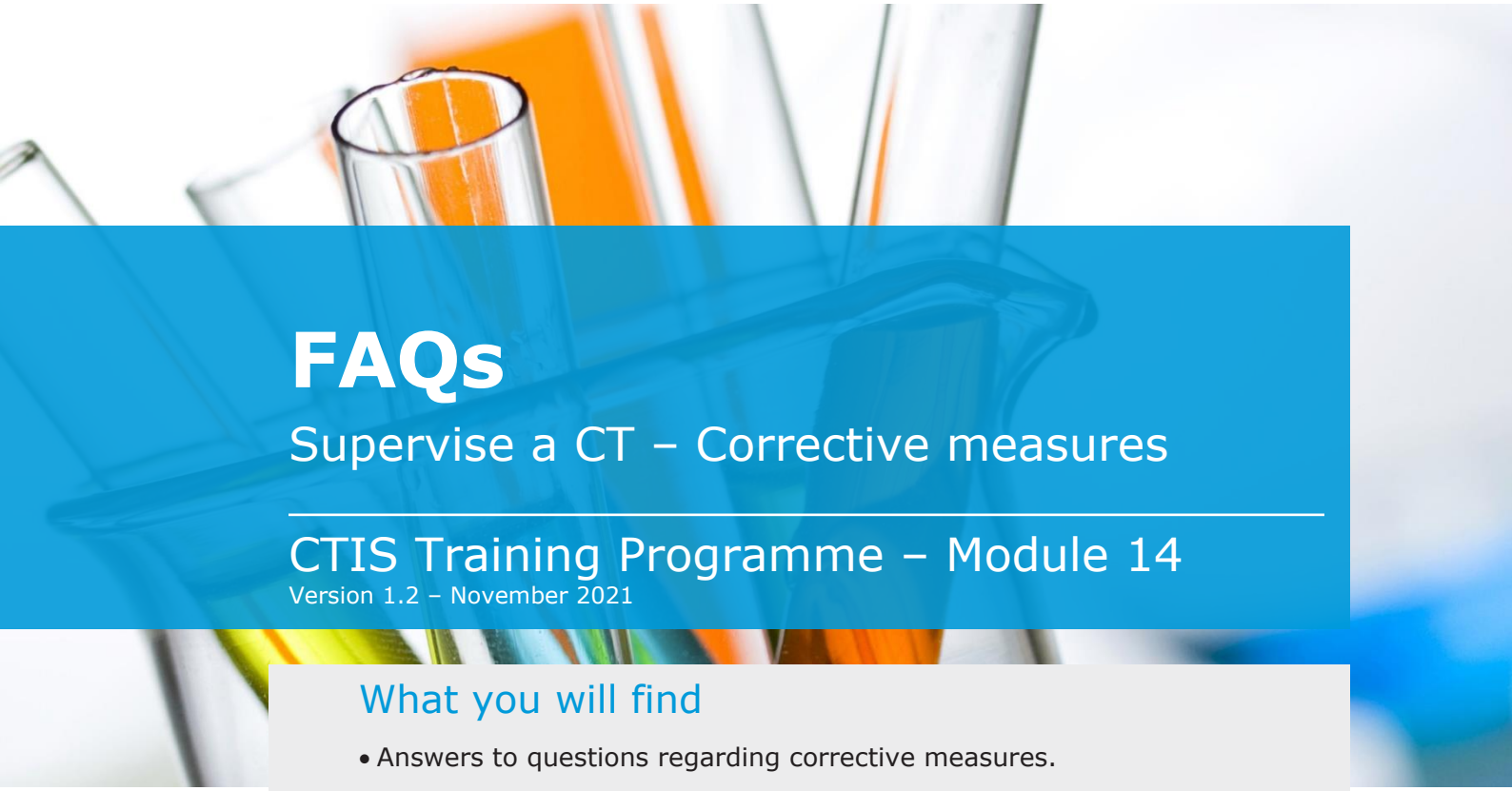

FAQs

Supervise a CT – Corrective measures

CTIS Training Programme – Module 14

Version 1.2 – November 2021

What you will find

- Answers to questions regarding corrective measures.
- Answers to questions regarding how users can create and cancel a corrective measure.
- Answers to questions regarding how users can consult with other Member States Concerned (MSCs) and the sponsor on a corrective measure.
- Answers to questions regarding how users can submit, update and revert a corrective measure.

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FAQs

In this document, we list common questions regarding *Module 14: Supervise a CT – Corrective measures*. They are categorised into: Questions of a general nature regarding corrective measures; questions on the creation of the corrective measure; questions on the consultation with other MSCs; questions on the request for sponsors' opinion; question on the submission of a corrective measure; questions on the roles and permissions involved in the management of the corrective measure. The specific learning objectives of this module are:

1. Understand what a corrective measure is, the situations in which an MSC can create one and the types there exist.

2. Understand how to create and cancel a corrective measure.

3. Understand how to consult other MSCs on an intended corrective measure.

4. Understand how to request the sponsor's opinion before applying an intended corrective measure.

5. Understand how to submit a corrective measure and its implications, and how to update, withdraw and revert an existing one.

6. Understand the roles and permissions involved in the corrective measure functionality.

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. General information

1.1. What is a corrective measure?

The corrective measure is a process defined in the Article 77 of the CT Regulation[1], 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.

A Clinical Trial Application (CTA) cannot have more than one corrective measure of the same type for each MSC, e.g. if the MSC submits a corrective measure for suspension, an additional corrective measure of the same type cannot be created. This process applies to all types except for 'Require modification', that can have more than one CM for the same type.

1.2. 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 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.

1.3. When can a corrective measure be created?

The corrective measure process starts with the monitoring of a previously authorised application. If during the supervision of a clinical trial, the MSC determines that the requirements of the CT Regulation[2] are no longer met, the MSC can decide to initiate the corrective measures process.

[1] 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

[2] Idem

Corrective measures are expected to be applied while a clinical trial is on-going. However, when follow up of patients for safety reasons is deemed necessary, MSCs may decide to apply a corrective measure once the CT has ended[3].

1.4. 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[4]. 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). Suspend means the CT is on hold while further investigation is performed, by the end of that investigation the CT could re-start again.

- **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). Revoke means the CT is no longer authorised in a Member State. It cannot be reinitiated unless legal procedures are taken. The sponsor may need to re-submit the new CTA.

- **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). There can be more than one CMs for the type 'Require modification'.

- **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. *For more information, refer to question 2.3.*

1.5. Why would an MSC create a corrective measure?

While completing the corrective measure form in CTIS, the MSC needs to specify the reason that triggers the corrective measure. The MSC can choose among the following options:

[3] European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 3, February 2021. Page 109 question 12.2. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[4] 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

- Result of inspection.
- Result of safety assessment.
- Additional information assessment conclusion.
- Unexpected event: This reason will appear on the drop-down list only if an unexpected event notification has been submitted by the sponsor for that particular Clinical Trial Application (CTA).

In addition to being able to select a specific reason, the MSC must provide a justification for the corrective measure either in writing or by attaching a document.

1.6. What are the implications of the 'Immediate action'?

The MSC should indicate whether the corrective measure requires an Immediate action. This can be indicated in the 'Immediate action' drop-down field in the corrective measure form.

If immediate action is required, the MSC can proceed to 'Submit' the corrective measure. If necessary, the MSC may also consult with other MSCs. *For more information, refer to question 3.2.*

If immediate action is not required, the MSC needs to save the draft of the corrective measure and continue with the process, the MSC can either consult with other MSCs and/or request sponsor's opinion. *For more information, refer to question 4.2.*

2. Create a corrective measure

2.1. How can users create a corrective measure?

Within the 'Corrective measures' sub-tab, users can find a list of the existing corrective measures (if applicable) and the 'New' button to create one. Once the MSC clicks on the 'New' button, it is possible to start populating each of the sections of the corrective measures form.

A CTA cannot have more than one corrective measure of the same typology for each MSC, e.g. if the MSC submits a corrective measure for suspension, an additional corrective measure of the same typology cannot be created.

This process applies to all typologies except for 'Require modification', that can have more than one CM for the same type.

2.2. What is the difference between a draft corrective measure and a submitted corrective measure?

A draft or intended corrective measure is created after an MSC clicks on the 'New' button. During the consult MSCs process and/or the request for the sponsor's opinion, it remains draft. A draft CM can be edited and submitted only by the MSC that initiated the corrective measure.

A submitted or applied corrective measure, means that it has been submitted to revoke a CT authorisation, suspend a CT, or request for modification of a CT. In this case, some information and documents will be made public.

It should be noted that the MSC can create a draft corrective measure and decide after consulting with the sponsor to cancel it. *For more information, refer to question 2.3*.

2.3. How can users cancel a draft corrective measure?

Users can cancel a draft corrective measure through the 'Cancel CM' button at the bottom of the corrective measure form. However, in order to cancel a draft of a corrective measure, it is important to take into account three aspects:

- The corrective measure must not have been submitted. In case it has already been so, the corrective measure can only be updated or reverted, but not cancelled.
- If users have neither previously consulted the other MSCs or have requested the sponsor's opinion on the draft corrective measure, or submitted the corrective measure (e.g. a draft corrective measure that requires immediate action), they can still 'cancel' the corrective measure by simply closing it on the 'x' button on the upper-right corner of the form.
- If users have previously consulted other MSCs or have requested the sponsor's opinion on the draft corrective measure *(refer to sections 3 and 4 for more information)*, they need to change the corrective measure type in the form to 'No further action needed'. This will enable the 'Cancel CM' button.

3. Consult other MSCs

3.1. What is a consultation with MSCs?

MSCs may consult the other MSCs before a corrective measure is submitted. Such consultations are a communication channel for MSCs to be used for discussions and to express support on draft corrective measures.

3.2. How can users consult other MSCs?

As part of the corrective measure form, the MSC can consult other MSCs in writing or by attaching a document. To consult with other MSCs, users need to complete the corrective measure form and click on the 'Save' button at the bottom of the form. This will enable the consultation with MSCs, a field to provide the reason for the consultation and attach documents if necessary, and a field to specify the expected date for receiving the response from the other MSCs.

Once the MSC has completed the consultation, the MSC shall click on the 'Submit request for consultation' button. *See image below:*

3.3. What are the timelines of consulting with other MSCs?

The form enables the user to include a proposed response date for an MSC to provide their comments on the draft corrective measure. However, the MSC that created the corrective measure can submit the corrective measure and submit the form at any moment.

3.4. Which MSCs receive the consultation?

All MSCs involved in the CTA will receive notification of the consultation.

3.5. How can MSCs search and respond to a consultation?

MSCs will receive alerts regarding the consultation sent by another MSC, which can be accessed via the 'Notices & alerts' tab.

MSCs that have been involved in the consultation are able to see the full details of the corrective measure. By clicking on the alert, users will access the corrective measure form and will have the option to include their comments in the text box provided on the form.

The MSC user and the response date are included in the comments. Also, comments are visible to all MSCs.

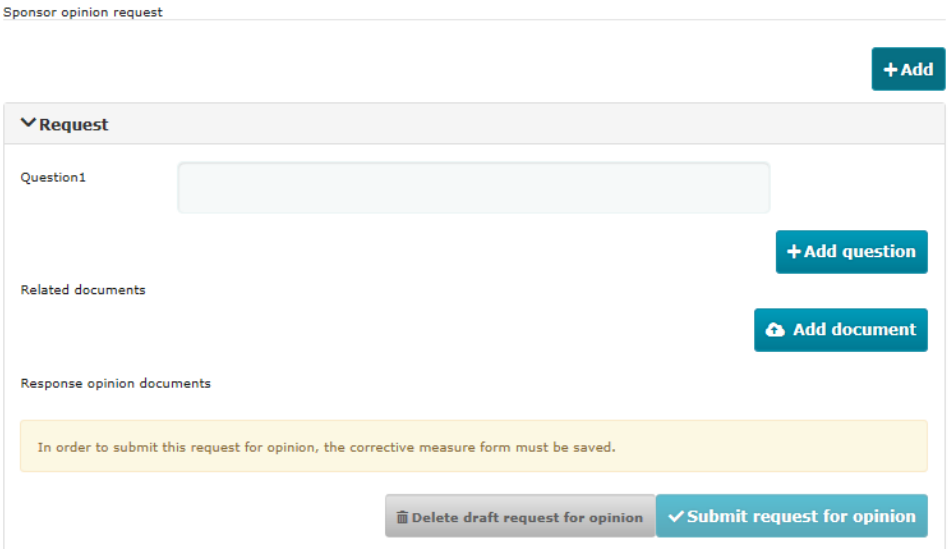
4. Request for sponsors' opinion

4.1. What is a request for opinion?

A request for opinion is a consultation for information and/or documentation from the MSC to Sponsors to ensure compliance with the requirements of the CT Regulation[5]. Before the MSCs take any of the measures referred to in question 1.5, they shall, except where immediate action is required, ask the sponsor and/or the investigator for their opinion.

4.2. How can users request the sponsor's opinion?

This request to the sponsor is made by the MSC through the corrective measure form, where all necessary questions and documentation can be included. To request sponsor's opinion, users need to complete the corrective measure form and click on the 'Save' button at the bottom of the form. This will enable the fields for the sponsor opinion request and the respective 'Submit request for opinion' button, which users will need to click after they fill out the sponsor's opinion request form. *See image below:*



4.3. What are the timelines of requesting the sponsor's opinion on a draft corrective measure?

According to the CT Regulation[6], sponsors have 7 days to respond to the request. The sponsors are notified that an opinion in the context of a corrective measure has been requested via both the 'RFI' tab and the 'Notices and alerts' tab.

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

[6] European Commission, *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*, EU Official Journal L158. 16

Once the sponsor has provided the opinion to the corrective measure or the deadline has passed, the MSC can take action in the system and decide whether they wish to submit the corrective measure.

4.4. How does the MSC know when the sponsor has replied to its request?

Once the sponsor has responded to the request for opinion, the MSC will receive an alert via the 'Notices & alerts' tab to view all the information in detail.

4.5. 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.

4.6. 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, it may re-submit a request for opinion to the sponsor through the corrective measure form.

4.7. It is possible to cancel a draft corrective measure once the sponsor's response is received?

Yes. To do so, users need to change the corrective measure type to 'No further action'.

5. Submit a corrective measure

5.1. How can users submit a corrective measure?

After the corrective measure has been drafted; saved; and sponsors and MScs have been consulted (if applicable), the corrective measure can be submitted. To submit a corrective measure, users should open the populated corrective measure form, click on the 'Submit' button, and click on the confirmation button that appears. Corrective measures cannot be submitted if the sponsor responses are still pending within the 7 days, they have to respond.

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

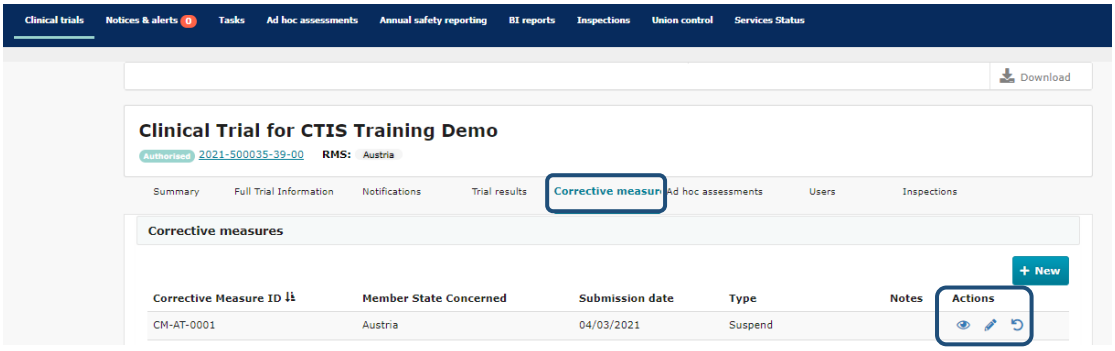
5.2. How can users modify a corrective measure?

After the corrective measure has been submitted, the MSC can view and modify its information if necessary.

In order to do so, the MSC must access the 'Corrective measures' sub-tab available in the CT page and select the action to be taken. *See image below:*

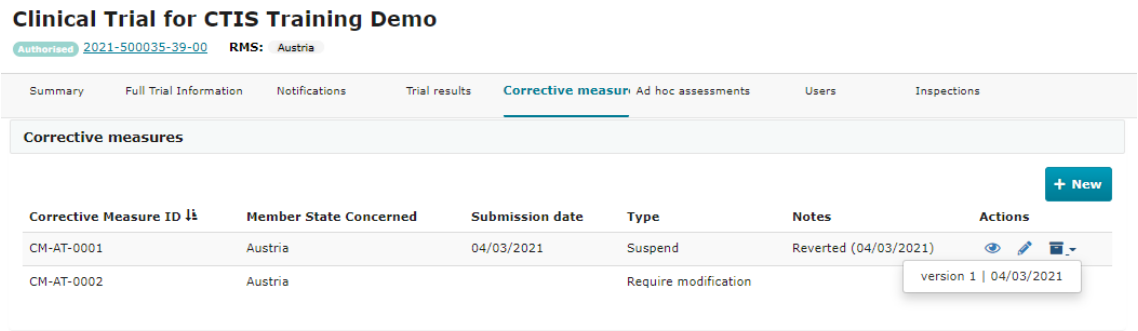
- **View:** MSCs can view the full details of the corrective measure and download the documents attached to the form.
- **Update:** This functionality allows the MSC to modify only the information filled in the form or to add related documents. The MSC needs to indicate the reason for the modification through a comment or supporting documents.

  If the user wishes to change the corrective measure type, for example from suspend to revoke, the user cannot use the update functionality. For this purpose, the user can use the revert functionality.
- **Revert:** If the MSCs wish to revert the corrective measure type (e.g. suspend or revoke), they can use the revert functionality. If the corrective measure is reverted to 'Suspend', the user can further revert it to 'Require modification'. Therefore, the CTA can be changed back to either of the following status, 'Authorised' or 'Authorised with conditions'. In the case of modifying it to 'Authorised with conditions', details of the conditions must be included before the corrective measure can be resubmitted. Sponsors receive a notice after a corrective measure is reverted.



5.3. How can users view all the corrective measures versions submitted?

Users will be able to access the previous versions of the corrective measure by clicking on the 'Previous versions' button located in the 'Corrective measure' sub-tab. *See image below:*



5.4. Does the information related to corrective measures become public?

All documentation added to the corrective measures form will not become public on the CTIS public website while the corrective measure is in draft status and not yet submitted (i.e. during consultation with MSCs and requesting sponsor's opinion). *For more information, refer to sections 3 and 4.*

Once the corrective measure has been submitted, the relevant information and specific documentation (i.e. justification document, and sponsor/investigator opinion documents sent by the sponsor) regarding the corrective measure will become public. Nevertheless, communication exchanges in writing and documents between the MSCs via consultation will not become public.

6. Roles and permissions

6.1. What roles and permissions are involved in a corrective measure?

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

Submit/update/revert a corrective measure: Decision Maker-Submitter.

Create corrective measure: Supervisor Preparer; Supervisor Submitter.

Comment on a corrective measure: Decision Maker-Submitter; Supervisor Preparer; Supervisor Submitter.

View a corrective measure: Viewer Part I Full rights/Restricted rights; Viewer Part II; Validator (Preparer/Submitter) Full rights (Part I and Part II); Validator Preparer restricted rights (Part I exc IMPD and Part II); Validator Part II (Preparer/Submitter); Assessor Part I (Preparer/Submitter) full rights/restricted rights; Assessor Part II (Preparer/Submitter); Decision Maker-Submitter; Supervisor (Preparer/Submitter); Inspector (Preparer/Submitter).

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