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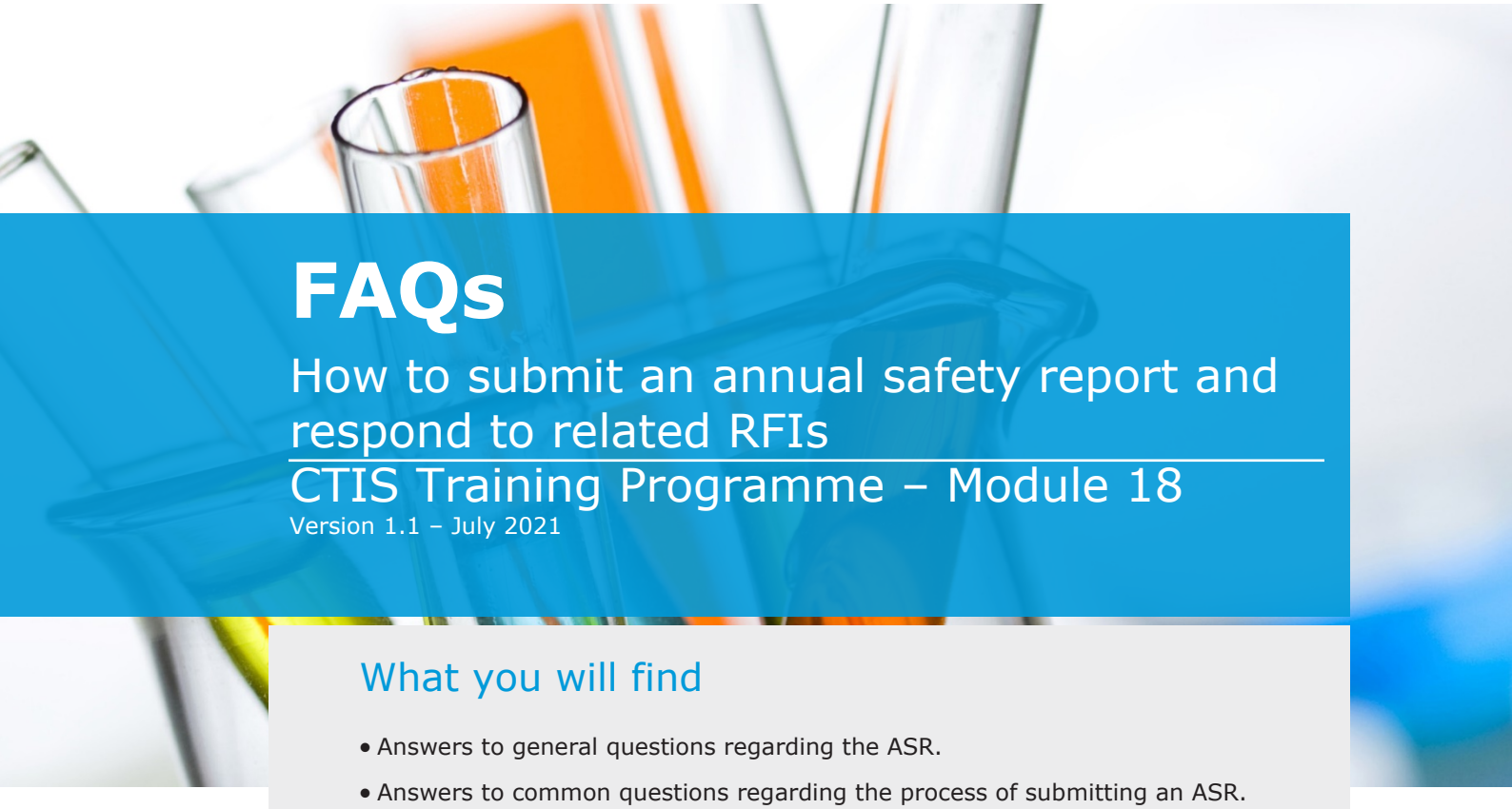

FAQs

How to submit an annual safety report and respond to related RFIs

CTIS Training Programme – Module 18

Version 1.1 – July 2021

What you will find

- Answers to general questions regarding the ASR.
- Answers to common questions regarding the process of submitting an ASR.
- Answers to common questions regarding the phases of assessment of an ASR.
- Answers to common questions regarding the process of responding to an RFI related to an ASR.
- Answers to common questions regarding the ASR roles and permissions.

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FAQs

In this document, we list common questions regarding *Module 18: How to submit an annual safety report and respond to related RFIs*. They are categorised into general questions regarding the annual safety report (ASR), the process of submitting an ASR, the phases of assessment of an ASR, the process of responding to an RFI related to an ASR, and the ASR roles and permissions. The specific learning objectives of this module are:

1. Remember what an annual safety report (ASR) is and when a sponsor can create one.
2. Understand how to create, cancel, and submit the ASR submission form.
3. Remember the phases and associated timelines for the assessment of an ASR.
4. Understand how to respond to RFIs received during the assessment of an ASR.
5. Understand how to search, view, and download an ASR.
6. Understand the roles and permissions involved in the ASR process.

We encourage you to read these questions and answers carefully. If you have any questions that 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 questions

1.1. What is an annual safety report?

The annual safety report (ASR) is a document provided by the sponsors to the authorities regarding the monitoring and evaluation of the evolving safety profile of the Investigational Medicinal Product (IMP) and the mitigation of potential risks. According to Article 43 of the Clinical Trial Regulation[1], sponsors shall submit annually a report on the safety of each IMP used in a trial. This obligation starts with the first authorisation of a trial and finalises with the end of the last trial conducted with the IMP. With the information provided via the ASR, the National Competent Authorities (NCAs) are able to both assess each IMP's safety profile and also enquire further information from the sponsors.

1.2. Who are the actors involved in the ASR process?

The two main actors involved in the ASR processes are the sponsor organisations and the Member States. The actions that each of them is expected to perform are the following:

- The sponsor users submit the ASR so that the Member States can assess it, as well as to respond to the Requests for Information (RFIs) created by the safety assessing Member State (saMS) in the context of the assessment of the ASR.
- The Member States users assess the ASR submitted by the sponsors, and the saMS creates RFIs after consolidating the Member States' considerations regarding the draft assessment report, if applicable. In addition, Member States are expected to assess the ASR RFI responses from the sponsors (if applicable) and provide a finalised assessment of the ASRs.

1.3. What is a safety assessing Member State?

The safety assessing Member State (saMS) is the Member State Concerned (MSC) that is both leading the safety assessments and responsible for the assessment of a specific ASR. In case there is a single MSC involved in the ASR, that MSC will be automatically appointed as the saMS.

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

2. Submit an annual safety report

2.1. When can users create an ASR for a trial?

As referred to in question 1.1, according to Article 43 of the Clinical Trial Regulation[2], sponsors shall submit annually a report on the safety of each Investigational Medicinal Product (IMP) used in a trial. This obligation starts with the first authorisation of a trial and finalises with the end of the last trial conducted with the IMP. Considering this, the only pre-condition to create an ASR submission form is that the trials related to such ASR must be authorised. Furthermore, the search functionality of the clinical trial details section in an ASR submission form will not retrieve clinical trials that are not authorised.

2.2. What is the process to create an ASR submission form?

The steps that the sponsors have to follow to create an ASR submission form are the following:

1. Open the Annual safety reporting tab.
2. Click on the '+ New ASR' button.
3. The ASR submission form is articulated in 4 steps *(refer to question 2.3* for details of each section), and users have to fill in the mandatory fields in each section.
4. Submit the ASR.
5. Respond to the ASR RFIs received from the saMS.

2.3. What are the sections of an ASR submission form?

The ASR submission form is articulated into four steps with multiple mandatory fields. In each step of the form, users should populate specific details:

1. **Sponsor information (step 1)**: Select the sponsor organisation to include the organisation details and the contact details for ASR submission.
2. **Clinical Trial detail (step 2)**: Add through the search functionality the trials involved in the ASR and select the IMP(s) and Auxiliary Medicinal Product (AxMP) of the clinical trial selection.

[2] Idem

3. **ASR reporting period details (step 3)**: Include the ASR data lock point, the reporting period, what the ASR includes, and other relevant reporting period details.

4. **Supporting documents and submit (step 4)**: Upload the ASR document and the supporting documents (i.e. Summary of Product Characteristics (SmPC), the Investigator Brochure (IB), and/or others) in the respective fields.

2.4. Can an ASR be related to more than one trial?

Yes, when users launch the search for trials in the 'Clinical trial detail' section (step 2) of the ASR submission form, they will obtain a list of all the authorised trials for which they have an ASR user role. From that list, users can select all the trials related to the ASR.

2.5. Can an ASR be related to more than one IMP?

Yes, when users launch the search for trials in the 'Clinical trial detail' section (step 2) of the ASR submission form, they will obtain a list of all the authorised trials for which they have an ASR user role. From that list, users can select all the trials related to the ASR, which can involve multiple IMPs. After the selection of trials involved in the ASR, users must select at least one IMP per trial selected.

2.6. Can an ASR be related to more than one MSC?

Yes, when users launch the search for trials in the 'Clinical trial detail' section (step 2) of the ASR submission form, they will obtain a list of all the authorised trials for which they have an ASR user role. If the user wants to search by multiple MSCs in the search functionality, they can keep the 'CTRL' key pressed on their keyboard, click on the Member States, and then launch the search. From that list, users can select all the trials related to the ASR.

2.7. How many IMPs can be selected per trial?

For all the selected trials related to an ASR, at least one IMP per trial should be selected in the ASR submission form to be involved in the ASR. Users can also add more than one auxiliary medicinal product per trial by clicking on the respective button below the IMPs.

2.8. How can users populate in the ASR submission form what the ASR includes?

When populating the form, in the ASR Reporting Period details (step 3), users provide what events occurred during the reporting period of the ASR. A drop-down list allows users to select more than one value from the following:

- Novel combination.
- New combination.
- First in class product/IMP (in EU).
- Advanced therapy medicinal product (ATMP).
- New signals or concerns or risk for the product.
- Temporary halt or suspension of any trial due to safety reason.
- Premature ended trial/s.
- Unexpected event changing benefit risk of any trial.
- Substantial modification of protocol or IB for risk mitigation any trial.
- Refused approval due to safety reason.
- Serious breach safety related or impact on safety.
- Urgent safety measure.

2.9. What type of documentation can be uploaded as part of an ASR submission form?

In the 'Supporting documents and Submit' section (step 4) of the ASR form, sponsor users can upload at least one ASR document created outside of CTIS, only PDF and Word file types are allowed. Users can also upload other documents such as the SmPC, the IB, and other documents relevant documents in a field for that purpose only in PDF.

2.10. Can an ASR submission form be saved?

No. The ASR submission form features four buttons that allow users to 'Clear', 'Check', 'Cancel', and 'Submit'. Neither the ASR submission form nor the RFI responses can be saved before submission. Therefore, they have to be populated and submitted in one go. Otherwise, users will lose the information already populated.

2.11. What are the possible statuses of an ASR?

The ASRs that have been submitted by the sponsors can have three possible statuses:

- **ASR submitted**: The ASR has been submitted, but the assessment has not started (i.e. the saMS appointment process is ongoing).
- **ASR Assessment in progress**: The saMS has been appointed, and the assessment is ongoing.
- **ASR Assessment completed**: The assessment has been finalised.

2.12. How can users access a submitted ASR?

Users can access an ASR page by clicking on the Annual safety reporting tab. This automatically retrieves all the ASRs submitted by the sponsor organisation on the search results list below the search functionalities. To retrieve a specific ASR, users can use the basic search or use specific criteria of the Advanced search and then click on 'Search ASRs'. Users can click on the ASR ID on the search results list to open the ASR page.

2.13. How can users download the search results list?

On the top right side of a search results list of the Annual safety reporting tab, users can click on the 'Download' button. This will download all the results from the search results list in a spreadsheet file type.

2.14. What is the ASR ID code?

The ASR ID is the unique identification number of the ASR that can be used, for example, to search for it using the basic search functionality in the Annual safety reporting tab. The ASR ID is a composition of unique details separated by a hyphen. For example, the code ASR-2021-00001 is structured the following way:

Acronym	Current year	Sequential number of ASRs created
ASR	2021	00001

2.15. When is the ASR ID code created?

The ASR ID code is only created only when the ASR has been correctly submitted.

2.16. Can users download specific ASR documents?

Yes. In both ASR Submission and Assessment sub-tabs of an ASR page, users can first locate the specific section and document they are looking for; and then click on the blue download icon next to each document. This action allows users to download the document in the file type and with the title in which it was initially updated to the ASR submission form.

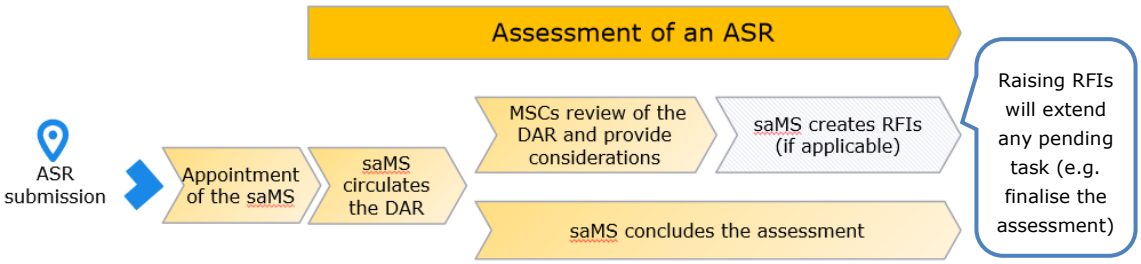
2.17. Does the ASRs documentation become public when the ASR is submitted?

The ASR documentation will not be publicly available. This means that the information of the ASR will not be reflected on the CTIS public website. Nevertheless, the Member States that are not MSCs will also have access to the ASR information.

3. Annual safety report assessment phases

3.1. What are the phases of the ASR assessment process?

After the sponsor submits an ASR, the appointment of the saMS process starts (in case the ASR involves multiple MSCs). Once appointed, the MSCs can start the assessment tasks of the ASR such as the circulation of the Draft assessment report (DAR) or the conclusion of the ASR assessment. The saMS can decide to extend, only once, some of the tasks such as the circulation of the DAR or the conclusion of the ASR assessment. See the image below for a visual representation of the assessment process of an ASR.



3.2. Can all the MSCs create ASR RFIs?

No. Only the saMS can create an RFI related to an ASR. However, once the saMS has circulated the ASR Draft assessment report among MSCs, they can provide considerations, which will be consolidated by the saMS, who can create RFIs for the sponsor, if necessary.

4. Requests for Information related to an annual safety report

4.1. How long do sponsor users have to respond to ASR RFIs?

When the saMS creates an RFI, the due date for the sponsor to respond to the ASR RFI is set automatically on 14 days. However, it is up to the saMS to modify this due date before submitting the ASR RFI to the sponsor (with either a shorter or longer period of time). It is important for the sponsor to pay close attention to the due date of the ASR RFI, and also to be mindful that creating RFIs will extend any pending task for the saMS (e.g. finalise the assessment).

4.2. How can users access the RFIs received in the context of an ASR?

During the assessment of a submitted ASR, the saMS can create RFIs for the sponsor in the context of an ASR. To view the details of an ASR RFI, users can click on the RFI to expand it and show the details such as considerations and supporting documents. Sponsor users can access the ASR RFIs through three different ways:

1. **Annual safety reporting tab:** Users can view the ASR RFIs by opening the Assessment sub-tab of an ASR page; users can access it via clicking an ASR ID on the search results list of the Annual safety reporting tab.

2. **Notices & Alerts tab:** Users receive an alert that an ASR RFI has been sent by the saMS on the Notices & Alerts tab. When users click on the alert, they are re-directed to the Assessment sub-tab of an ASR page, where the RFI is displayed outlining all the details, including considerations and supporting documents.

3. **RFI tab:** This tab lists all the RFIs received in the whole life-cycle of a CT, including ASR RFIs and other types of RFIs. When the user clicks on the RFI number, it is displayed in the Assessment sub-tab of an ASR page, where the RFI is displayed outlining all the details, including considerations and supporting documents.

4.3. What are the sections of an ASR RFI?

An ASR RFI is composed of four sections:

- **RFI details:** Includes the details such as the ASR RFI ID; saMS; submission, due and response dates; and the RFI reason.

- **Considerations:** List of considerations received; by clicking on the 'respond' button, the user can type responses to each consideration.
- **Supporting documents:** The documents section allows users to see the documentation that the saMS has added to the RFI. It will also enable the sponsor user to add documentation by clicking on the 'Add document' button.
- **RFI response submission:** Checkbox to agree with the submission statement and the 'Submit' button to submit the sponsor's response to the ASR RFI.

4.4. How can users respond to the RFIs received in the context of an ASR?

Users can respond to the ASR RFI in writing to each consideration in the considerations section of an ASR RFI, and uploading the necessary documents for the ASR RFI response in the supporting documents section. The proposed process users should follow to respond to an ASR RFI is:

1. Understand the requested RFI details and considerations.
2. Review the supporting documentation provided by the saMS, located in the supporting documents section.
3. Respond in writing each consideration by clicking on the 'Respond' button on the right side of each consideration, which opens a field to type the response.
4. Upload the additional supporting documentation to support the ASR RFI response.
5. Tick the checkbox to agree with the ASR RFI response submission statement and click on the 'Submit' button.

4.5. What is the ASR RFI ID code?

In the same way as the ASR ID *(refer to question 2.14 for more information)*, the ASR RFI ID code is a unique identification number for the RFIs received in the context of an ASR, which can be used, for example, to search for it using the basic search functionality in the RFI tab. The ASR RFI ID is a composition of unique details separated by a hyphen. For example, the code RFI-ASR -2021-00001-001-01 is structured the following way:

Acronym	Current year	Sequential number of ASR created	Sequential number of the RFI	Each consideration sequential number
RFI-ASR	2021	00001	001	01

4.6. What type of documentation can be uploaded in an ASR RFI response?

At the bottom of an ASR RFI, users can see the documents section, which will allow users to see the documentation that the Member State has uploaded as part of the RFI. This section will also enable users to add documentation via the 'Add document' button on the bottom right side of the documents section. Users can only upload supporting documents, as part of an ASR RFI response, in PDF file type.

This document upload will allow users to, as a response to the RFI, upload a new document of any type of documents submitted by the sponsor at the moment of creating the ASR. Users can upload a new document and classify it by using the 'Type' drop-down list (i.e. Additional document, ASR document, IB, Protocol, Sponsor Discussion Response Supporting Document, SmPC). It is possible to add more than one document, if necessary.

Submitting an ASR RFI with new documentation (e.g. a new ASR document) will not replace the original documents of the ASR submitted before the ASR RFI, neither create a new version of the ASR. To access the new documents, both sponsor and authority users can access them by going to the ASR RFI response section on the Assessment sub-tab of an ASR page.

4.7. Can an ASR RFI response be saved?

No. As referred to in question 2.10, the ASR submission form features four buttons that allow users to: 'Clear', 'Check', 'Cancel', and 'Submit'. Neither the ASR submission form nor the RFI responses can be saved before submission. Therefore, they have to be populated and submitted in one go. Otherwise, users will lose the information already populated.

4.8. What is the assessment of the ASR RFI responses?

The ASR RFI response from a sponsor follows an assessment process alike the responses to other types of RFIs. An ASR RFI response is assessed by the saMS, which has the task to submit an assessment of the ASR RFI response and the possibility to reply in written to each written consideration sponsor response. After the saMS has assessed the response, the MSCs can comment on the assessment of the ASR RFI response made by the saMS.

5. Roles and permissions

5.1. What user roles are involved in the ASR process?

In order to view, create an ASR submission form, or submit an ASR, the role needed to be assigned is the ASR submitter role. The permissions an ASR submitter has can be summarised as follows:

- View, create, submit an ASR.
- View an RFI and create and submit an ASR RFI response.
- View, upload, and download ASR documents and details.
- View ASR RFI Assessment comment.
- View ASR summary conclusion.

5.2. Can the CT Admin create and submit an ASR submission form?

No. The CT Administrator user does not have ASR permissions to its role. In order to be able to perform ASR related activities; the CT administrator, as an administrator, should assign the ASR submitter role to him/herself.

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Clinical Trials Information System (CTIS).

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