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SCIENCE MEDICINES HEALTH

Safety reporting in CTIS

Webinar for SMEs and Academia on the Clinical Trial Regulation (Regulation (EU) No 536/2014) and the Clinical Trials Information System (CTIS)

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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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Future changes to clinical trial safety reporting

Changes to clinical trial safety reporting - overview

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- CTR demands electronic submission of SUSARs and ASRs
- SUSARs will be submitted to the EudraVigilance database (EV CTM)
- ASRs will be submitted via CTIS
- COM will adopt implementing regulation
- saMS will assess safety relevant data substance based
- Communication between MSs and with sponsors will be via CTIS (ASR, ad hoc assessment, corrective measures)
- IT support not yet fully developed, will be further developed post go live
- CTFG will develop and adapt internal guidance

Requirements for the transition period

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SUSAR:

- SUSARs to EV unless the NCA requires direct reporting
- Reporting obligations as of CT-3 to investigators and ECs according to national legislations in MSs with CTs within Directive

ASR:

- With first trial for a substance under the CTR: ASR to CTIS
- Informative cover letter essential: name all MSCs for ongoing CTs in EU/EEA within Directive and CTR.
- Obligation as of CT-3 to investigators (new safety data or change in B/R) and ECs according to national legislations in MSs with ongoing CTs within Directive remains

Submission of Annual Safety Reports

Initiate ASR submission (ASR submitter)

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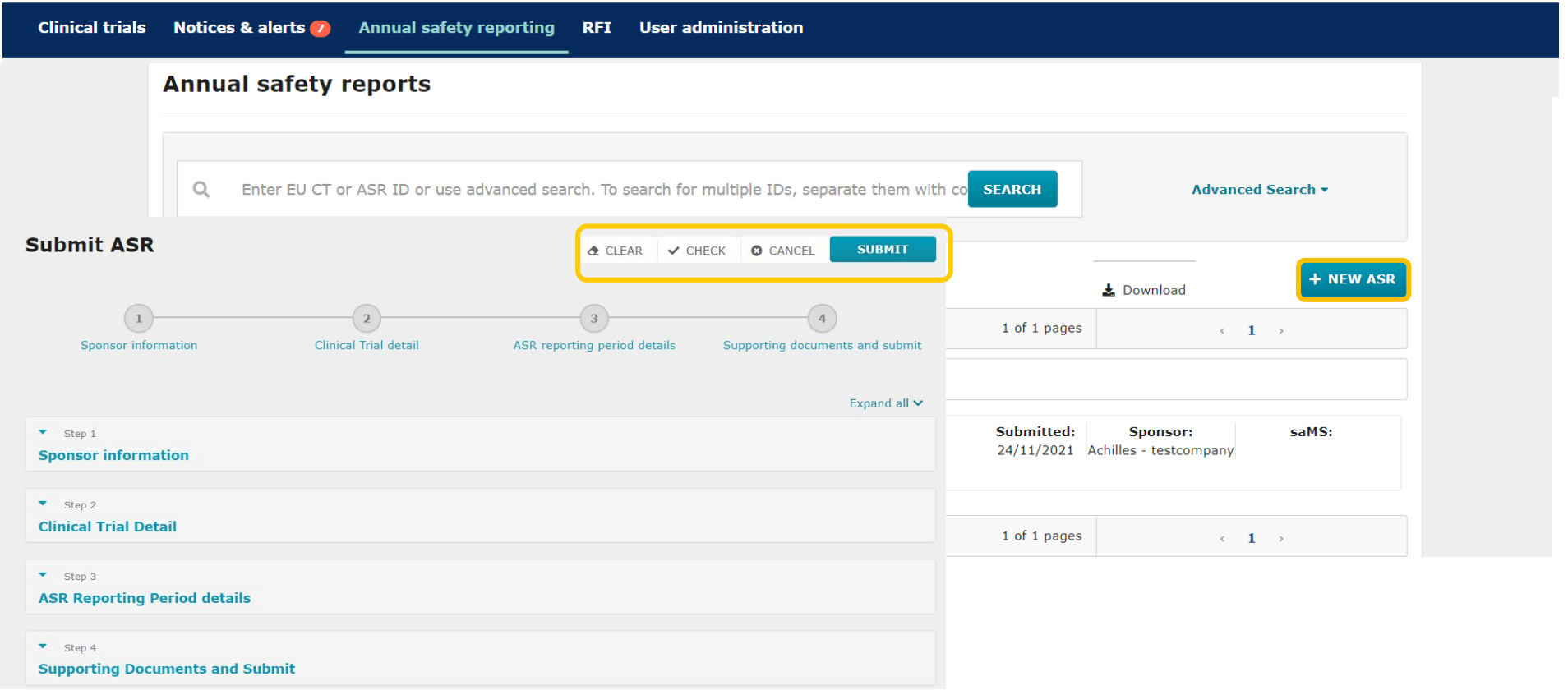
Clinical trials There is no save button; make sure you have all documents available before you start



1. Enter Sponsor Information

Step 1
Sponsor information

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Organisation details of the selected sponsor

☐ This ASR is a consolidated report following a co-development agreement

Organisation responsible for the ASR submission *

Organisation name

Address

Address 2

Address 3

Address 4

Post Code

City

Country

Phone Number

Tick boxes for co-development and sponsor status (commercial)

Contact details for ASR submission

Full name *

☐ Contact or legal representative is same from sponsor

Organisation name *

Address *

Email address *

Phone Number *

☐ Are any of the sponsors or co-sponsors commercial
(Select if the sponsor or any of the co-sponsors are commercial)

Make sure all clinical trials for the IMP selected are included in ASR submission

Contact details for ASR submission +

Drop down menu provides sponsor information according to affiliation

Address details are auto-populated by selecting an organisation

Partially auto-populated if identical affiliation is selected

Phone number without interpunction

Section contact details for ASR submission shows mandatory fields when opened

2. Enter Clinical Trial Details

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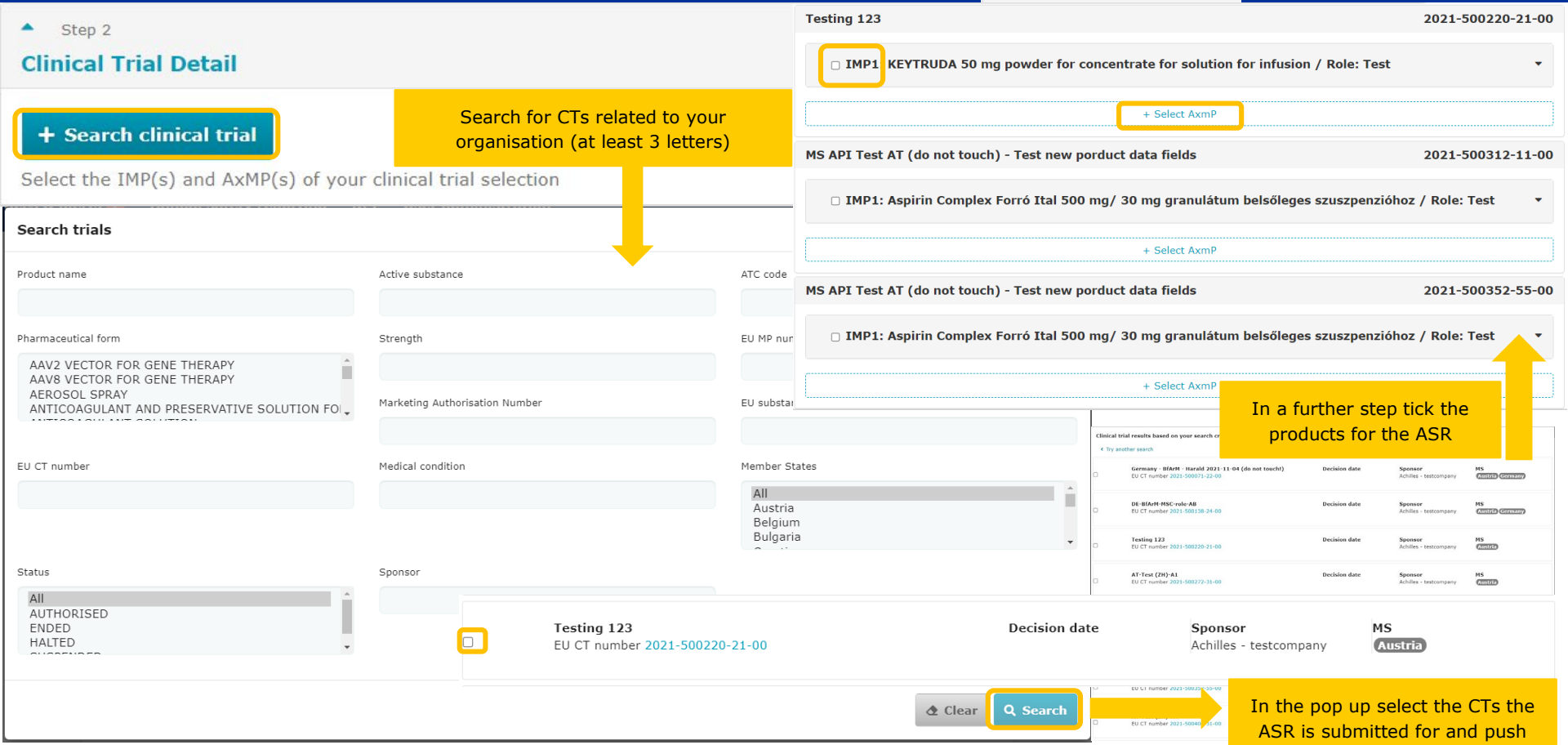

3. Enter ASR reporting period details

Step 3

ASR Reporting Period details

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Is this the sponsor's first ASR for any of the IMP(s) selected? ○ **Yes** ○ **No**

If yes, indicate which IMPs

KEYTRUDA 50 mg powder for concentrate for solution for infusion
Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szus
Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szus

Data lock point

ASR reporting period *

dd/mm/yyyy dd/mm/yyyy

No technical validation for the dates entered in the system

RSI Updated during the reporting period * ○ **Yes** ○ **No**

Substantial modification on RSI submitted and approved during the reporting period * ○ **Yes** ○ **No**

RSI changes submitted and approved in SM?

During the reporting period ASR includes *

Premature ended trial/s	Novel novel combination
Unexpected event changing benefit risk of any trial	New combination
Substantial modification of protocol or IB for risk mitigation any trial	First in class product/IMP(in EU)
Refused approval due to safety reason	Advanced therapy medicinal product (ATMP)
Serious breach safety related or impact on safety	New signals or concerns or risk for the product
Urgent safety measure	Temporary halt or suspension of any trial due to safety reason
Other	
None	

More than one information criterion can be selected

4. Upload documents and submit

Step 4
Supporting Documents and Submit

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ASR Document *

Only mandatory, single document slot, limited file size, PDF

SmPC

(if the SmPC includes RSI and not submitted as part of the ASR document)

Investigator's Brochure

multiple documents are possible for those slots (old and new version)

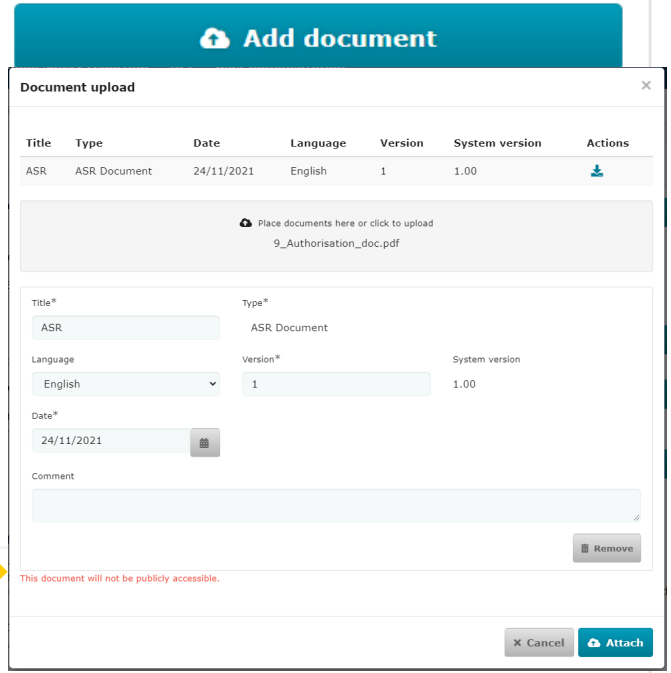
(if the Investigator's Brochure includes RSI and not submitted as part of the ASR document)

Other

Include cover letter (essential especially for transition requirements) here

Submit

Documents are not published



I, on behalf of the sponsor, confirm that the:

1. Information provided is complete
2. Attached documents contain an accurate account of the information available
3. The Sponsor, Achilles - testcompany, declares that the Annual Safety Report is prepared and hereby submitted to the Agency in accordance with Article 43 of Regulation (EU) No 536/2014 and all other applicable legal provisions.

☐ * RSI Document/.s (Old and new version where applicable)

☐ * I agree with the above statements

For submission scroll to the top of the page

CLEAR | CHECK | CANCEL | SUBMIT

Find the RFIs according to type in the RFI tab

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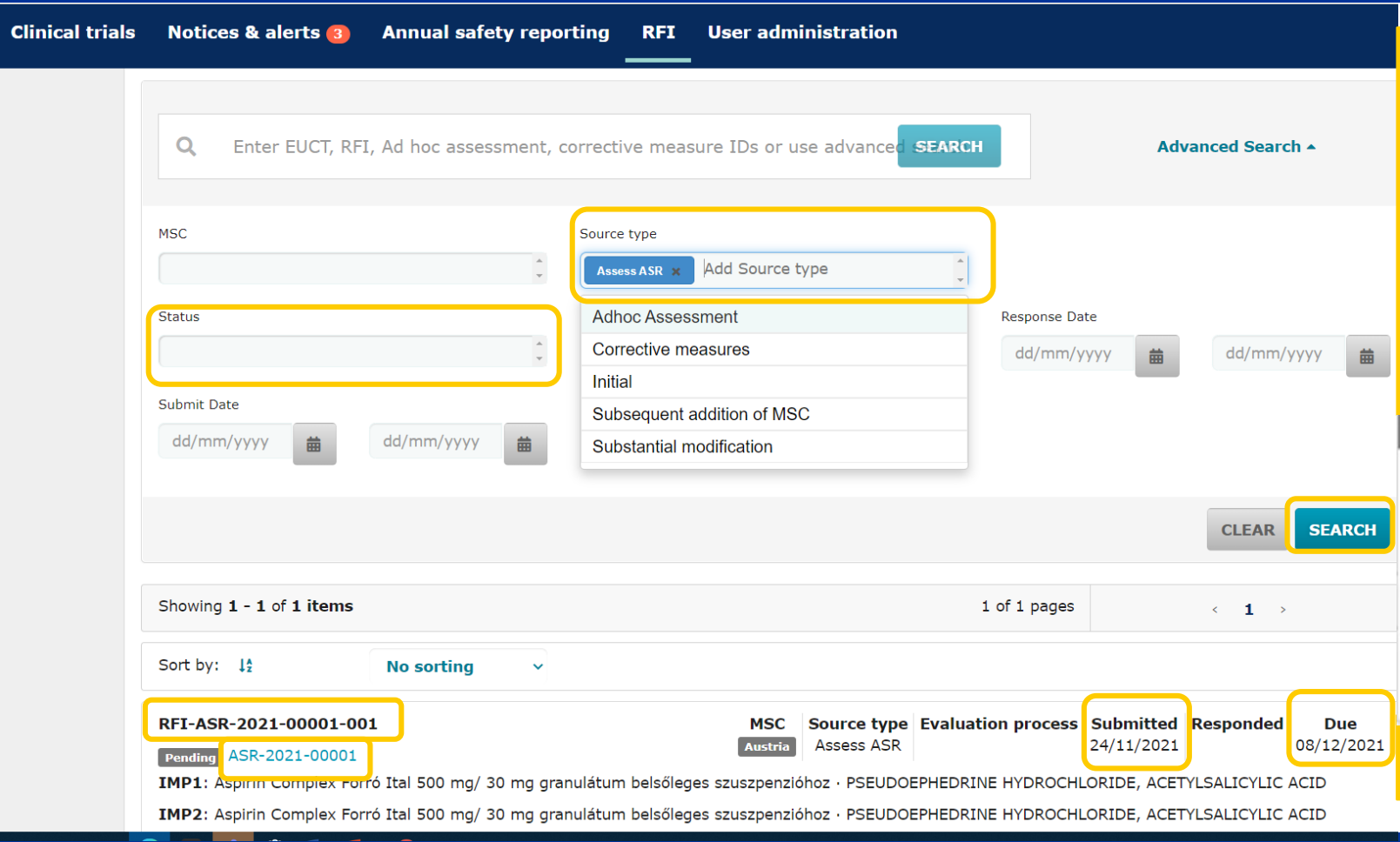
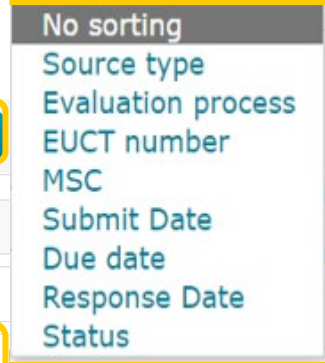


- Open RFI advanced search
  Select the RFI **source type „Assess ASR"**
- Select **status "Pending"**
- View submission date and due date
- Sort search results by many different criteria



- Click on RFI number to respond directly

Respond to the RFI and attach missing/supporting documents

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ASR-2021-00001

Achilles - testcompany

IMP: Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsé
szuszpenzióhoz, Aspirin Complex Forró Ital 500 mg/ 30 mg granu
szuszpenzióhoz, KEYTRUDA 50 mg powder for concentrate for sol
Submitted: 24/11/2021

ASR Submission | **Assessment**

Respond to RFI

REQUEST FOR INFORMATION - RFI-ASR-2021-

saMS	Submitted	Due	Responded
Austria	24/11/2021	08/12/2021	

CONSIDERATIONS

ID: RFI-ASR-2021-00001-001-01

Please explain

RESPOND

Sponsor response:

Respond to considerations directly via the chat field and add documents if needed

DOCUMENTS

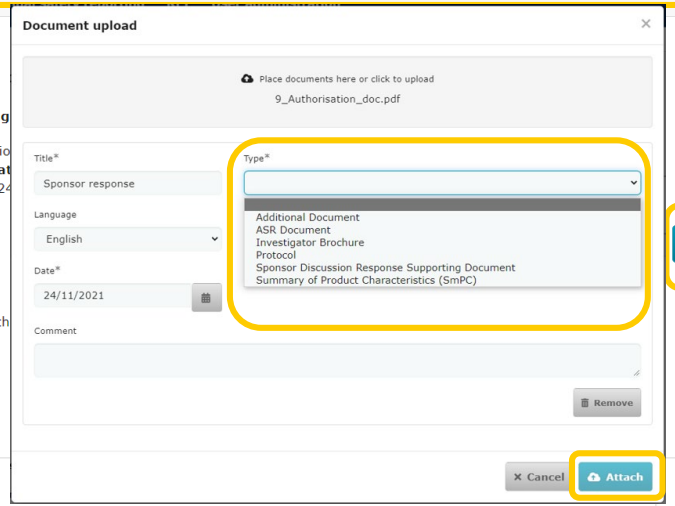
MS Documents

MS supporting

English · Additio
Submission dat
· **Version 1** · 24

Sponsor Documents

I, on behalf of the sponsor, confirm that the:
a) Information provided is complete
b) Attached documents contain an accurate account of th
c) No personal data included
☐ *I agree with the above statements



Add document

Submit

CONSIDERATIONS

ID: RFI-ASR-2021-00001-001-01

Please explain

Multiple question rounds possible if need
After satisfactory response to the RFIs the MSs finalise the assessment

RESPOND

End of assessment information available for the sponsor

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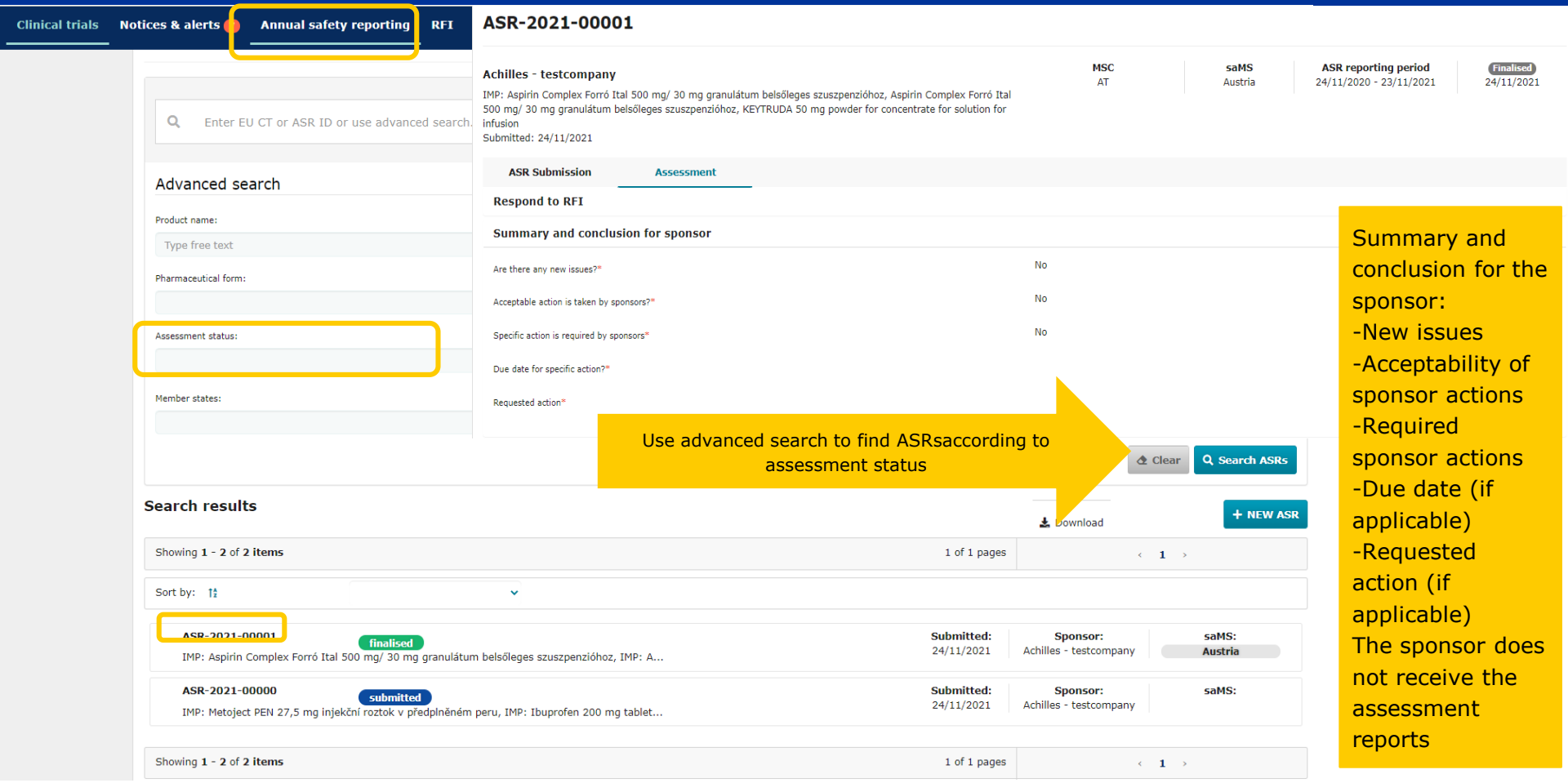

Summary and conclusion for the sponsor:
-New issues
-Acceptability of sponsor actions
-Required sponsor actions
-Due date (if applicable)
-Requested action (if applicable)
The sponsor does not receive the assessment reports

EU Network cooperation

Legal Framework: Implementing Regulation

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Article 44.2 of the CTR allows COM to set up and modify rules for cooperation in the assessment of SUSARs and ASRs. New concepts were created:

- Safety assessing Member state (saMS)
- saMS is in charge of the surveillance for a substance (all SUSARs and ASR for all trials)
- saMS develops general recommendations in relation to safety concerns
- RMS/MSC implement them if applicable to their trials via corrective measures
- Cooperation between saMS, RMS and MSCs in CTs using the same active substance
- IT support not yet fully developed
- CTFG develops internal guidance for assessment and work around to overcome missing IT support

Any questions?

Further information

emaevents@diaglobal.org (CTIS sponsor Master Trainer programme)
CT.Sponsortraining@ema.europa.eu (general queries on other (sponsor) training)

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Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

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Legal Framework: Regulation (EU) No 536/2014

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Article 42: **Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency** (abbreviated and adapted wording)

1. The sponsor shall **report electronically** all SUSARs to IMPs occurring in that clinical trial, **irrespective of location of occurrence** (in the Union or in a third country) **regardless of pharmaceutical form and strength or indication** investigated, even after the EOT.

2. The reporting period for SUSARs if **fatal or life-threatenin**g as soon as possible not later than **7 days**, if **non-fatal or non-life-threatening** not later than **15 days** after becoming aware; if initially non-fatal or non life threatening turning into fatal or life-threatening, as soon as possible not later than 7 days after this change. Where necessary submit an initial incomplete report followed up by a complete report.

3. Where a sponsor does not have the possibility to report to EV and with MS agreement it may report to the MS where the SUSAR occurred. That Member State shall report to EV.

Legal Framework: Regulation (EU) No 536/2014

Article 43: **Annual reporting by the sponsor to the Agency**

1. Regarding investigational medicinal products other than placebo, the sponsor shall submit **annually** through the database referred to in Article 40(1) to the Agency a **report on the safety of each investigational medicinal product** used in a clinical trial for which it is the sponsor.

2. In the case of a clinical trial involving the use of **more than one investigational medicinal product**, the sponsor may, if provided for in the protocol, submit a **single** safety **report** on all investigational medicinal products used in that clinical trial.

3. The annual report referred to in paragraph 1 shall only contain **aggregate and anonymised data**.

4. The obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with this Regulation. It **ends with the end of the last clinical trial** conducted by the sponsor with the investigational medicinal product.

Legal Framework: Regulation (EU) No 536/2014

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Article 44: **Assessment by Member States**

1. The Agency shall, by electronic means, forward to the Member States concerned the information reported in accordance with Article 42 and 43.
2. **Member States shall cooperate in assessing** the information reported in accordance with Articles 42and 43. The **Commission** may, by means of implementing acts, **set up and modify the rules on such cooperation**. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(2).
3. The responsible **ethics committee shall be involved** in the assessment of the information referred to in paragraphs 1 and 2, **if** it has been **provided for in the law of the Member State concerned**.

CTR Questions & Answers (Chapter 7 safety reporting)

Reference Safety information (RSI)

Reporting of AEs/ARs: Provide worldwide unique case identification number

Annual Safety Reports: Provide patient numbers in SAE tables

Safety Issues of AxMPs: authorised AxMPs to EVPM, non-authorised AxMPs to EVCTM

Safety during Transition Period of Clinical Trials Regulation (EU) No 536/2014 Implementation:

With first trial for a substance under the CTR: ASR to CTIS (name all MSCs for ongoing CTs in EU/EEA within Directive and CTR). Obligation as of CT-3 to investigators (new safety data or change in B/R) and ECs according to national legislations in MSs with ongoing CTs within Directive remains.

SUSARs to EV unless the NCA requires direct reporting. Reporting obligations as of CT-3 to investigators and ECs according to national legislations in MSs with CTs within Directive

https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf