CTIS GUIDANCE FOR SPONSORS - SPAIN -

Version 1

March 2023

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Abbreviations

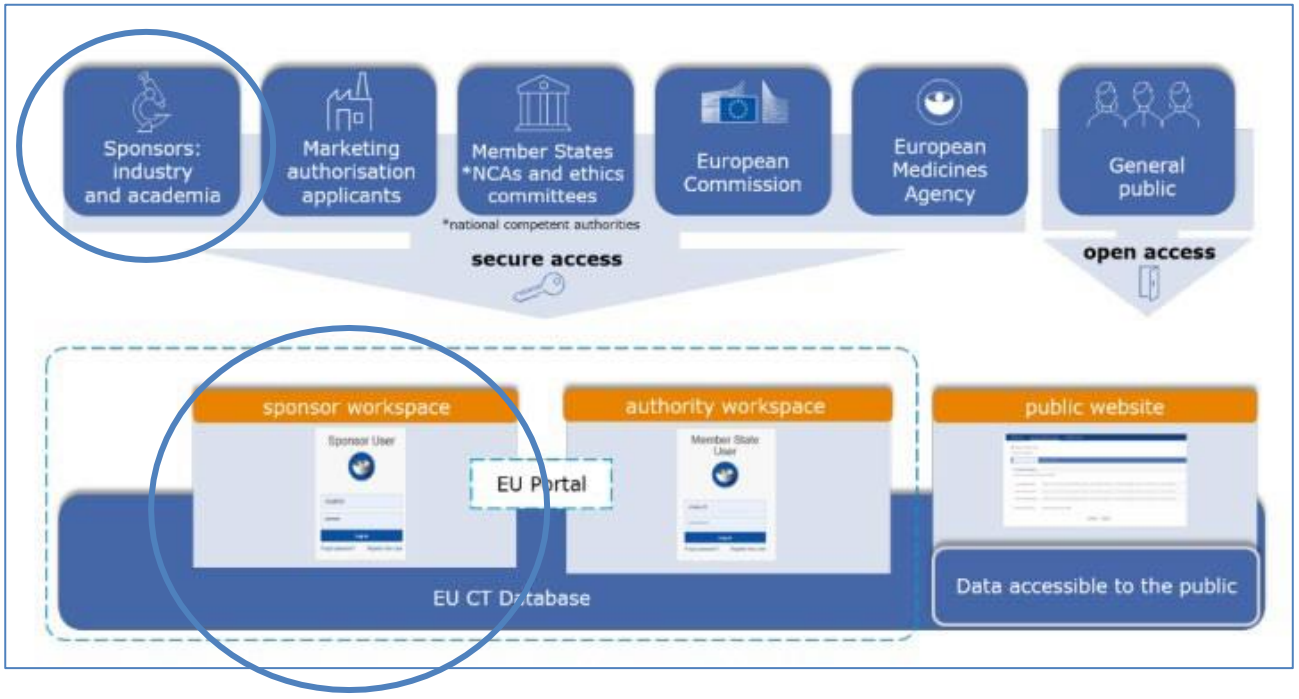
AEMPS	Spanish Agency for Medicines and Medical Devices
ASR	Annual Safety Report
AR	Assessment Report
BE/BA	Bioequivalence/Bioavailability
CT	Clinical Trial
CTA	Clinical Trial Application
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
DAR	Draft Assessment Report
EC	Ethics Committee
EMA	European Medicines Agency
FAR	Final Assessment Report
FIH	First in Humans
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MSC	Member States Concerned
NCAs	National Competent Authorities
OMS	Organisation Management System
PK/PD	Pharmacokinetics/Pharmacodynamics
RFI	Request for Information
RMS	Reporting Member State
RSI	Reference Safety Information
SM	Substantial Modification
SmPC	Summary of Product Characteristics
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction

1. Introduction

The Clinical Trials Regulation (Regulation (EU) No 536/2014) came into application on 31st January 2022 and submission of clinical trials with medicinal products shall no longer be submitted through the ECM Portal; submission has instead to take place via **Clinical Trial Information System (CTIS)**. CTIS is the single-entry point for submitting clinical trials information in the EU, which is stored in the system. All communications, including final decision from the authorities, is received via CTIS. With CTIS, sponsors can apply for clinical trial authorisation in multiple EU/EEA countries with a single application.

CTIS is structured in two restricted and secured workspaces, only accessible to registered EMA account users, and a website with open access to the general public:

- The **sponsor workspace**, accessible to commercial and non-commercial sponsors. It supports the preparation, compilation and submission of clinical trial data for its assessment by Member States.
- The **authority workspace**, accessible to national competent authorities, ethics committees, the European Commission, and the European Medicines Agency (EMA). It supports the activities of Member States and the European Commission in assessing and overseeing clinical trials.
- The **public website**, accessible to patients, healthcare professionals, scientists, clinical research associations, media, and members of the public. It supports the open access to clinical trials data in the European Union, in line with the transparency goal set out in Regulation (EU) No 536/2014 (Clinical Trials Regulation, CTR).



This guidance covers the process on how to start up, complete and maintain a clinical trial application (CTA) as a sponsor, using the **trial-centric approach** or **the organization-centric approach**, as well as management of relevant notifications and information throughout the life cycle of clinical trials.

There are two possible approaches to user management in CTIS and sponsors should carefully consider which user management approach best fits their organisation:

- **Organisation-centric approach**: intended to serve the needs of organisations and/or sponsors that run multiple clinical trials. This approach means that user management is done at organisation level.
- **Trial-centric approach:** intended to serve the needs of small organisations and specifically academic

sponsors, which may initiate trials on an ad-hoc basis. It allows the management of a smaller number of users and one or very limited numbers of clinical trials. This approach allows a faster process (no need for registration of a high-level sponsor administrator) when submitting a first initial, and subsequent application. Further allocation of other CT Administrator (CT Admin) roles or business roles is assigned to users at the clinical trial level. The CT Admin can manage users only for the particular trial(s) of his/her concern and can perform all sponsor business activities in CTIS related only to the particular trial.

For further information regarding management of users and organisations in CTIS, please see the Handbook for clinical trials sponsors and this video.

This guidance is based on and can be used as a supplement to the following CTIS training guides from EMA:

- Clinical Trials Information System (CTIS) - Online modular training programme
- Clinical Trials Coordination Group (CTCG) Key Document List
- Documents published on Chapter V of EudraLex - Volume 10 - CT guidelines, with special attention to:
  - Quick guide for sponsors - Regulation 536/2014 in practice
  - Questions and Answers Document - Regulation (EU) 536/2014

How to get started for working in CTIS

In order to access the CTIS Sponsor workspace, a user will need to have an active EMA Account. If the user already uses other EMA applications (e.g. Eudralink, SPOR, IRIS, EudraVigilance, OMS or the EU Clinical Trials Database), the user already has an EMA Account and can access the CTIS Sponsor workspace using his/her existing EMA Account credentials. If the user does not have an active EMA Account, please consult these instructions on how to create a new one.

In addition, organisations must be registered in EMA's Organisation Management System (OMS). For instructions on how to register organizations in OMS, please consult this guide.

Access to CTIS

When a Sponsor User logs into the system and initiates a new CTA in CTIS, the system will automatically check if a high-level sponsor administrator has been appointed for the sponsor organisation selected (this happens in the organization-centric approach).

In case of trial-centric approach, the user will be able to proceed becoming the CT Administrator for that particular trial and can then assign other roles in the particular trial to other users also holding an EMA account.

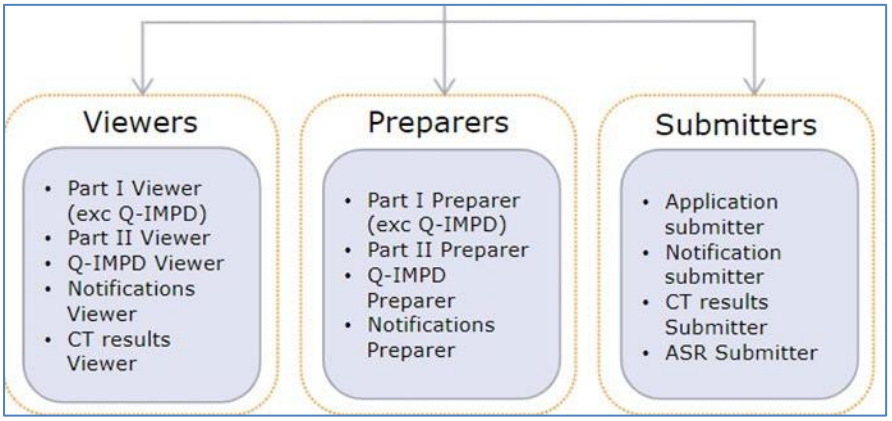
❖ **TIP:** all EMA accounts are automatically disabled after 6 months of inactivity. Prior to disabling the account, the system sends three reminders to the user (two weeks, one week and one day before the account is disabled).

To re-activate your account you will need to use the Forgot Password? process. By re-setting your

password your account will be re-activated and a notification sent to your email address. If you are affiliated to an organisation, your 'User Administrator' will also be notified that your account has been re-activated.

To find out more about how to re-activate your account reference the guidance Recover your credentials - Re-activate your account - Forgot Password?

The sponsor workspace comprises **13 different business roles**:



More information on this topic can be found in:

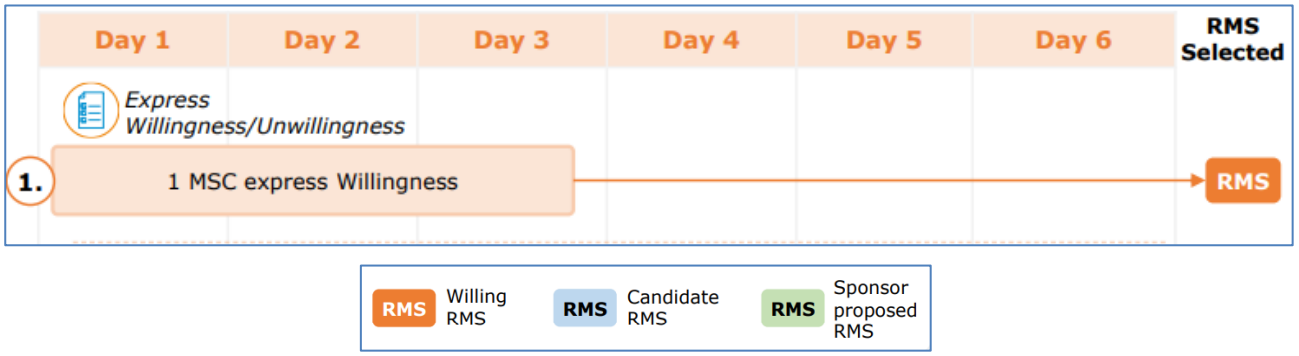
- Video and supporting materials: Step-by-step guide and Frequently asked questions (FAQs) in EMA training **Module 7**.
- For additional information concerning business roles please consult **Module 7** Roles and permissions matrix summary - Sponsors Workspace and Sponsors Business Processes and Roles.
- Academic sponsors can consult the quick guide and the step-by-step guide in **Module 19: CTIS for SMEs and academia.**

2. RMS selection process

To select the RMS between all the MSC involved in the assessment of a CTA, there are three possible scenarios:

Scenario 1: Only one MSC is willing to be RMS at day 3

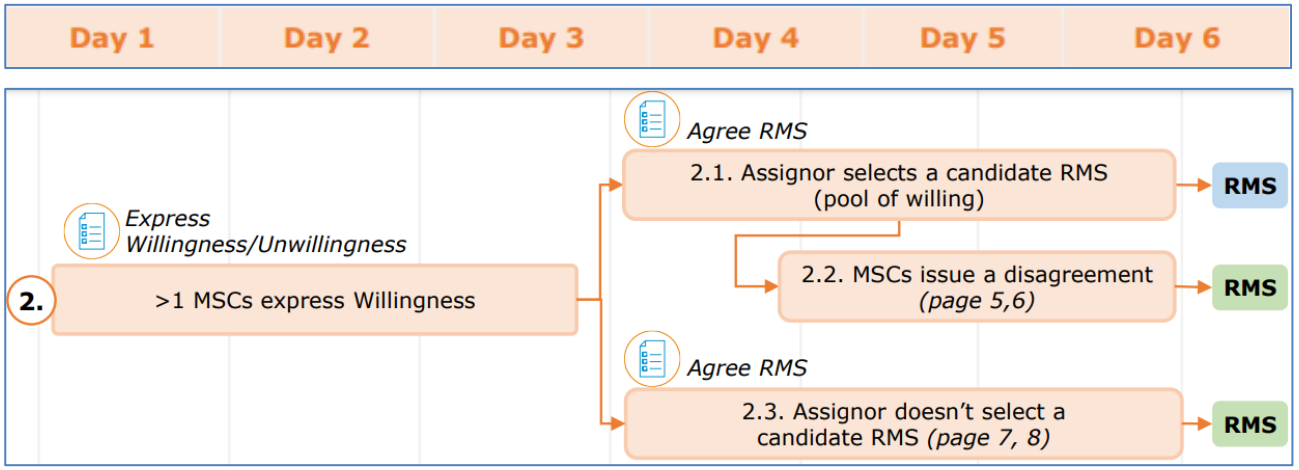
That MSC will be selected as RMS at day 3 (or even before if the task "Express willingness/unwillingness" is set as completed by the rest of MSCs).



Scenario 2: More than one MSC is willing to be RMS at day 3

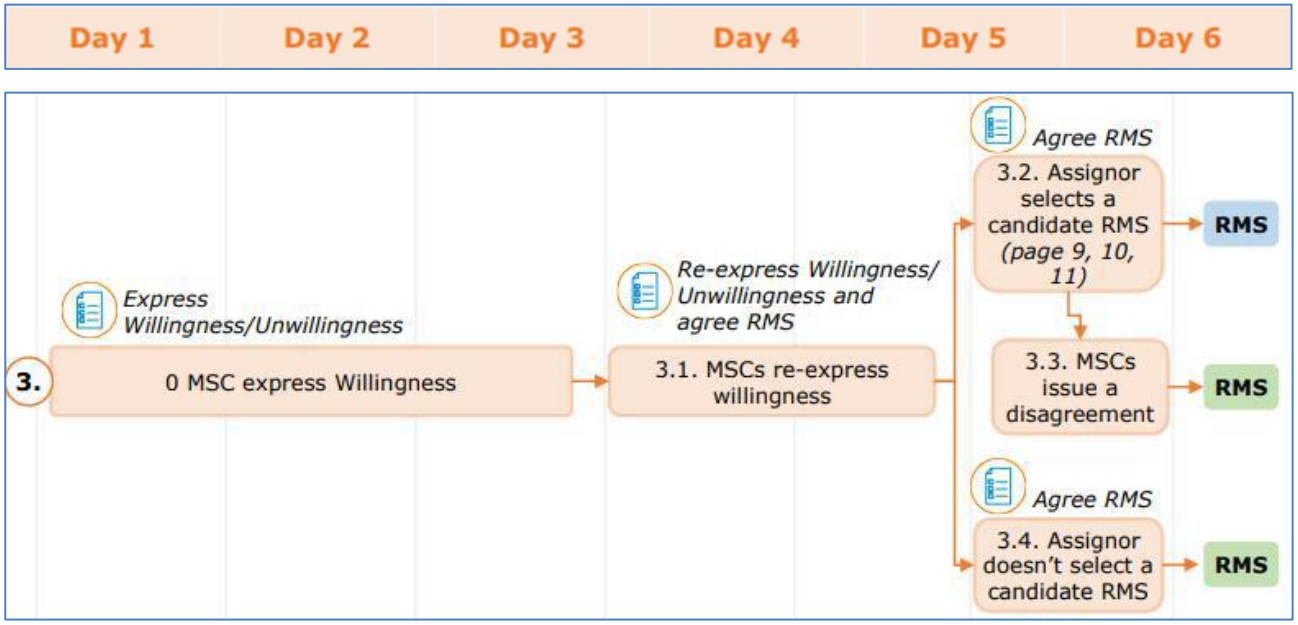
The MSC that has expressed willingness and has the lowest workload will become **assignor**:

- The assignor will select one of the MSCs (pull of willing) to be RMS at day 5. This MSC selected by the assignor is called candidate. This candidate will be appointed RMS at day 6 if there is not disagreement.
- If assignor does not select any MSC as candidate or if there is a disagreement among the MSCs, the MSC proposed by the sponsor will become RMS at day 6.



Scenario 3: No MSC has expressed willingness at day 3

In this case, at day 3 the task re-express willingness is triggered. MSC proposed to be RMS by the sponsor will become assignor. This MSC will become RMS if there is not any MSC express willingness or if there is disagreement among the MSCs.



When does the MSC proposed by the sponsor become RMS?

- It is the only willing RMS.
- More than one MSC expresses willingness but there is disagreement among MSCs.
- None of the MSCs wants to become RMS.

For further information on this topic, please see Step-by-step guide in **Module 6**.

3. How to create and submit an initial Clinical Trial Application (CTA)

Before creating a CTA which involves Spain, **the sponsor must select an Ethics Committee** in Spain between those which figure in the list that can be consulted in the AEMPS website. This Ethics Committee has to agree to assess the CTA on the submission date, whether or not Spain is going to be proposed as RMS. In all CTAs submitted through CTIS, the sponsor must indicate in the cover letter the selected Ethics Committee in Spain. It is important that if sponsor asks several CEIms to assess their CTA, they should inform the non-selected ones.

The cover letter must also include a list of medical devices (including in vitro diagnostic medical devices) which are to be investigated in the clinical trial but which are not part of the IMP, together with a statement as to whether the medical devices are CE-marked for the intended use or not. For specific instructions for submission of this type of applications please see Annex 1.

If the IMPs are manufactured in a hospital pharmacy service (please see Instruction document of the AEMPS for conducting clinical trials in Spain and Article 34 of the Royal Decree 1090/2015), the sponsor must indicate it in the cover letter.

For clinical trials concerning COVID-19 treatments (not vaccines), it is possible to request an expedited assessment in the context of the **Joint Action CT_CURE of the program EU4Health**. These clinical trials must involve several member states in the UE and the expedited assessment has to be requested during the CTA submission. For further information please visit website CT Cure |and AEMPS website. For any consultation on this topic please contact EU4HEALTH_CT-CURE@fagg-afmps.be.

For a better understanding of the following section, please consult EMA training material of Module 10 on how to Create, submit and withdraw a clinical trial.

Dossier for the initial application content

The content of the application dossier for the initial CTA is collected in Annex I of the CTR.

Available European templates can be found in Chapter I of EudraLex - Volume 10 - Clinical trials guidelines and available national templates can be found in the Annexes to the Instruction document of the AEMPS for conducting clinical trials in Spain located in the section “Guías” of the AEMPS website.

Language requirements for Part I documents can be found in the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines. Documents can be in Spanish for trials running only in Spain, and for which no additional member state application is foreseen.

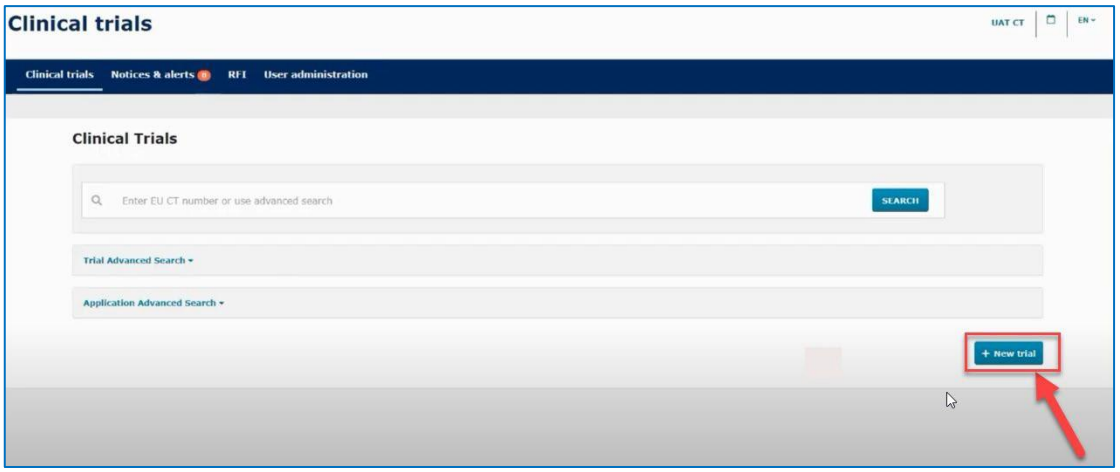
Language requirements for Part II documents are described in Table 1 of this document.

Please notice that it is acceptable to include the EU CT Number without the last two digits (2022-123456-12 instead of 2022-123456-12-00) in the documents submitted with the application. This is useful in order to prevent the necessity of updating the EU CT Number in all documents in case of resubmission, as in a resubmission the final digits change (for example, -01 instead of -00).

How to create a CTA

CTIS fields should be completed initially in English, adding the translations indicated in section 2.1 – Part I: EU application form.

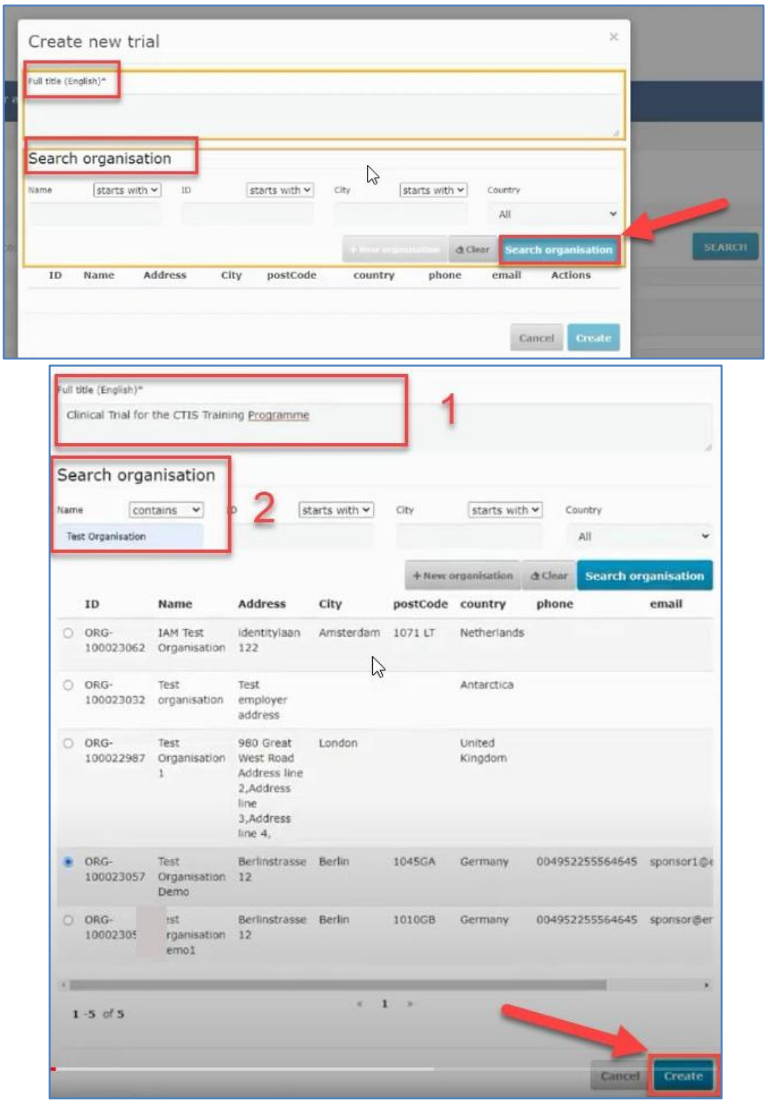
When you are logged into CTIS, click on the tab **New Trial** to create a new CTA:



In the generated pop-up, type the full title of the trial in English and indicate your organization.

- TIP: Remember to click Save on the top of the page. This should be done often as there will be no automatic saving.

This point is further explained in CTIS Training Module 10, Step-by-step guide.



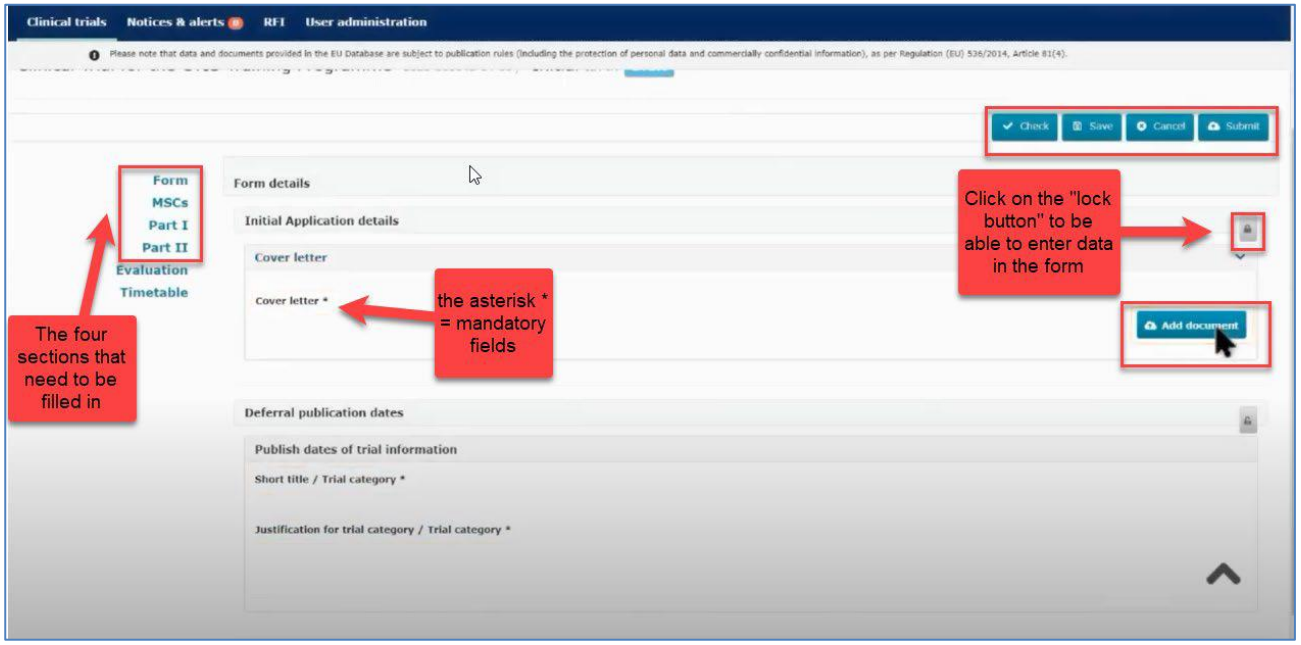
When the two fields are filled in, click on the **Create** button and the draft CTA will be created.

When creating the draft CTA, on the top right side of the screen there are four buttons:

- **Check:** Identifies the mandatory fields in the sections which have not been filled in.
- **Save:** Save the data which have been filled in up to that moment.
- **Cancel:** To cancel your application. This can only be done while your trial is an "draft" mode.
- **Submit:** Submit the application when all information is entered and it is completely ready.

❖ **TIP:** The lock button needs to be **locked** to enter data. Remember to unlock after uploading data in each section. Save the data before going to the next section.

The four different sections of the application which needs to be filled in with data and documents are: **Form, MSCs, Part I** and **Part II.**

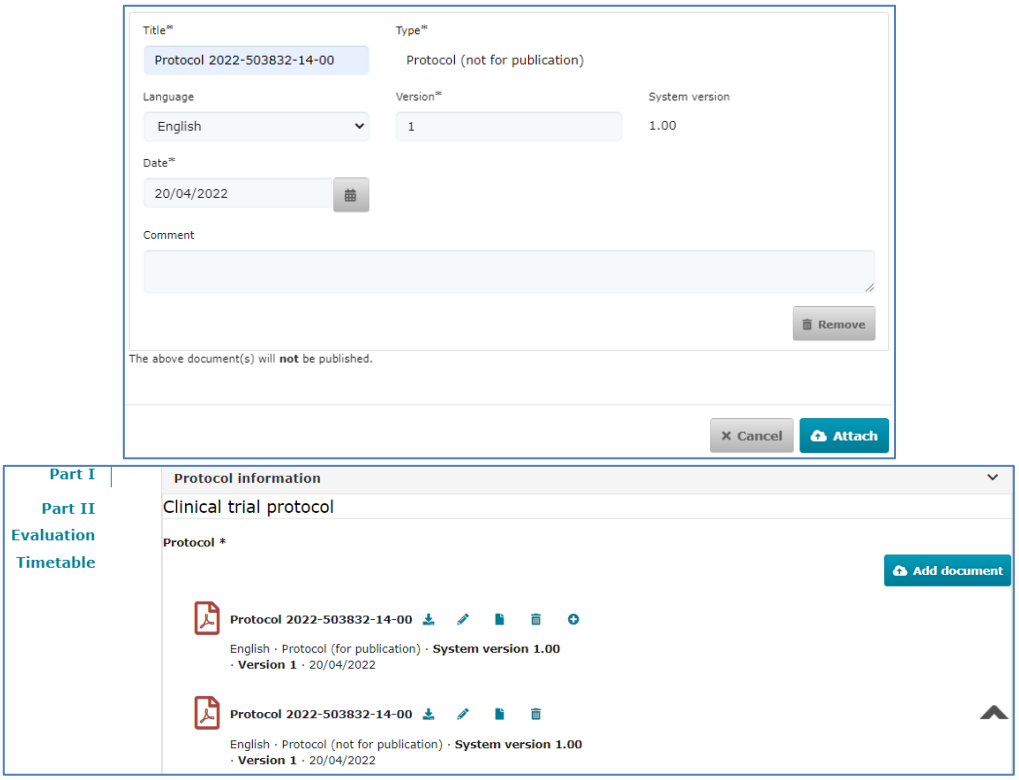


In CTIS it is possible to upload two versions of the same document: one **for publication** (it will be public, and it should not contain confidential or personal data → redacted) and other one **not for publication** (unredacted)**.**

By default, the first uploaded version is **"For publication"**.

Because of that, sponsor will have to upload the redacted version (for publication: without personal or confidential data) first. After that, the unredacted version (not for publication) has to be uploaded using the

tab “Add”. Title (“Title” field in CTIS) must be the same in both versions of the document.



❖ **TIP:** The **Check** button can be used to validate for missing sections at all times during completion. The **asterisk*** in CTIS indicates mandatory fields to be filled in or mandatory upload of documents.

Form

- Cover letter (section B in Regulation Annex I) containing a reference to the selected Ethics Committee in Spain, a list of medical devices investigated in the CT and an indication if the IMPs are manufactured in a hospital pharmacy service.
- Compliance with Regulation (EU) 2016/679: Template available in Eudralex Volume 10 (R)
- Proof of payment (Q). Unique fee applies either if Spain acts as RMS or as MSC.
- Deferral publication dates: section where the sponsor has to establish the trial category (in relation with transparency rules) and possible deferrals. See the Draft guidance document on how to approach the protection of personal data and commercially confidential information in documents uploaded and published in the Clinical Trial Information System (CTIS).

Add the cover letter and category of the trial in relation with transparency rules. To select the trial category you must use the drop down menu. The category can be from 1 to 3. Thereafter you need to add the “justification for the trial category”.

Available video on this topic in EMA training module 10: Training video: Fill in the Form and the MSC sections.

The “deferral publication dates” section must only be filled in if the sponsor has applied for a deferral date of the publication of the documents in the application.

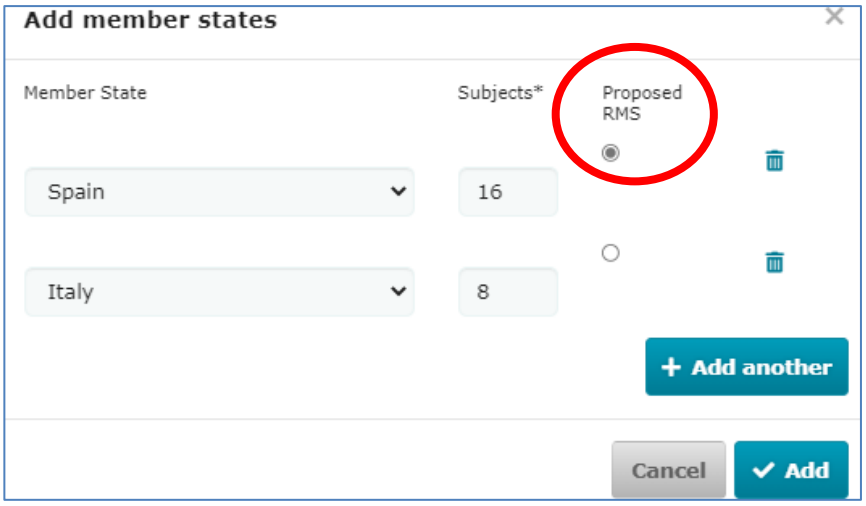
In the following table the different categories and possible deferrals are shown in relation to the different types of structured data and documents contained in CTIS (please see also EMA’s Appendix, specially points 4.3.3 and 4.3.4):

Grouping	Category 1 FIH, PK/PD, BE/BA, Bio similarity	Category 2 Phase II and III	Category 3 Phase IV Low interventional CT
• Main Characteristics	Publication of final **summary of results**		
• Notifications	Publication of final **summary of results**		
• Subject information sheet	Up to **7 years** after the end of the trial in EU/EEA	Up to **5 years** after the end of the trial in EU/EEA	
• Protocol	Up to **7 years** after the end of the trial in EU/EEA	Up to **5 years** after the end of the trial in EU/EEA	Publication of final **summary of results**
• IMPD S&E sections and Investigator Brochure	Up to **7 years** after the end of the trial in EU/EEA	Up to **5 years** after the end of the trial in EU/EEA	Publication of final **summary of results**
• Responses to RFI	Up to **7 years** after the end of the trial in EU/EEA	Up to **5 years** after the end of the trial in EU/EEA	Publication of final **summary of results**
• Clinical trial results summary for an intermediate data analysis	1. 12 months after interim analysis date 2. up to **30 months** after the end of the trial in the EU/EEA		
• Clinical trial results summary and lay person summary	1. 12 months after the end of trial date in the EU/EEA 2. Up to **30 months** after the end of trial in the EEA		

Table 2. Trial categories and deferrals information

MSCs

Member states concerned. Add the countries (member states) where the trial application should be submitted, and the number of subjects that are expected to participate in each country. If there are more than one country participating in the trial, sponsor have to propose a country as RMS, which is the country that will be responsible for the overall scientific assessment.



Available video on this topic in EMA training module 10: Training video: Fill in the Form and the MSC sections.

Part I

- EU Application form (C): data entered directly in CTIS.

  According to transparency rules, a translation into Spanish of the fields to be published in REEC (Spanish Clinical Studies Registry) shall be included: Title, investigated disease, objectives, endpoints and inclusion and exclusion criteria.

- Protocol (D)
- Patient facing documents linked to the CT endpoints shall be provided together with the protocol in part I of the CTA (D14 and D17l)
- Protocol synopsis (D.24): it must content all the information described in question number 5.8 of the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines. Spanish version of the protocol synopsis is required.
- The two pages requirement is only orientative. Sponsors should consider to make the synopsis understandable to a layperson. If a lay person version is created by sponsor, only this version is to be submitted.
- Charter of the Data Safety Monitoring Committee, if applicable (D.23)
- Investigator's Brochure/Summary of Product Characteristics (E)
- Documentation relating to compliance with good manufacturing practice for the IMP (F)
- IMPD quality, safety and efficacy/Simplified IMPD with reference to the valid SmPC (G)
- Auxiliary medicinal product dossier (H)
- Scientific advice and paediatric investigation plan (PIP) if available (I)

- Content of the labelling of the IMPs in local languages (J)

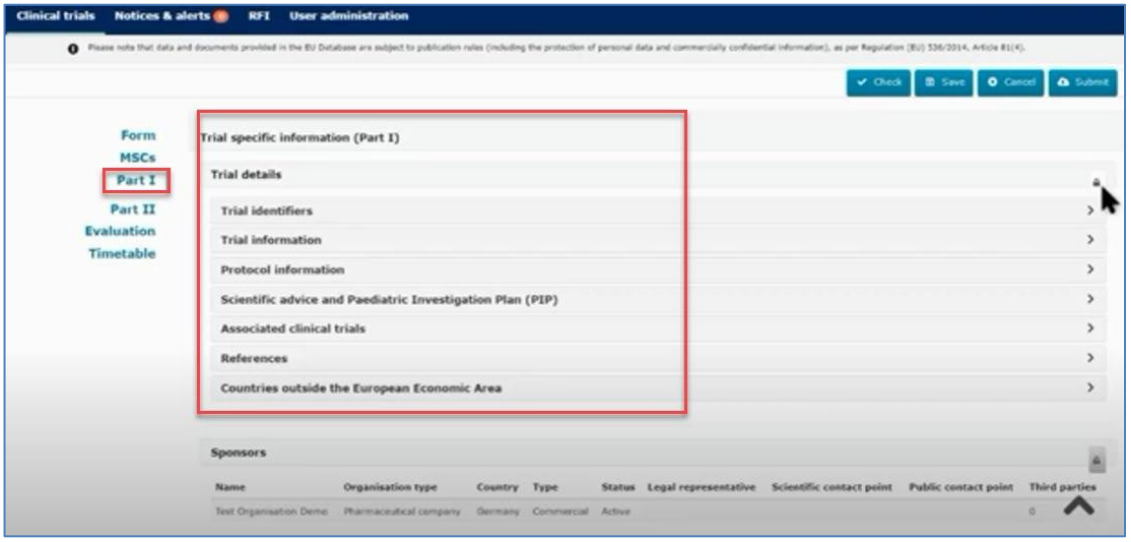
Fill in the Part I section

Available videos on this topic in EMA training module 10:

- Training video: Fill in the Part I section
- Training video: Fill in the trial details of Part I section
- Training video: Fill in the Sponsor details of Part I section
- Training video: Fill in the Product details of Part I section

Trial details

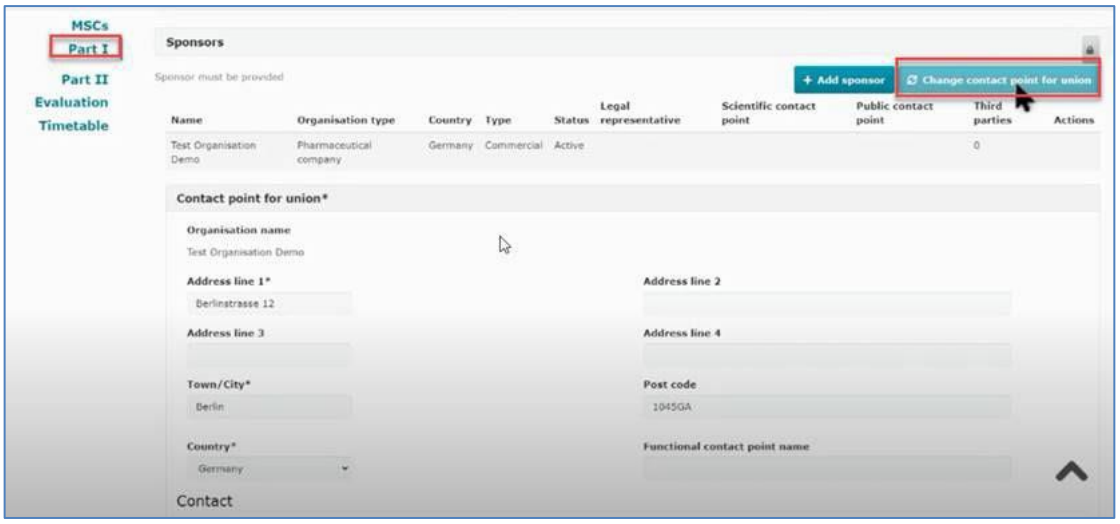
Medical condition, trial objective, inclusion and exclusion criteria, end points, trial duration, population of trial subjects and upload of protocol.

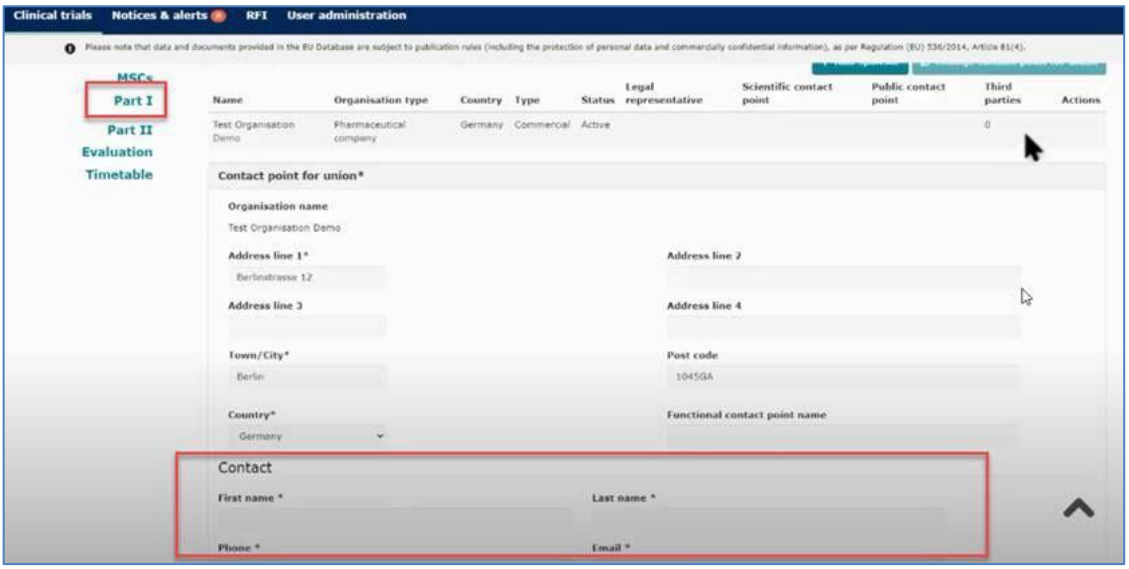


Sponsor details

Includes sponsor information which was added when the application was first created. All these contacts must also be registered in OMS. This information is not registered directly in CTIS but it is retrieved from OMS.

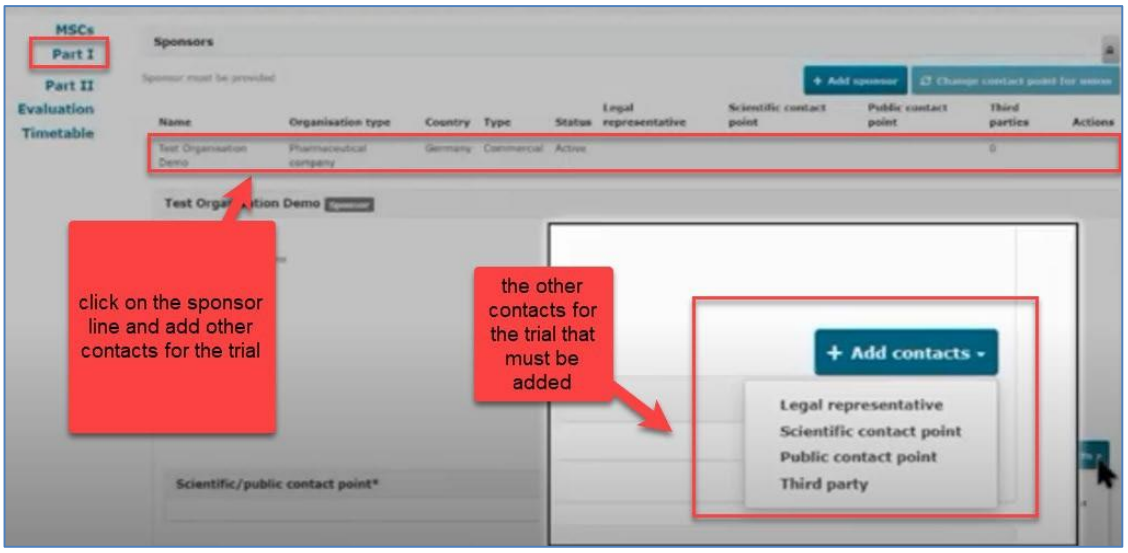
At first, contact point for union must be added. This person will be the contact point for sponsor. AEMPS will contact this person for urgent issues (e.g. if Ethics Committee has not been defined in the cover letter).





Click on the sponsor line and add:

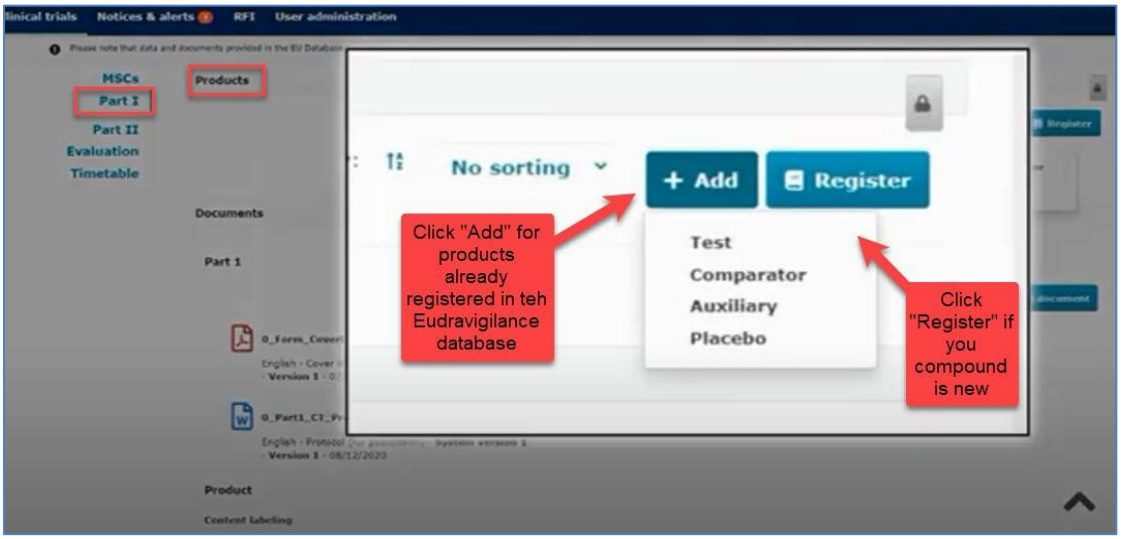
- Legal representative: an EU contact that only needs to be added if sponsor is located outside EU.
- Scientific contact point and public contact point: they must be added for all trials and they can be the same person.
- Third party (only if tasks or functions in the trial have been delegated to third parties). This is e.g. monitoring (the GCP unit) or laboratory facilities. All third parties must be registered in OMS.



❖ TIP: The full information (inlcuding Legal representative, scientific contact point and third parties) on section Sponsors will not be visible until the user clicks on the Sponsor line.

Product details

Information on the medicinal products used in the trial must be added. If the products have a marketing authorisation you need to click on the “Add” tab. Select the role of the product. It is mandatory to include at least one test product (investigational medicinal product (IMP)) in the application.



The Investigator’s Brochure (IB) or the SmPC, contanining the reference safety information (RSI) must also be uploaded.

According to the Article 67 of the CTR, the labelling must also be uploaded except in case the IMP has a marketing authorization, it is used according to its authorization and the clinical trial is not blinded.

All documents uploaded for the Part I can be found at the end of the section, in subsection “All documents”.

Part II

Section in CTIS (section in Regulation Annex I)	European template (Eudralex vol10, Chapter I)	Spanish template (AEMPS, Annexes to Instruction Document)	Accepted template	Accepted language	Need for signature
Recruitment arrangements (K)	Recruitment and Informed consent procedure template	No specific template for recruitment arrangements available	European template	Spanish or English	No
Subject information and informed consent form (L)	Not available	Annex VIIIA, which includes instructions for personal data protection section in its Appendix 1 Annex VIIIB	Spanish Annexes	Spanish	No
Suitability of the principal investigator (M65 and M66)	Investigator CV template Declaration of Interest template	Not available	European templates Investigator CV must be uploaded in CTIS subsection "Investigator CV*". CV must have been updated within the previous two years. It is not mandatory to indicate the EU CT Number in the CV. DoI must be uploaded in CTIS subsection "Suitability of the investigator". DoI must have been updated within the previous year. DoI submission is mandatory, whether or not there is a conflict of interests.	Spanish or English	No

Section in CTIS (section in Regulation Annex I)	European template (Eudralex vol10, Chapter I)	Spanish template (AEMPS, Annexes to Instruction Document)	Accepted template	Accepted language	Need for signature
Suitability of the facilities (M64 and N)	Site suitability form template	Annex IV	European template or Spanish Annex IV	Spanish or English	Yes
Proof of insurance cover or indemnification (O)	Not available	Annex VA Annex VB Annex VI in cases where the waiver to present the insurance within 30 days after the CT authorisaton applies, as per art. 9.3 of Royal Decree 1090/2015 Annex VII	Spanish Annexes	Spanish	No
Financial and other arrangements (P)	Compensation for trial participants	Financial budget according to Instruction Document's specific section	Financial budget according to Spanish instructions. European template for compensation for trial participants is acceptable.	Spanish or English	No
Compliance with national requirements on Data Protection	Not available. There is a Template statement on compliance Regulation (EU) 2016/679 to be uploaded in CTIS section "Form"	Covered already in Appendix 1 of Annex VIIIA	Spanish Annex VIIIA. To be uploaded only in CTIS subsection "Subject information and informed consent form"	Spanish	No

Section in CTIS (section in Regulation Annex I)	European template (Eudralex vol10, Chapter I)	Spanish template (AEMPS, Annexes to Instruction Document)	Accepted template	Accepted language	Need for signature
Compliance with use of Biological samples	Compliance with applicable rules for biological samples template	Annex XIII, which is the European template including a paragraph referent to Spanish legislation in section 5.1	Spanish Annex XIII	Spanish or English	No

Table 1. Spanish requirements for part II documents.

Requirements for part II documents for each MSC will be collected in a single point that will be available in EMA Website. When available, we will provide the link for access to this information.

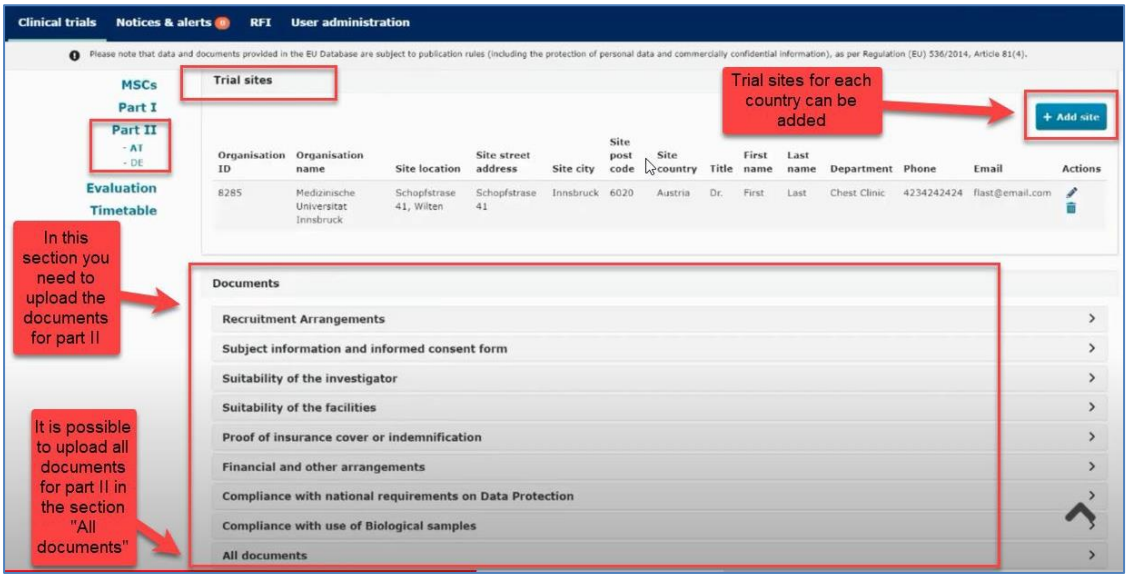
When uploading documents in CTIS be aware not to use date and version in the file name on your documents as this will be transferred to the "Title field" in CTIS and that "Title" will be the same during the entire life cycle of the clinical trial even if there are substantial modification updates. In any case, you can rename your documents in CTIS after upload.

For instructions on filling the field "Title" when uploading documents in CTIS, please see the Best Practice Guide for Sponsors of document naming in CTIS. It can be found in the CTCG Key Documents List. Names of documents on sponsors files can follow sponsor's SOP.

Fill in the Part II section

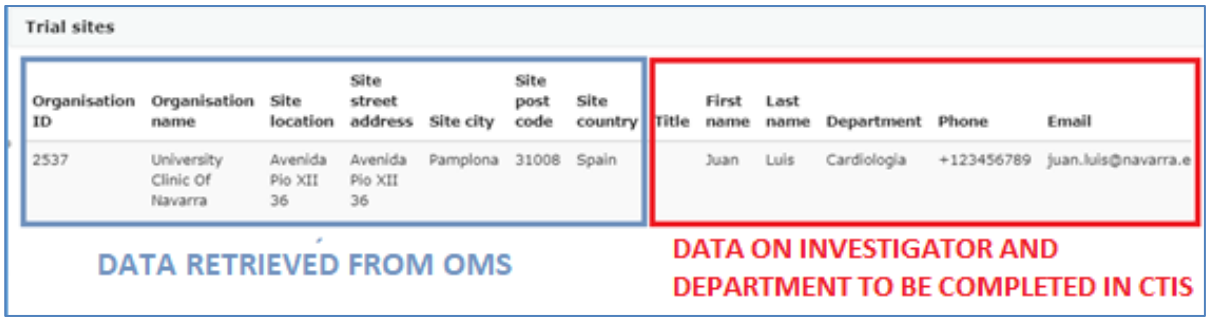
Available video on this topic in EMA training module 10: Training video: Fill in the Part II section.

Individual information for each country to be assessed by the selected Ethics Committee. Part II documentation is listed in Annex I of CTR, points K to P. For clarification about acceptable templates (Spanish vs European) for Part II documents, please see **Table 1**.



The name and address of the organisation must be registered in OMS before you can search and add the organisation (site) on the application in CTIS. If the organisation is not already part of the OMS system, the organisation must be added to OMS. This can be done by sponsor or by the organisation itself.

Information about the department and the investigator responsible for a specific clinical trial has to be registered directly in CTIS.

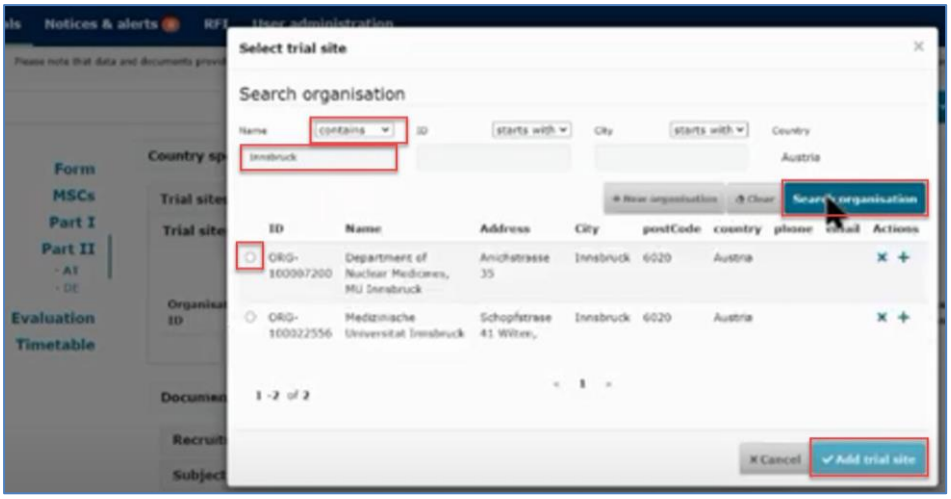


Organizations (sites) that are not included in the sites and hospitals catalogue of the National Health System can be included directly in CTIS when completing the CTA. For instruction on how to do it, please see Annex II.

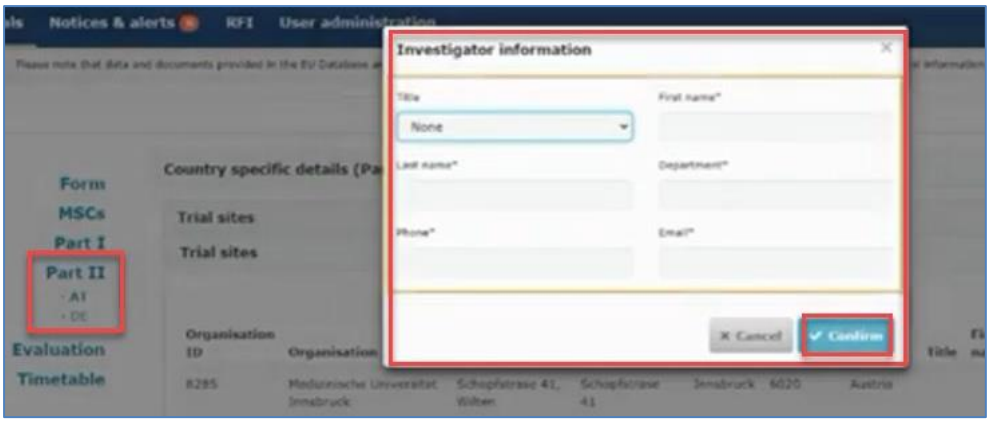
For further instructions on this topic, please see the guide How to use the Organisation Management Service (OMS) and the OMS website, when further instructions can be downloaded clicking on “Help” and on “About OMS”.

There is not a permanent connection between CTIS and OMS. CTIS takes the information from OMS at the moment the application is created, but it is not automatically updated. Sponsor will be able to update this information in CTIS with the subsequent SM submitted for the clinical trial.

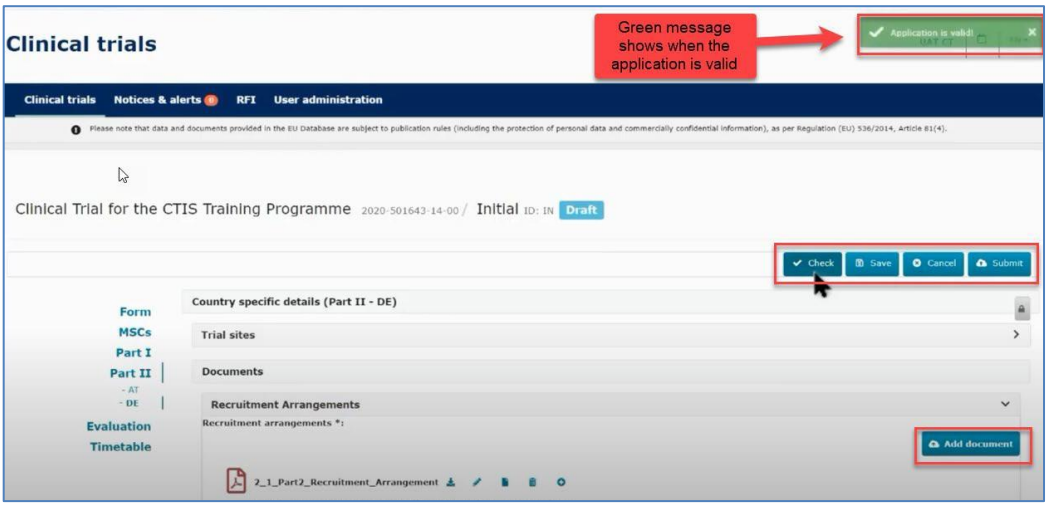
The address indicated in OMS has to be aligned with the information contained in the sites and hospitals catalogue of the National Health System.



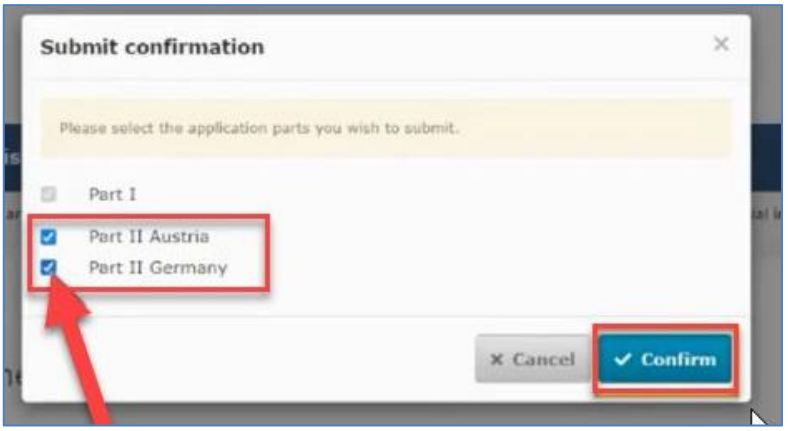
When the organisation is found via the search function, the details of the investigators must be added (first and last name, department, email address, phone).



Click on the **Save** button to save all uploaded documents and click on the **Check** to see if any documents or information are missing. The green message shows when the application is valid.



Remember to upload the Part II information relevant for each country. Part I is always included by default in the submission for all countries.



Applications limited to part I: Article 11 of the CTR

It is possible for sponsors to submit a partial application, according to Article 11 of the CTR. In these cases, CTA assessment and conclusion shall be limited to the aspects covered by Part I. After the notification of the conclusion on Part I, the sponsor may apply for an authorisation limited to aspects covered by Part II withing the next two years. Otherwise, the application on the aspects covered by Part I shall be deemed to have lapsed.

Nevertheless, this functionality is still not fully implemented and presents some disadvantages for the submission of subsequent substantial modifications (SM). With current implementation, if Sponsor needs to submit an SM once the clinical trial has been authorized in the full dossier MSCs, the sponsor needs to withdraw the application in the partial dossier MSCs in order to proceed with the SM application. Then sponsor needs to submit an additional MSC application once the SM is approved to add the MSCs previously withdrawn. As this "Workaround" brings a lot of workload for both parts (sponsor and NCAs) we recommend not to use this Article 11 until an IT solution is built in the CTIS.

For further information on this topic, please see questions 2.1, 2.2, 2.14, 3.6, 3.8, 3.9, and 4.1 of the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines, and Article 11 of the CTR.

Transition trials

If the application is for a transition trial from CTD to CTR, the Transition trial box must be checked before creating the draft CTA. In Form section, the former EUDRA CT number must be indicated in the Transition Trial subsection.

For transition trials, it is mandatory to submit the documents listed in questions 11.6 and 11.7 of the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines.

In order to harmonize document versions for a transition trial application, it is necessary to submit a previous substantial modification in each MSC. The document versions must be the same in all MSCs at the moment of submitting the transition CTA trough CTIS, even if the differences between versions are non substantial. For this reason in some cases a version containing non substantial changes versus the previous version authorised in Spain should be submitted as a substantial modification through ECM portal before submitting the transition application in CTIS (in this case, please explain in the cover letter that the changes are non-substantial but they are neccesary to obtain an harmonized dossier for latter transition of the application to CTR/CTIS).

4. Request for Further Information (RFI)

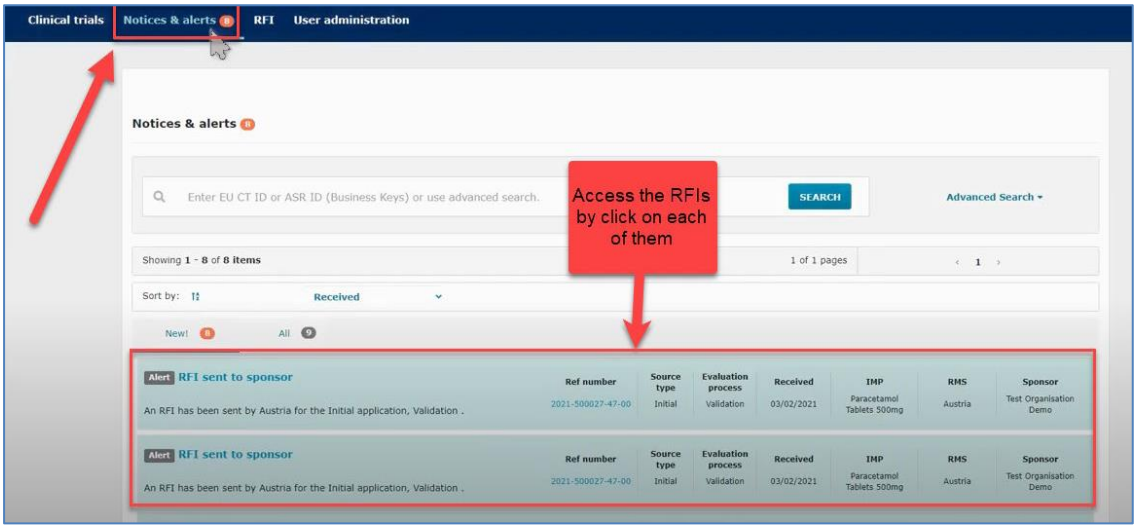
A request for further information (RFI) contains the considerations (questions or additional requirements) from authorities to sponsor. RFIs can be sent to sponsor during the validation, assessment, ASR assessment ad-hoc assessment, additional MSC applications, etc. The system is prepared for the submission of more than one RFI.

How to access and view a request for further information (RFI)

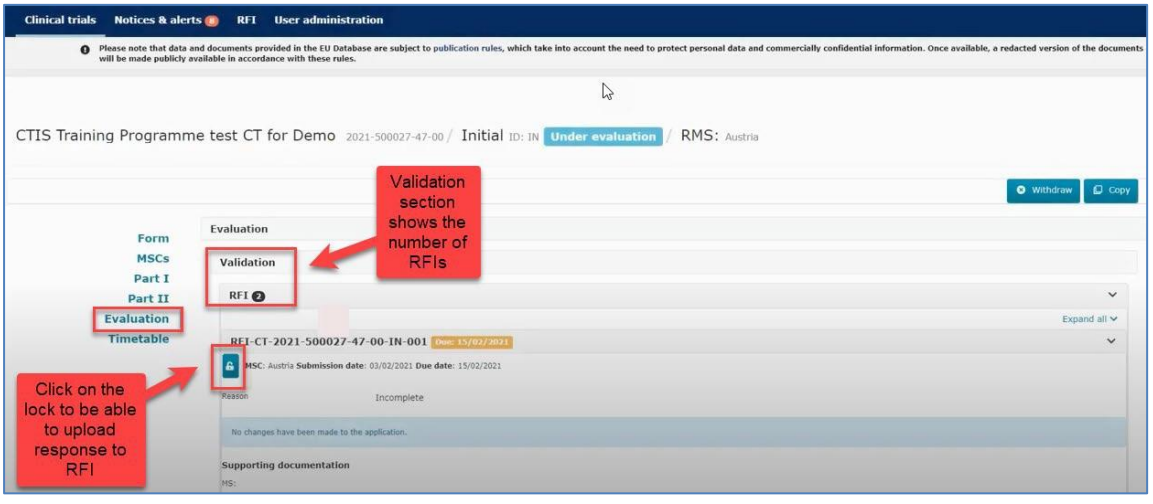
Step-by-step guide and videos on this topic in EMA training module 11:

- How to access and view an RFI in CTIS
- How to change a Clinical Trial Application as part of an RFI response
- How to respond to RFI considerations and submit an RFI response

In the sponsors workspace you will be able to see incoming RFIs in the “Notices and alerts” tab.

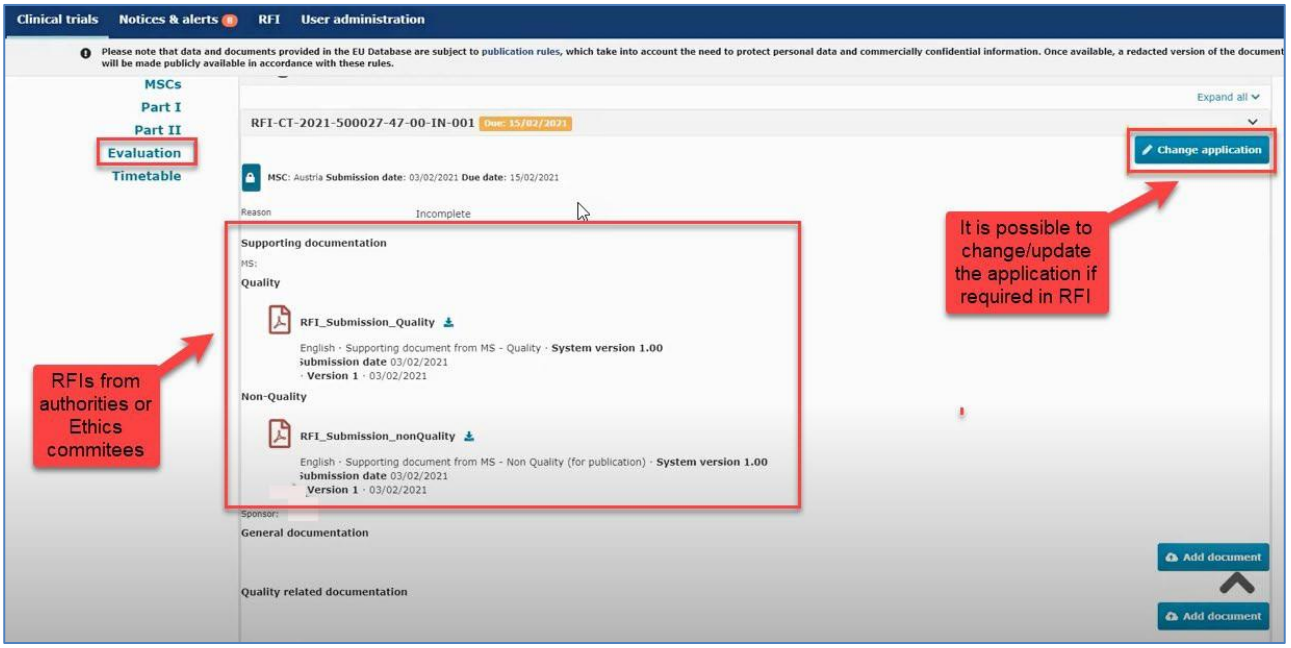


You can access the RFI by clicking on each of the alerts. They can also be accessed from the RFI tab next the “Notices and alerts” tab. Click on the RFI and you will be redirected to the “Evaluation” section where the RFI is shown.

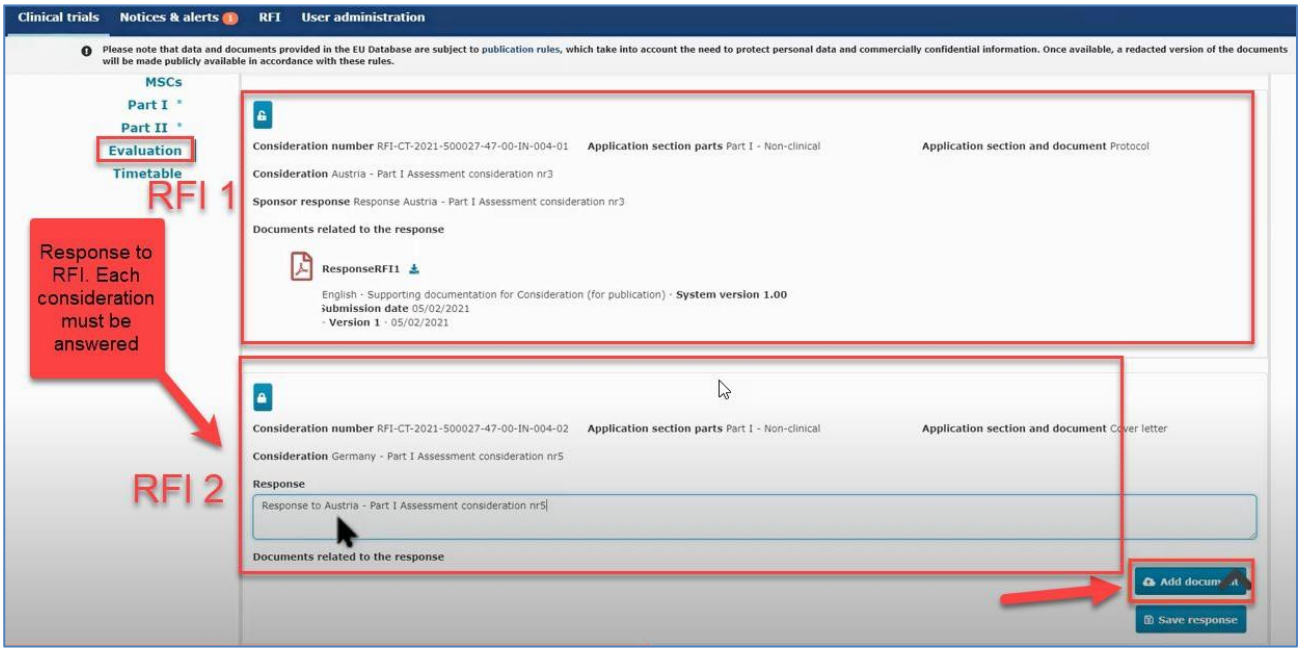


When you have clicked on the lock button you can see the documents that the authorities have attached to

the RFI. The RFI can be related to “quality” or “non quality”. Considerations and responses related to quality questions will not be subject of publication in CTIS public portal.



In the “Add document” tab you can upload supporting documentation for the RFI or for an specific consideration.

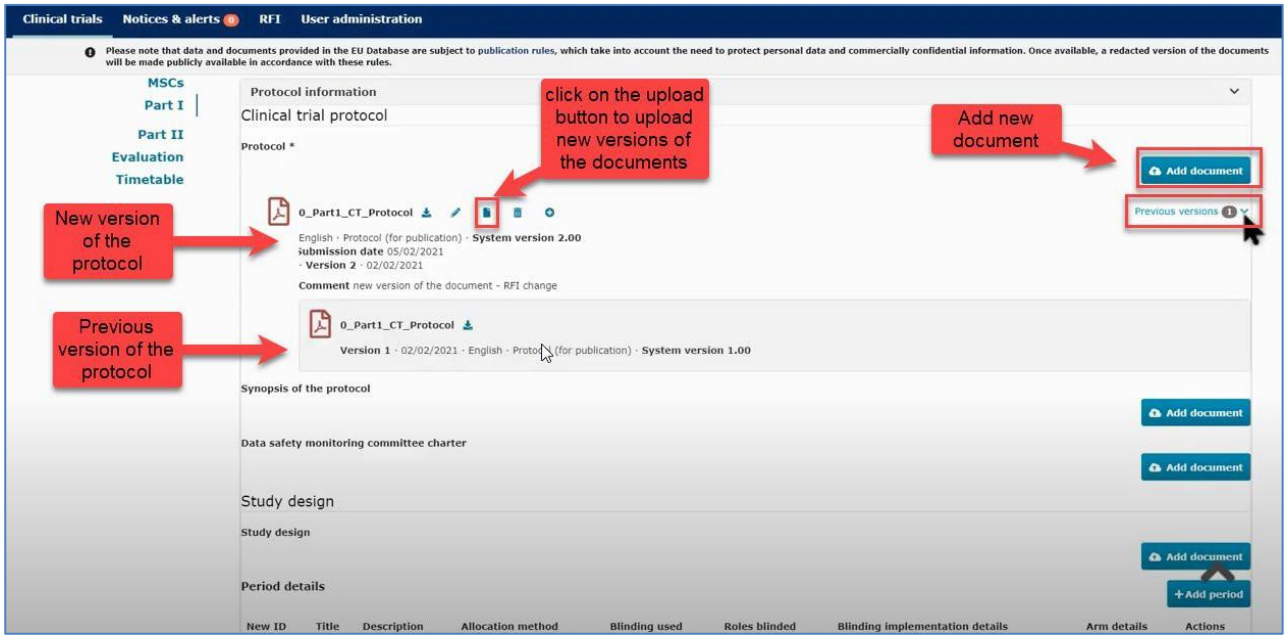


If core documents of the CTA should be updated as a consequence of a response of a RFI, the option “Change application” must be used and the updated documents must not be uploaded as supporting documentation.

How to change a Clinical Trial Application as part of a RFI response

To change the application, you must click on the change application button. Each RFI must be answered

separately. You can make changes in the sections Form, Part I and Part II.

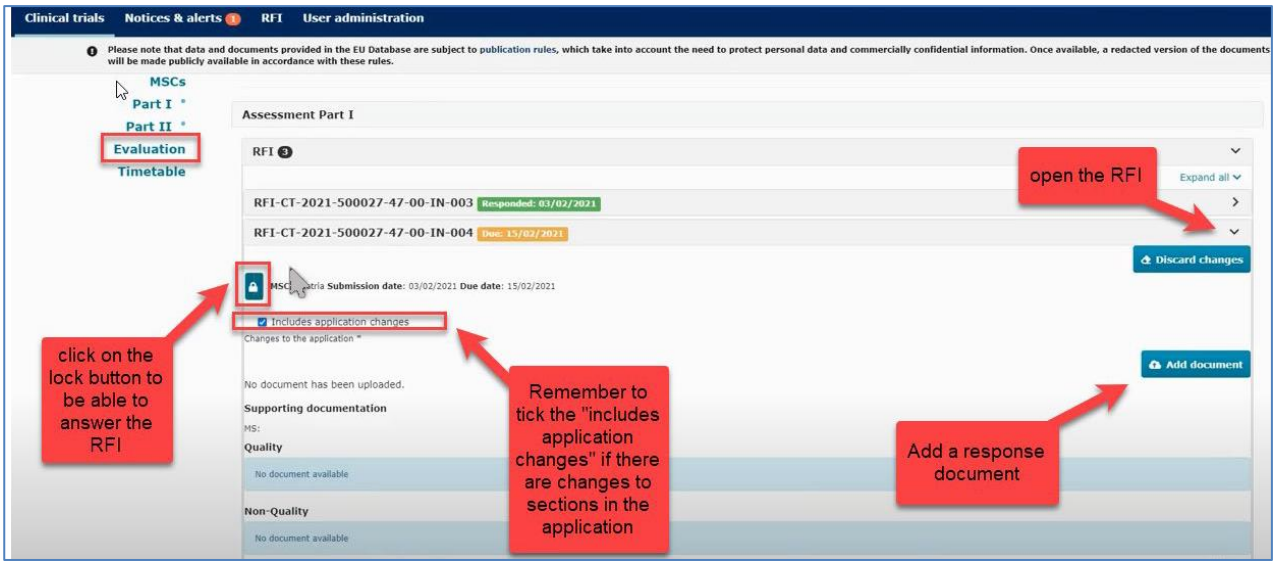


If there are RFIs from different countries concerning part II, it is necessary to make a draft application for each Part II RFI. During the assessment phase, there could be for example one RFI for Part I (all MSCs) and one RFI for Part II from each MSC.

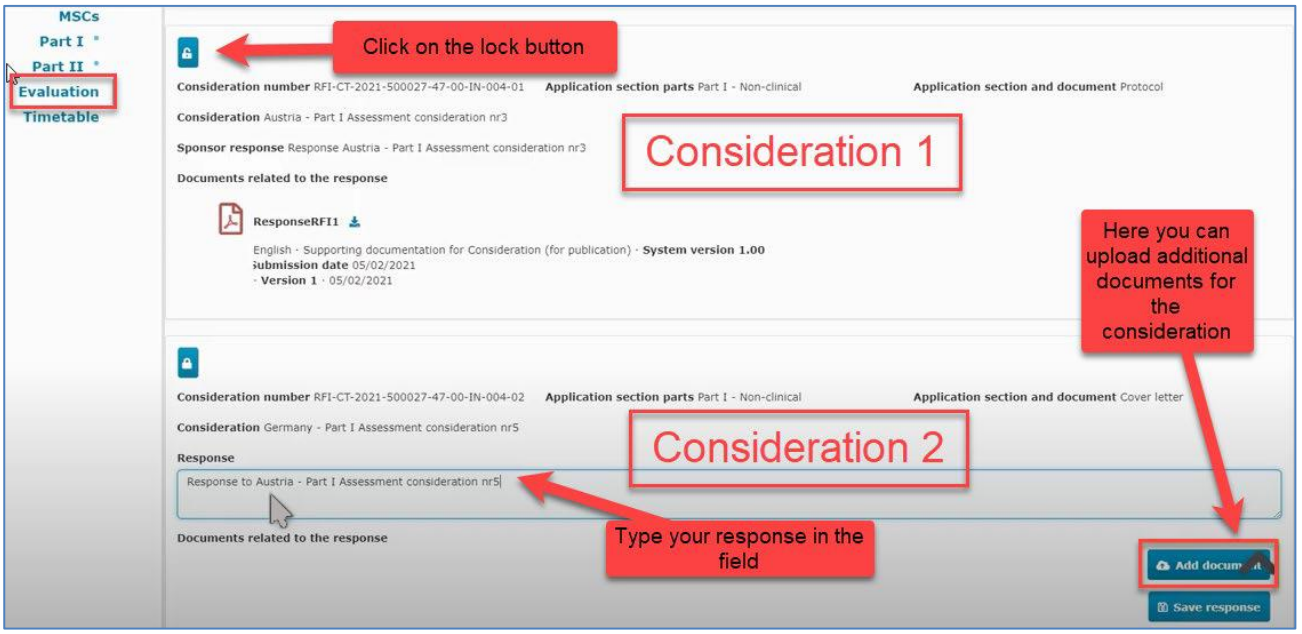
❖ TIP: Remember to unlock each section after completing the relevant information of each consideration.

How to respond to RFI considerations and submit an RFI response

Sponsor must reply to each of the RFI received from the authorities. In case of sponsor changes the application when answering the RFI, it is mandatory to upload a response document that describes the changes to the application.



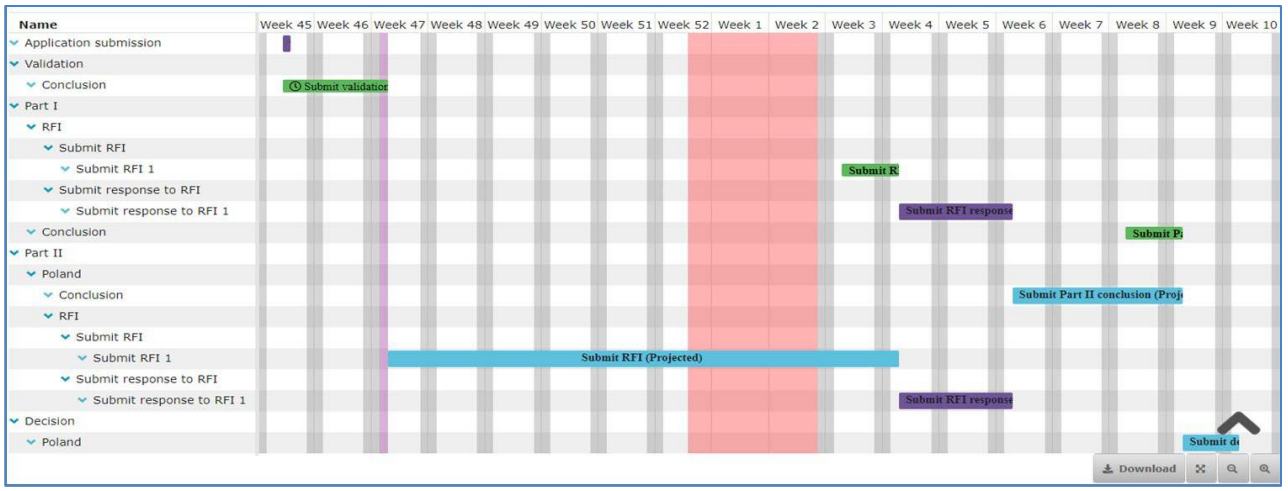
Each consideration of the RFI must be responded separately in order to be able to send the final RFI response.



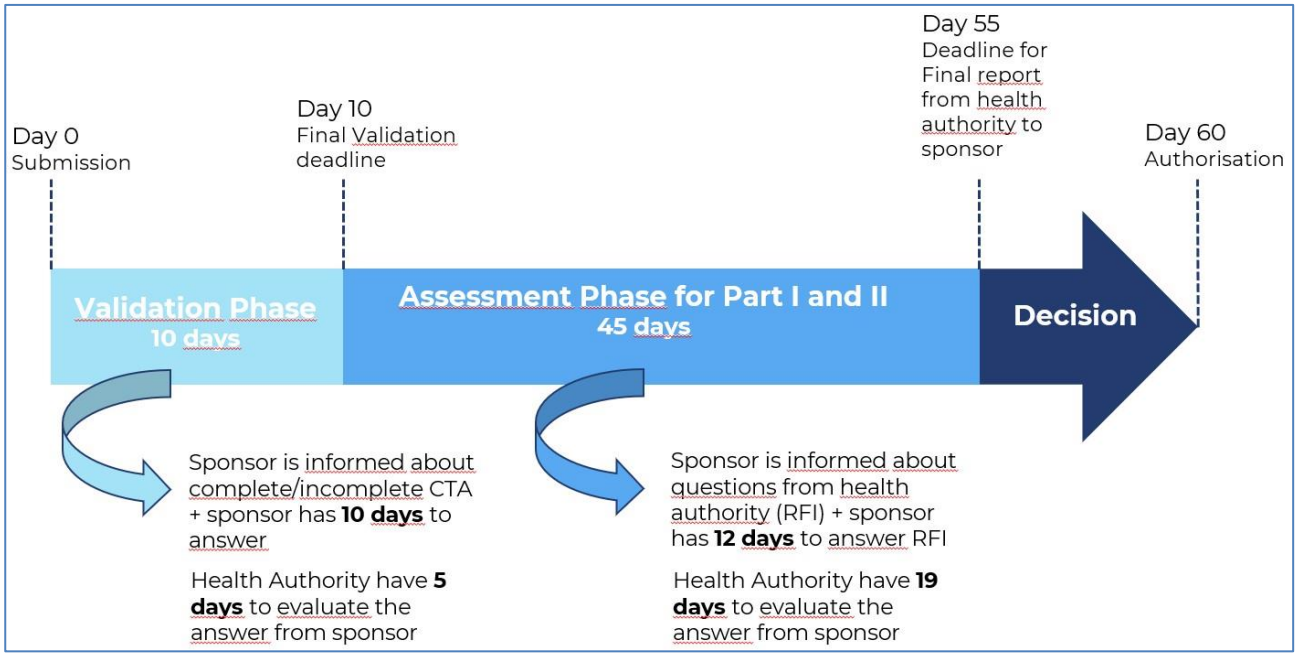
The “Submit response” button will be active when the changes have been saved on “Save response”.

5. Timetable

In the timetable tab on the left side of the page, CTIS shows the dates for the assessment schedule.



The figure below gives an overview of the general timetable and deadlines for authorities and sponsors.



All these days are natural days. If a due date falls in a weekend or a bank holiday, this date is moved forward to the next working day.

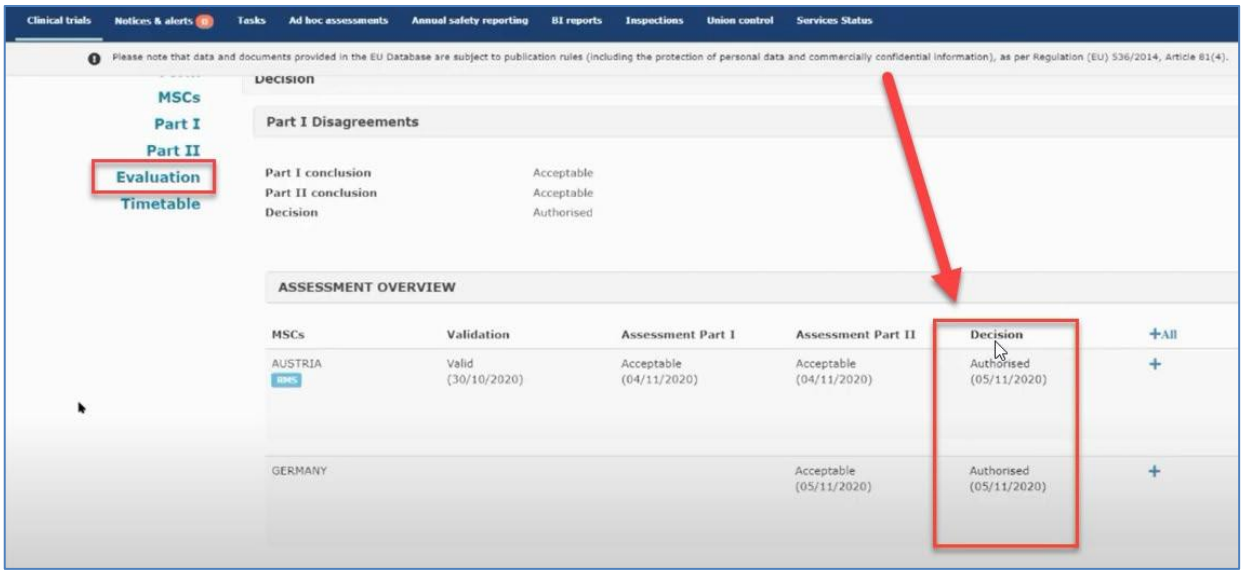
These timelines cannot be extended except in CT involving an advanced therapy IMP or a medicinal product as defined in point 1 of the Annex to Regulation (EC) No 726/2004, for the purpose of consulting with experts. In such cases, the RMS may extend the assessment phase by a maximum of 50 days.

During the validation bank holidays from all MSCs are considered, until the RMS is selected. From that day, the calendar of RMS applies.

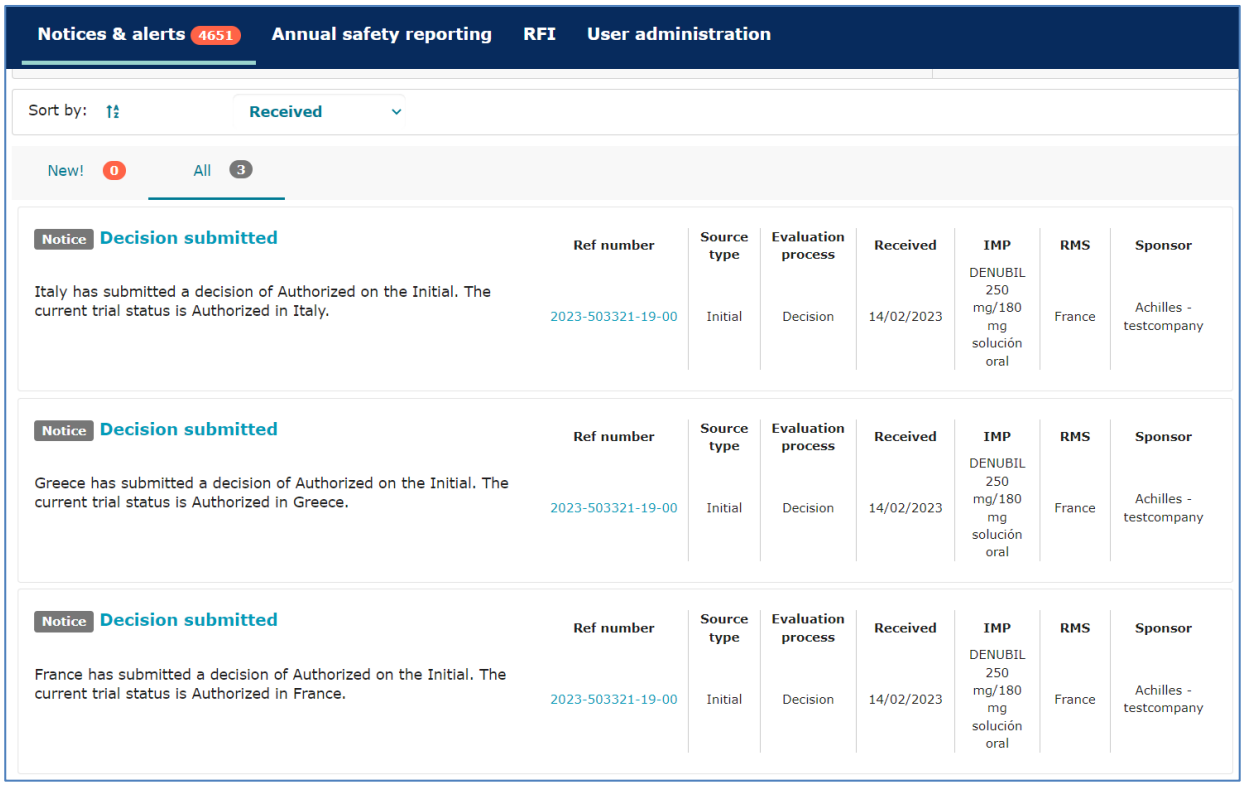
For further information on this topic, please see this video on the use of Timetable, this step-by-step guide and the CTIS Evaluation Timelines document.

6. Authorisation

In the assessment overview at the “Evaluation” page it is shown which countries have authorised the trial.



The sponsor will receive a notice indicating that the decision has been submitted in each MSC:



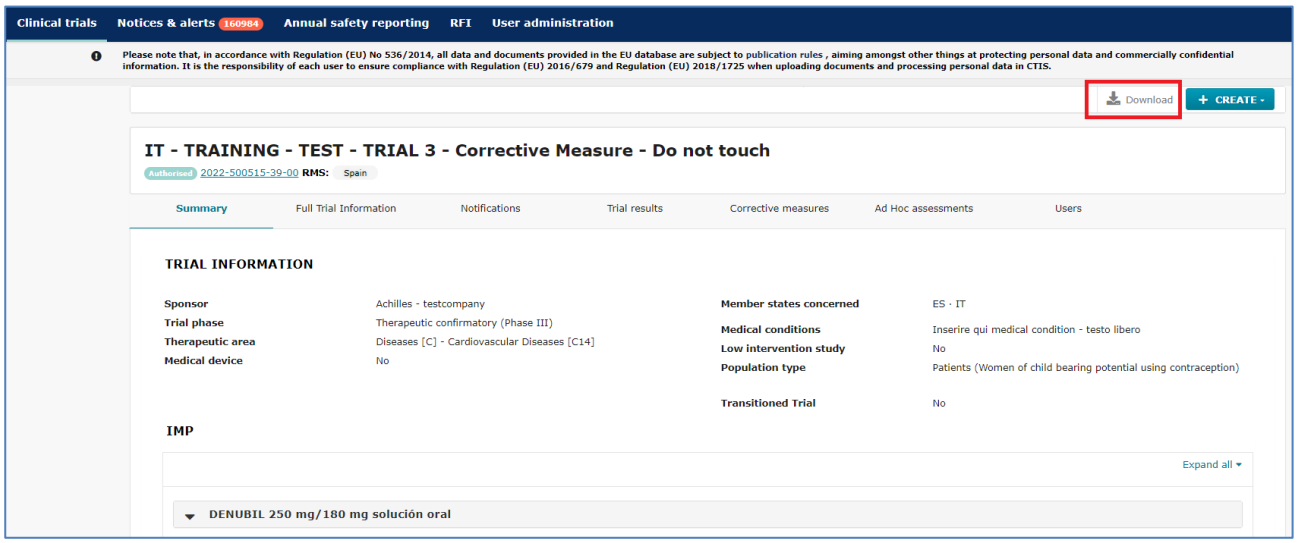
Clicking on the Notice title, sponsor will access to the CTA and will be able to download the Final Assessment Reports for part I and Part II in the conclusion sections of Assessment part I and Assessment part II tabs. Therefore, neither AEMPS nor EC will send any document to sponsor.

Please notice that the FAR for part II submitted by Spanish EC will not contain signatures, document versions nor a list of the EC members.

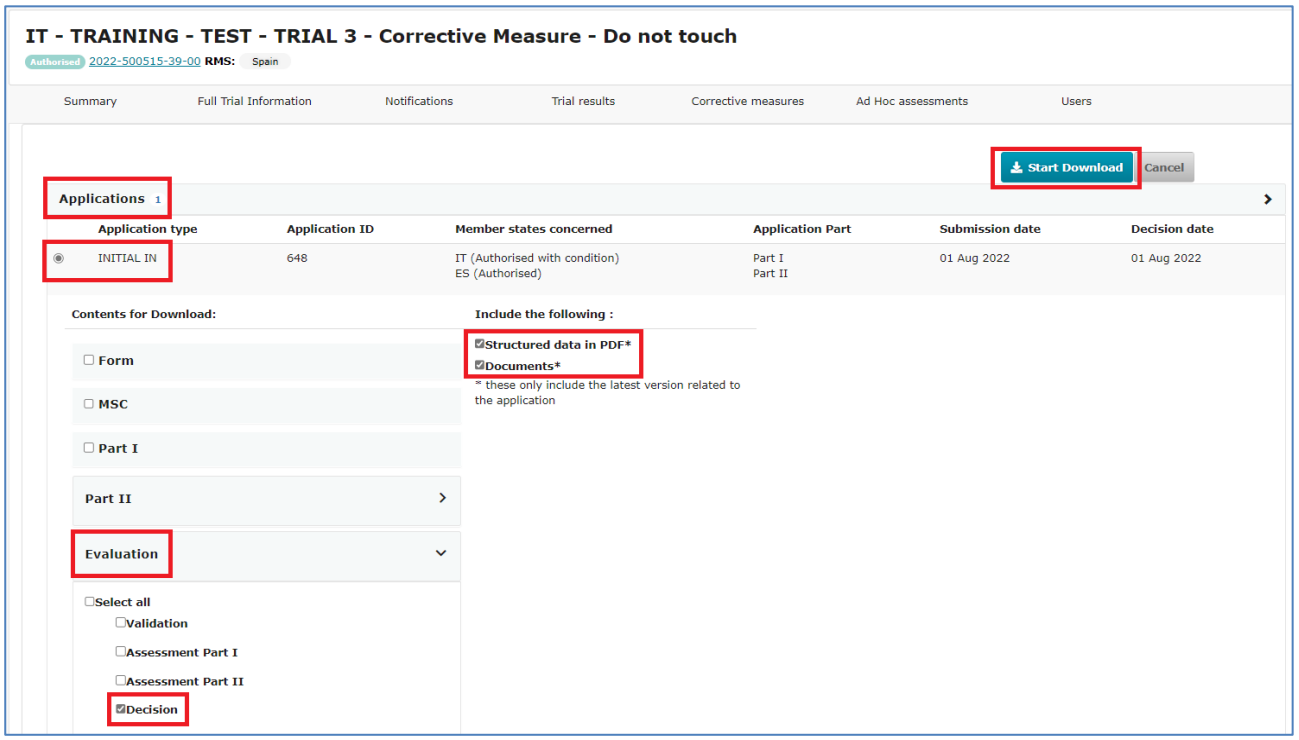
For transitioned trials, only simplified FARs will be uploaded by AEMPS and ECs.

In Spain, national authorization (or not authorization) letters are not going to be submitted. If necessary, the sponsor can **download the Decision document from CTIS** following these steps:

1- Search the Clinical trial and access to the summary page of the application. Click on the “Download” button.



2- Select Applications → INITIAL IN → Evaluation --> Structured data in PDF and Documents. Click on the **Start Download** button.



3- A zip file will be downloaded and the sponsor will find a folder called “Evaluation”, and other one called “Decision” inside it. Finally, going into the “Spain” folder, there will be a PDF file with the decision for Spain and the date in which it was submitted.

7. Withdrawal of an application

The sponsor has the option to withdraw an application for a clinical trial at any time until the decision is made.

In cases of withdrawal of an application before the reporting date, the withdrawal will apply to the entire application in all MSCs. If the withdrawal is done after the reporting date, but before the decision is taken by a particular MSC, the sponsor has the option to withdraw the application in one, two or all MSCs.

Additional information on withdrawal rules can be found in section 4 of the Questions and Answers Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines.

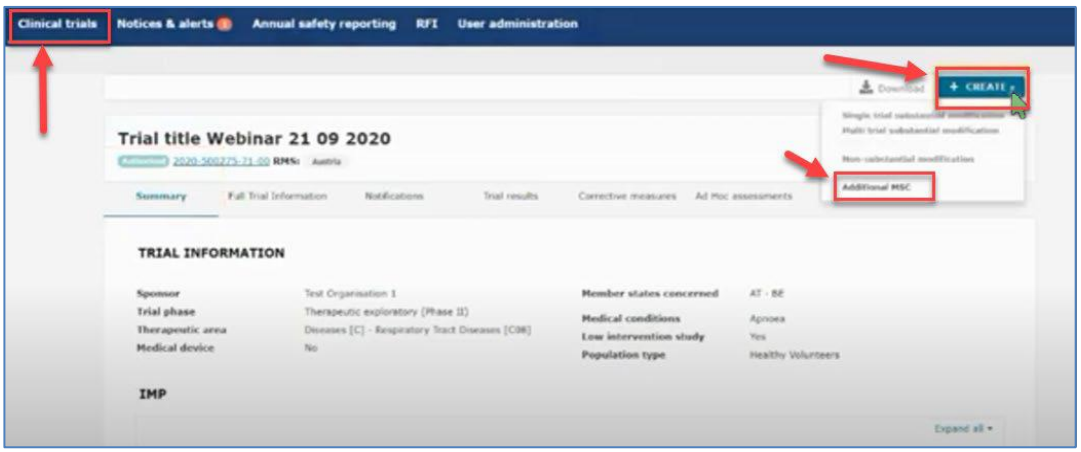
After opening the initial trial application which is under evaluation, select the “withdraw” button. A justification for the withdrawal should be provided.

The sponsor has the option to withdraw an application for a clinical trial at any time until the decision is made. However, in cases of withdrawal of an application before the reporting date, the withdrawal will apply to the entire application in all MSCs. After the reporting date, but before the decision is taken by a particular MSC, the sponsor has the option to withdraw the application in one, two or all MSCs.

8. How to submit an additional member state concerned (MSC) application (add a new country)

Available video and step-by-step guide on this topic in EMA training module 10.

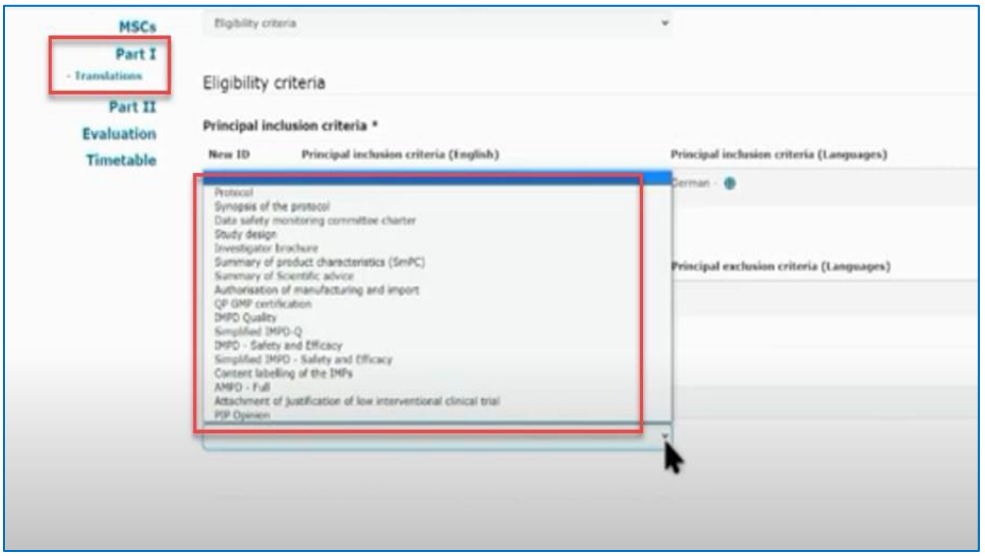
To add a new member state (MSC) to an already approved application, in the page of the authorised clinical trial click on the **Create** button and choose “Additional MSC”.



In the next pop-up window you can select one or several MSCs to add at the same time and specify for each country the number of subjects. Each application will be assessed individually by the country that has received the new application.

In the Form section a new cover letter and a proof of payment of fee (if applicable) must be uploaded for each added MSC.

In the Part I section you can provide translations if required by the new MSC. If you need to upload translations for documents, you can choose the document type on a list and thereafter upload the new document and add the language.



In the Part II you can add the site details for the new MSC.

It is possible that the sponsor receives RFI from the additional MSC during the process.

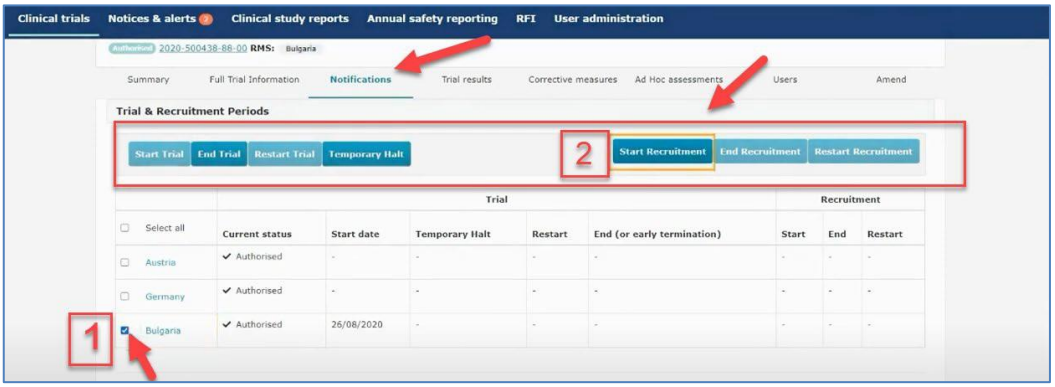
9. Notifications after authorisation

The notification tab can be found in each clinical trial in the sponsor workspace. Sponsors use the notification tab to inform each member state of important milestones in the clinical trial:

- Start of recruitment
- Start of inclusion
- Temporary halt of the clinical trial
- Temporarily halted clinical trial is resumed
- End of recruitment
- End of inclusion
- End of trial

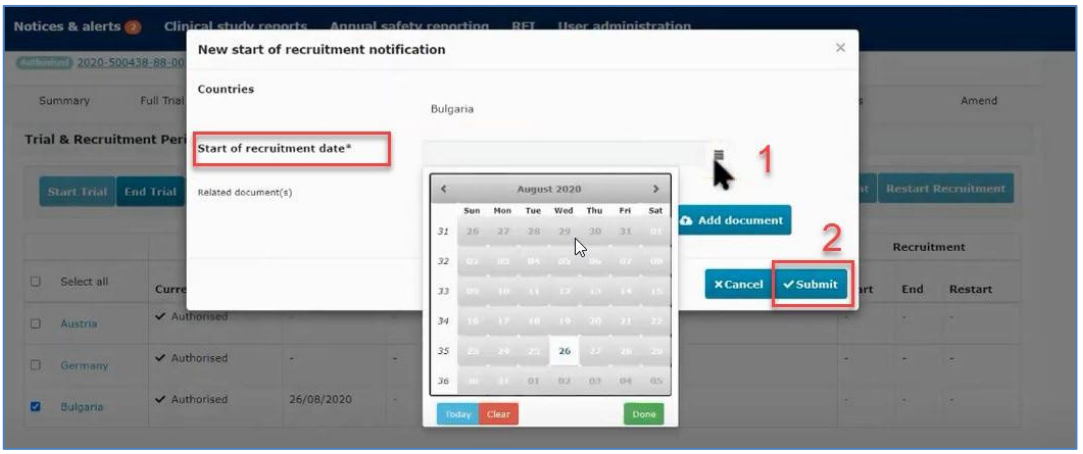
The deadline for reporting these notifications in CTIS is 15 days. The notifications should be made for each member state where the clinical trial is approved. The specific country must be selected and then click on the notification tab you want to enter.

All buttons found in the notification tab will be active once the clinical trial is authorized.



Select the specific country where you want to make a notification.

Click on the notification tab you want to enter either Start Trial, End Trial, Restart trial, Temporary Halt, Start recruitment, End recruitment or Restart recruitment. For example:



Choose the country where you want to notify about recruitment start. Enter the date where the recruitment will start and then click submit.

For further information on this topic, please see the Training Video: How to manage a CT in the CTIS sponsors workspace – Trial and recruitment periods notifications and the Step by step guide in EMA training module

For instructions on how to notify Unexpected events, Serious Breaches, Urgent Safety Measures or 3rd Country inspectorate inspections, please watch this video.

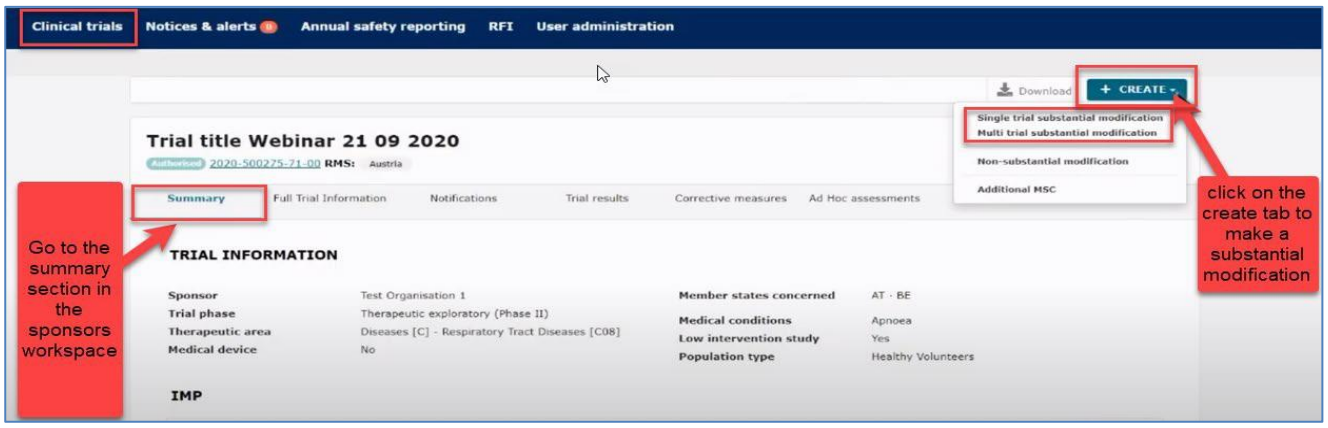
RFI mechanisms have also been implemented in the system to enable exchange of information between MSC and sponsors as part of an ad hoc assessment, following for example a notification of a serious breach, in case of evaluation of an annual safety report (ASR) or when a sponsor opinion needs to be provided in the context of a corrective measure.

For additional information on responding RFIs during the ASR assessment, please see the step-by-step guide and this video.

Sponsor can find further information on Clinical study reports submissions in this step-by-step guide in EMA training module 13.

10. How to create and submit a Substantial Modification (SM)

To create and submit a substantial modification after the clinical trial has been authorised, users can select the '+ CREATE' button in the sponsors workspace at the top-right corner of the Clinical Trial page.

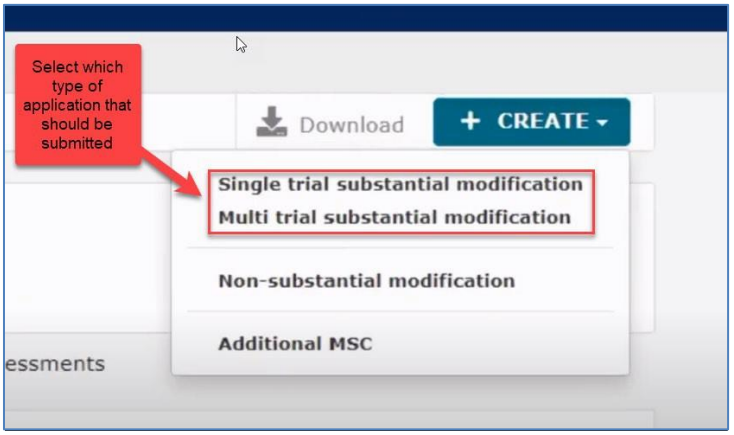


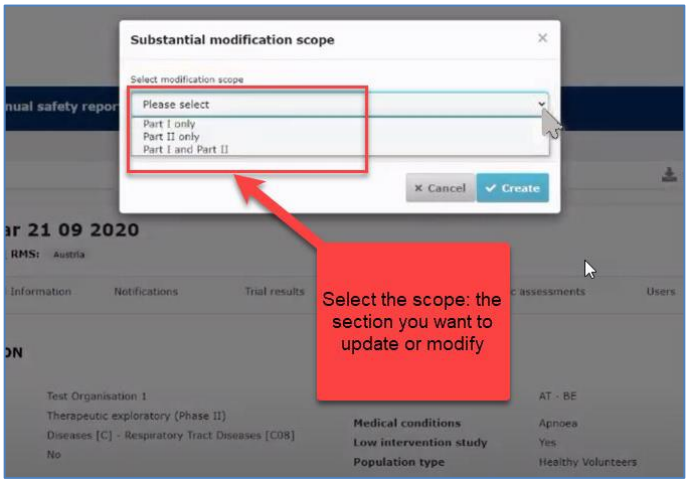
This will enable to select which type of modification you want to submit:

Single trial substantial modification: to update information for only one trial.

Multi trial substantial modification: to update information for trials that have the same IMP and the same sponsor. In this case it is possible to submit a single application covering several trials.

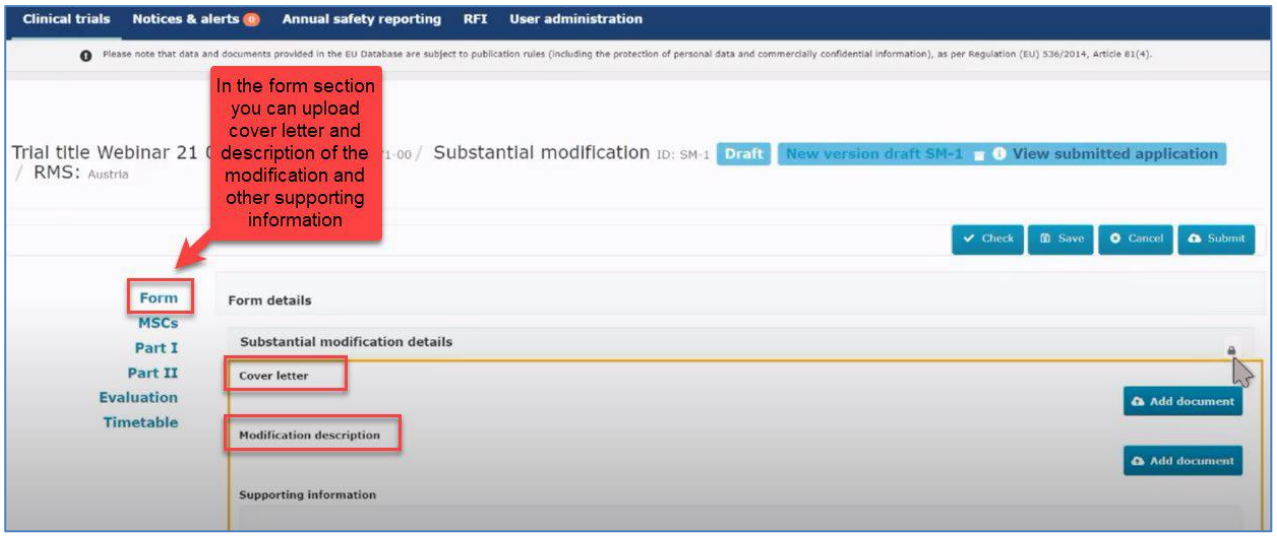
More information in question 3.8 of the Q&A Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines.



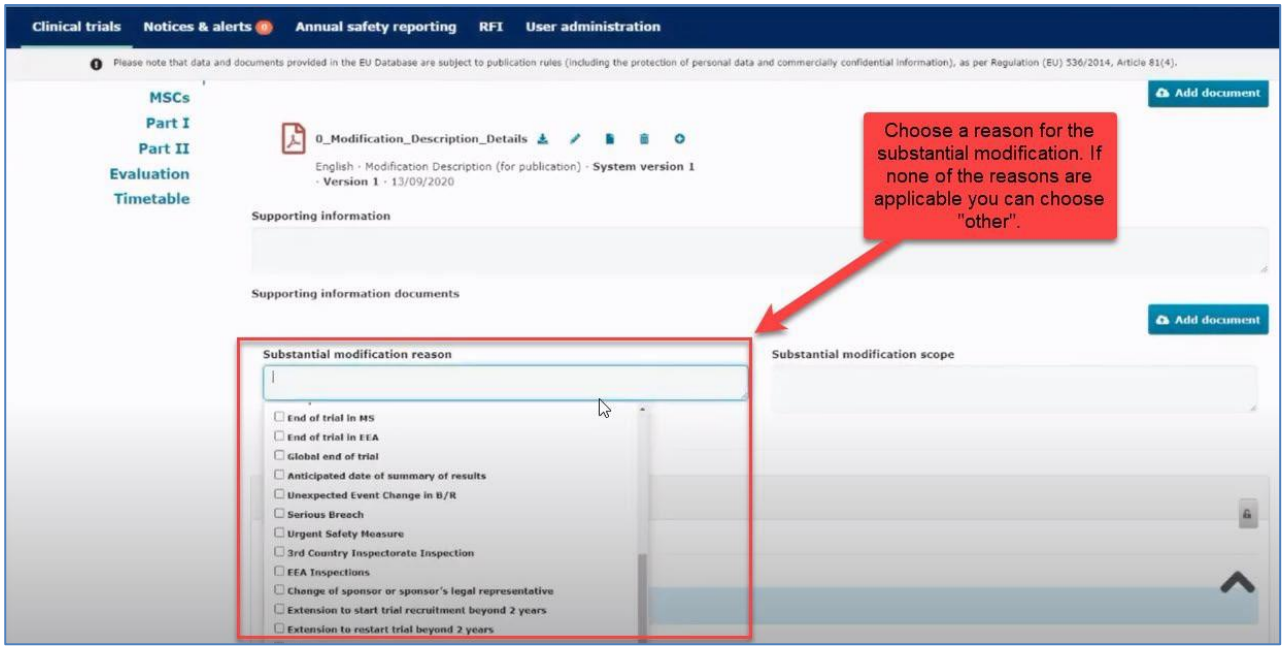


If you click on the **"Single trial substantial modification"** you will be redirected to a window where you need to enter the scope of the substantial modification. Thereby you will define the part which will be modified (Part I and/or II).

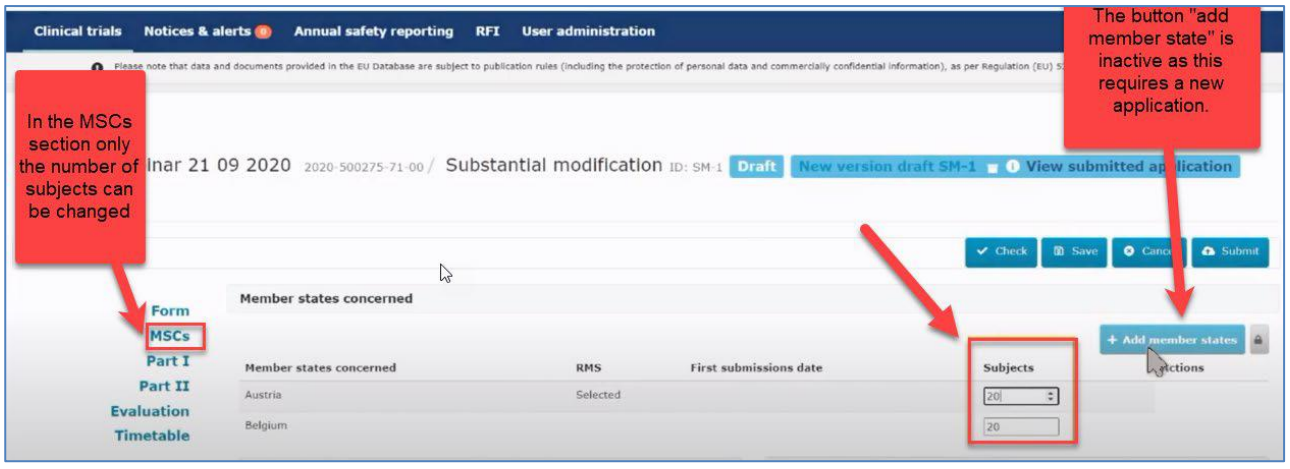
In the "Form" section, cover letter should be uploaded and additionally it is mandatory to upload a general description of changes in the field Modification description.

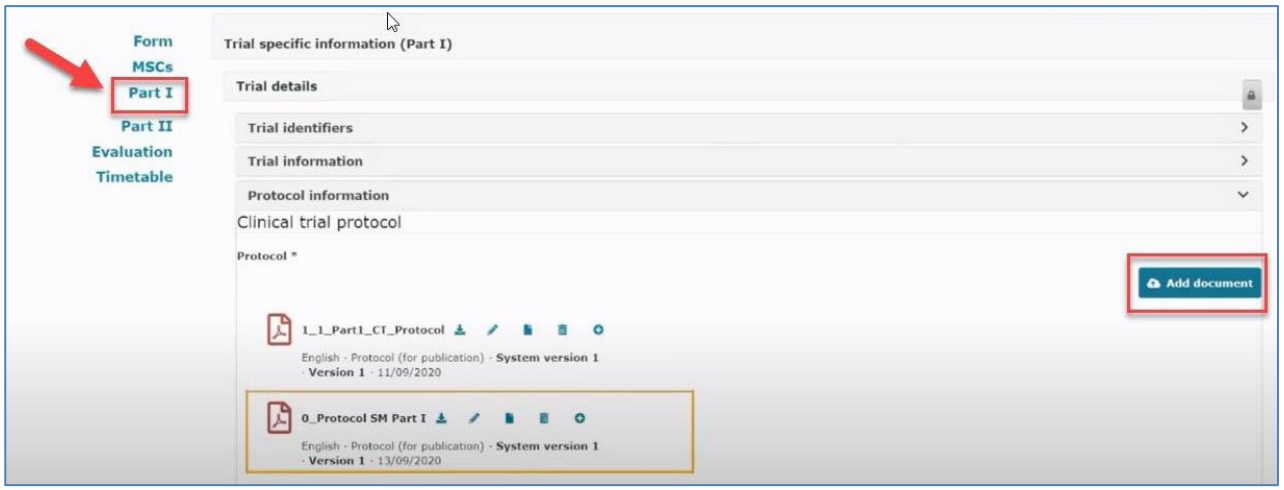


If you scroll down, the reason and the scope for the substantial modification must be added here.

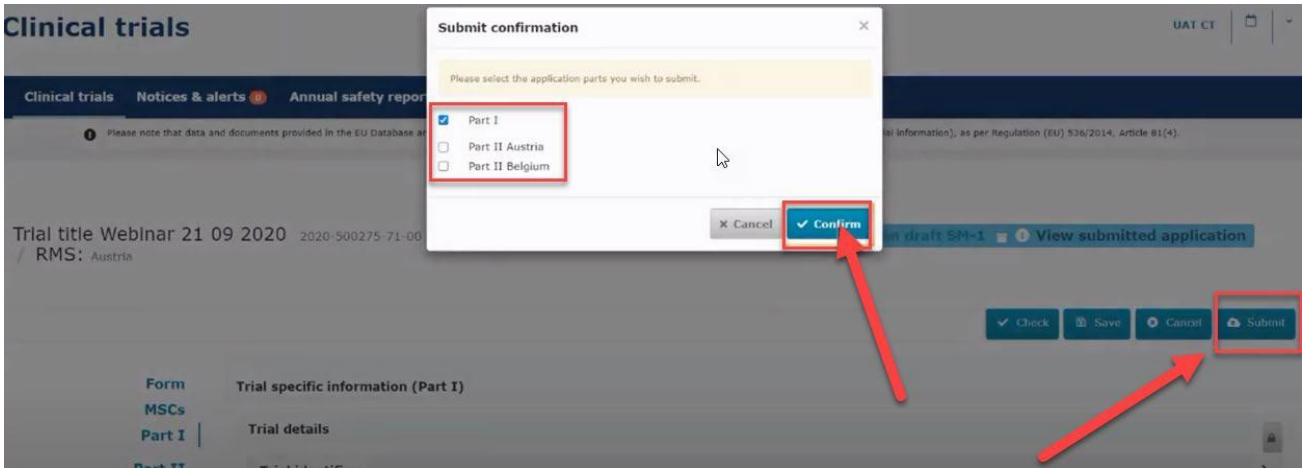


In the “MSCs section” only subject numbers (number of planned trial subject) can be modified.

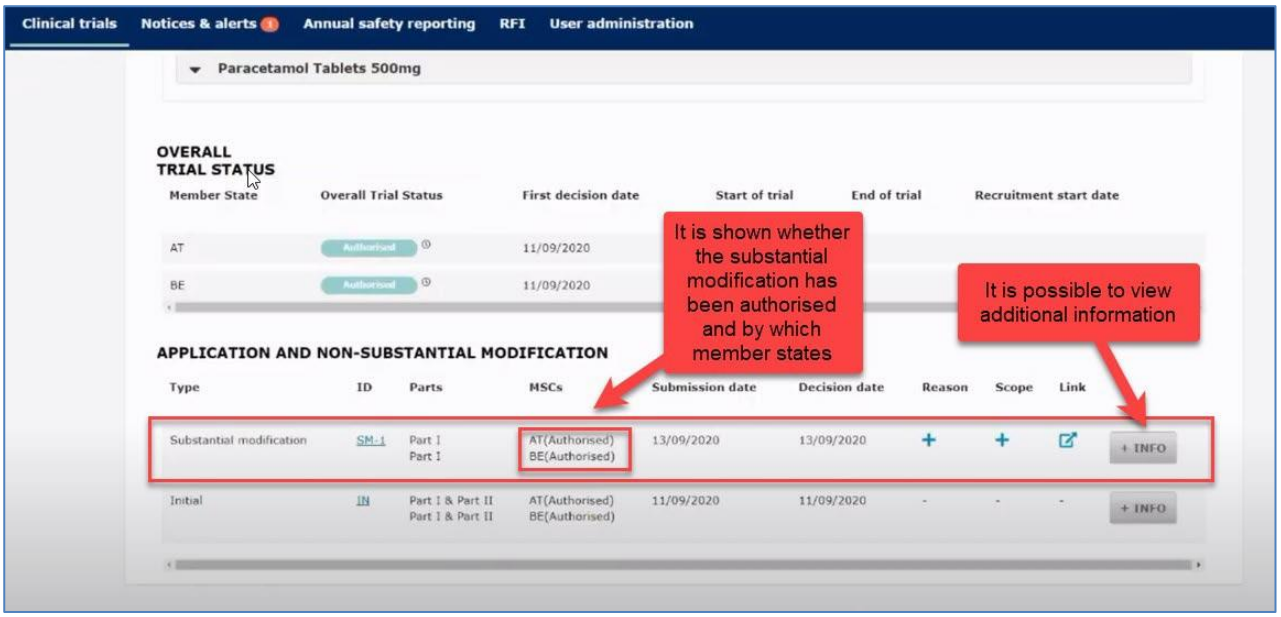




When all data and documents have been modified and uploaded, click on **Submit**. Then select the parts of the application you want to submit and click on the **Confirm** button.



In the Summary page you can scroll down and see the status of the substantial modification.



Additional information can be found in this training video and step-by-step guide in EMA training module 10.

Non-substantial modifications

Non-substantial modification (NSM, i.e. without substantial impact on the safety or rights of the subjects and/or the reliability and robustness of the data and when the information is not necessary for oversight) should not be notified as such. Correction of typos and other administrative changes with no impact on the content and meaning of the information are always expected to be updated as non-substantial modifications. NSM can be submitted with a SM application. These NSMs need to be listed and identified as NSMs in the cover letter of the SM application. We do not expect to receive NSMs notifications on a regular basis. Sponsor should accumulate non substantial changes and notify them within the next substantial modification submitted for the clinical trial.

For further information on this topic please see question 3.4 of the Q&A Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines.

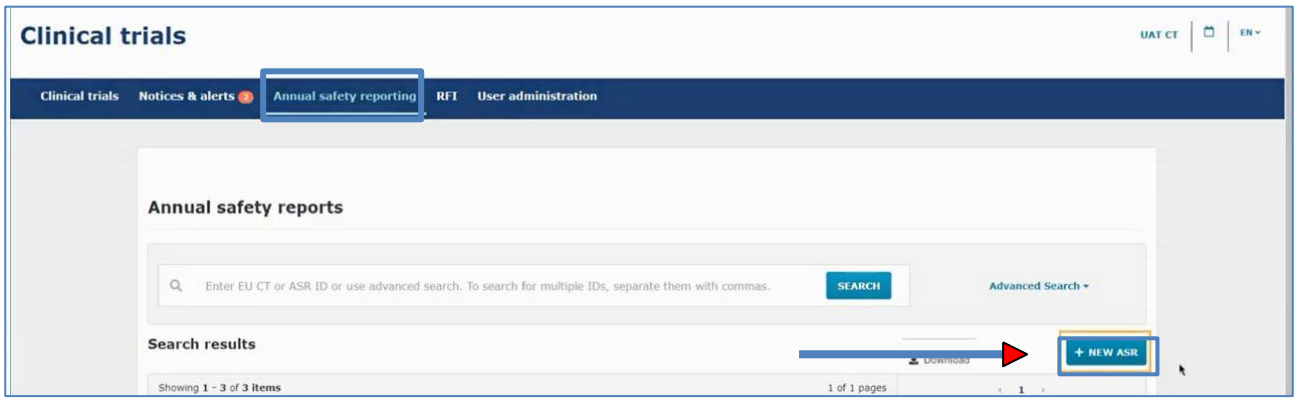
Changes to a clinical trial which are not SM but are relevant for the supervision of the trial (Art. 81.9)

Information on any changes to a clinical trial, which are not SMs but are relevant for the supervision of the clinical trials by the MSC, shall be permanently updated in CTIS by the sponsor, in line with Article 81.9 of the CTR. This route can be used to update information to fulfil a condition, depending on the instructions of the RMS (part I conditions) or the MSC (part II conditions).

For further information on this topic please question 3.3 of the Q&A Document - Regulation (EU) 536/2014, published in the Chapter V of EudraLex - Volume 10 - Clinical trials guidelines.

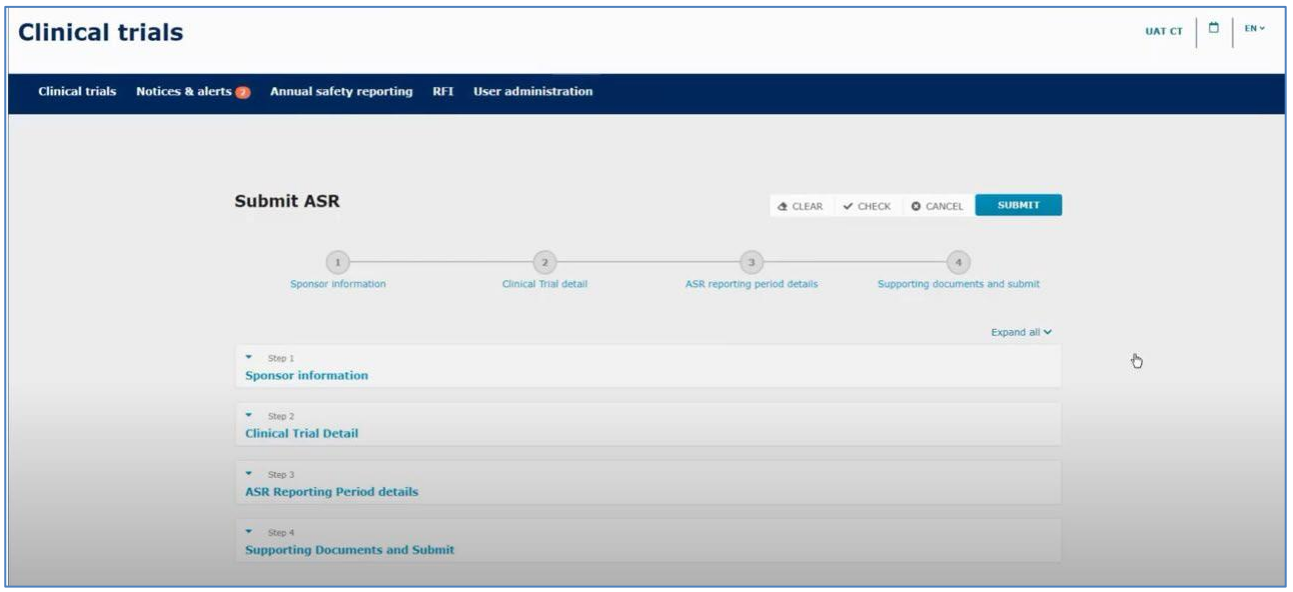
11. Create and submit an Annual Safety Report (ASR)

To create and submit an Annual Safety Report users can open “the Annual Safety Reporting form” by clicking on the ‘+New ASR’ button in the sponsor’s workspace.



❖ **TIP:** Make sure to have the ASR document in PDF prepared and all the relevant information ready (e.g. Investigational medicinal products, relevant events that occurred, reporting period, etc) before starting.

An ASR form opens:



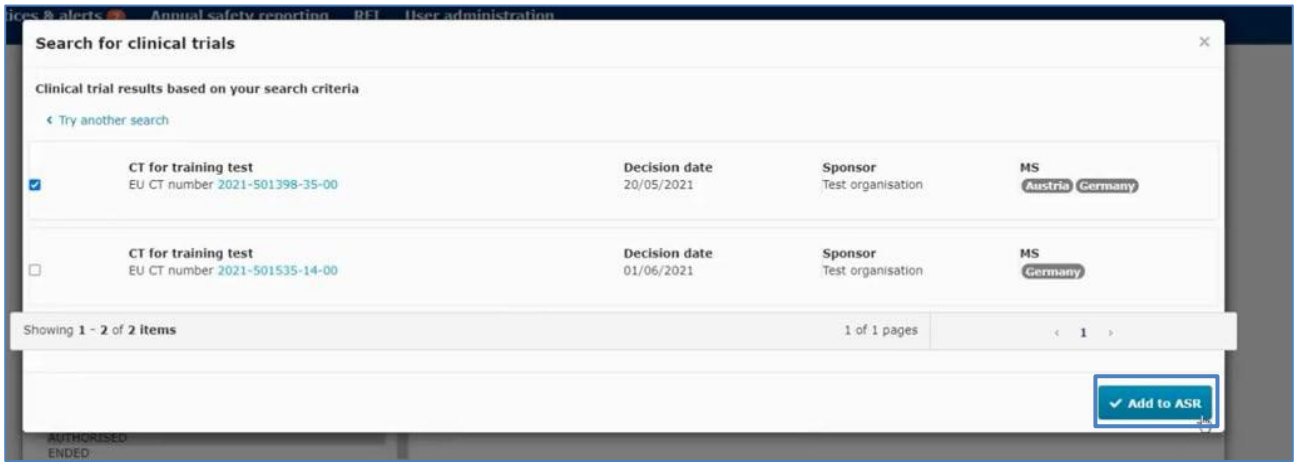
Fill in the information for the four steps (Sponsor information, Clinical trial details, ASR reporting period details and supporting documents) and submit on the **Submit** button. The ASR form has to be filled in and submitted in one go. You need to have all information ready because it cannot be saved.

Step 1: Sponsor information

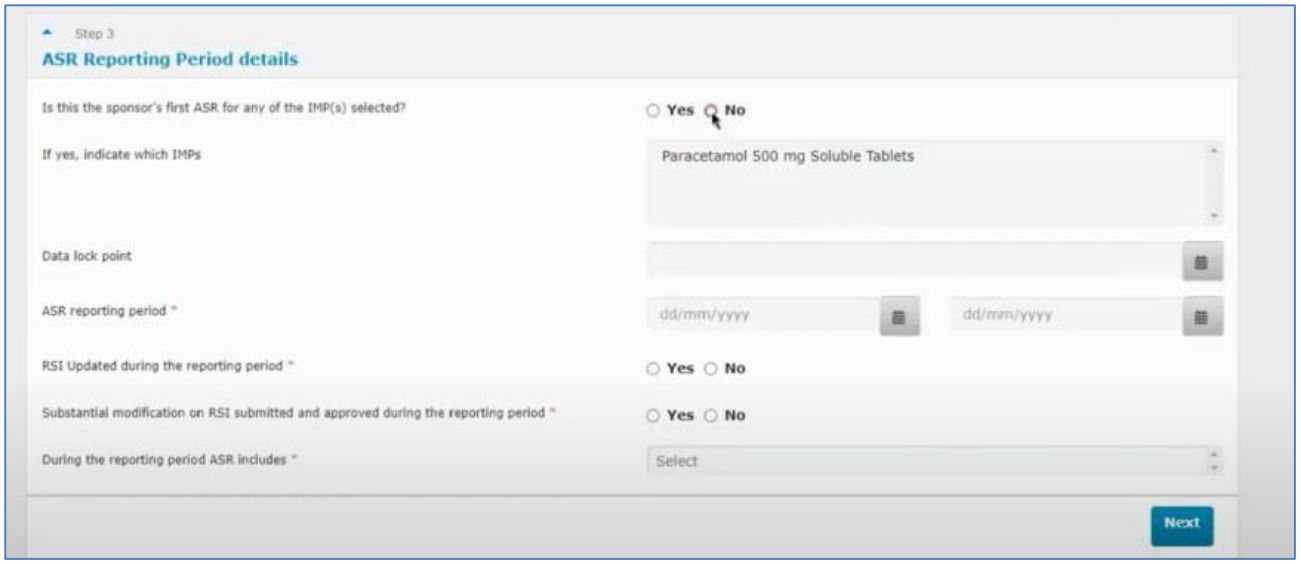
Fill in Organisation details of the selected sponsor and the contact details for the person who is responsible for the submission and can be contacted with an email address and or phone number.

Step 2: Clinical trial details

Search for the Clinical Trial (CT) to which you want to submit an ASR. You search for clinical trials that are authorised for the selected sponsor organisation and select the trial for which you want to submit an ASR.



When the form opens you can click on the related IMP or IMPs for the clinical trial you want to submit an ASR.



In this section you need to select and fill in the data lock point (DLP). That is the cut-off date of selecting data

for the ASR. The DLP must be as close as possible to the approval date.

If this is the first ASR in the clinical trial the ASR reporting period starts the date where the clinical trial is first authorised.

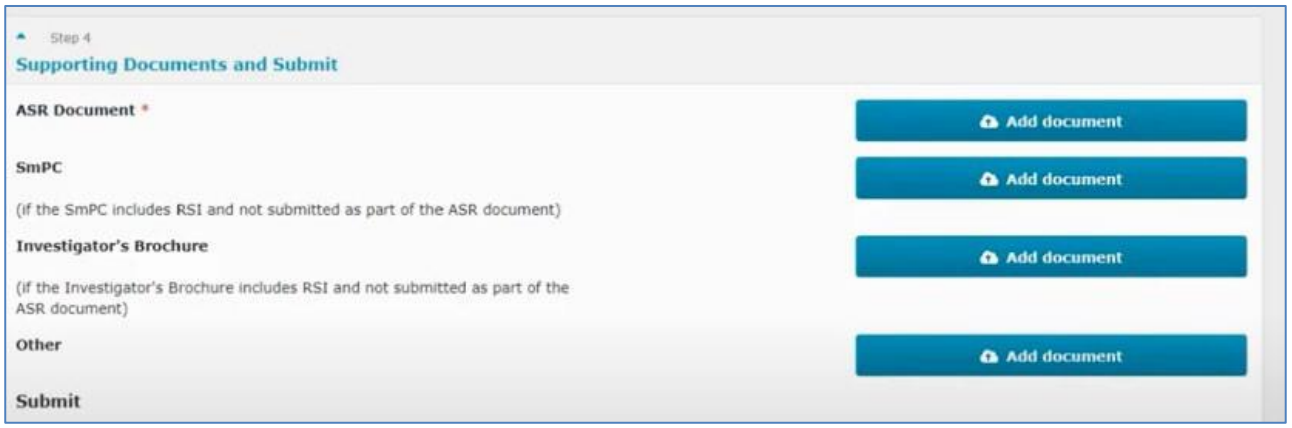
The deadline for submission of ASR is 60 calendar days after the date of the first authorisation. The following should also be answered:

- Has the RSI (reference safety information) been updated during the reporting period?
- Has a SM on the RSI been submitted and approved during the reporting period?

In most cases the answer would be no.

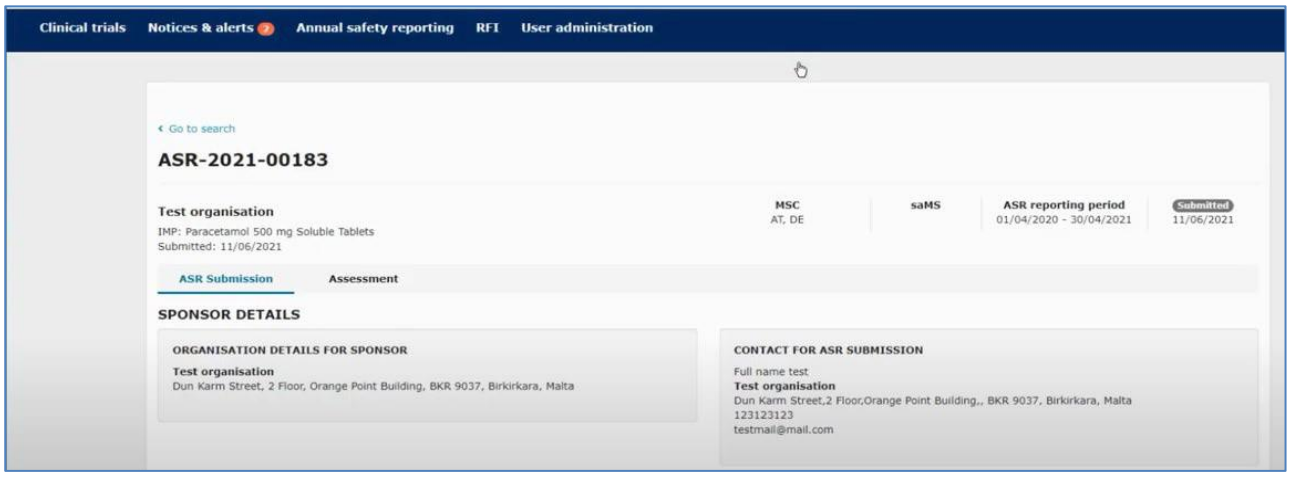
From the drop-down menu it is possible to choose what the ASR includes.

Step 3: Supporting documents and submit



In step 3 you add the ASR report document and you can also add other supporting documents. The ASR report should be uploaded as a PDF.

Then you can check if all information is valid or anything is missing by using the **Check** button and then you can submit. Once submitted you see this page where all the information that was populated will appear.



SUSAR reporting must be done only through Eudravigilance_CTM. It is not necessary the submission of semi-annual SUSAR reports. It is not neccesary to report ASRs or SUSARs to the sanitary authorities of the Spanish Autonomous Communities (CCAA).

For more information on this topic, please see this training video in in EMA training module 18.

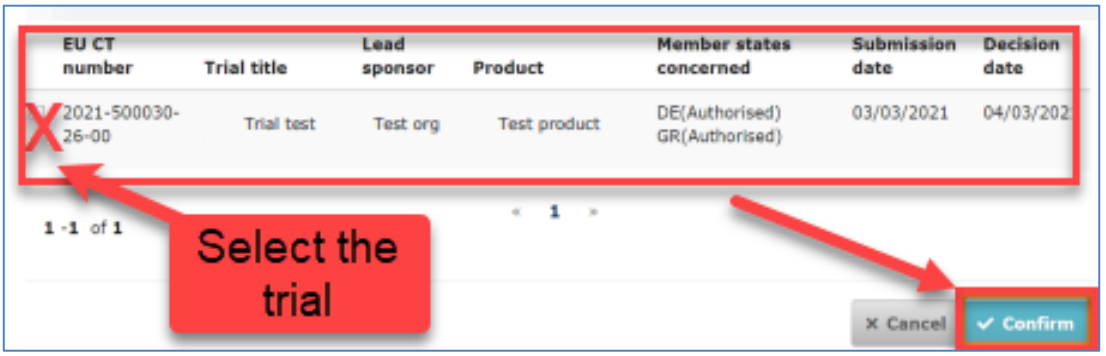
12. Summary of results and summary for laypersons

The sponsor shall submit a scientific summary of results of the Clinical Trial and a summary of results for laypersons. The deadline for uploading the results in CTIS is one year after the end of trial.

The content of the summary of results is set out in Annex IV of the CTR. It shall be accompanied by a summary written in a manner that is understandable to laypersons, whose content is described in Annex V of the CTR. Summary of results for laypersons must be submitted at least in Spanish, while scientific summary of results may be submitted in English and/or Spanish.

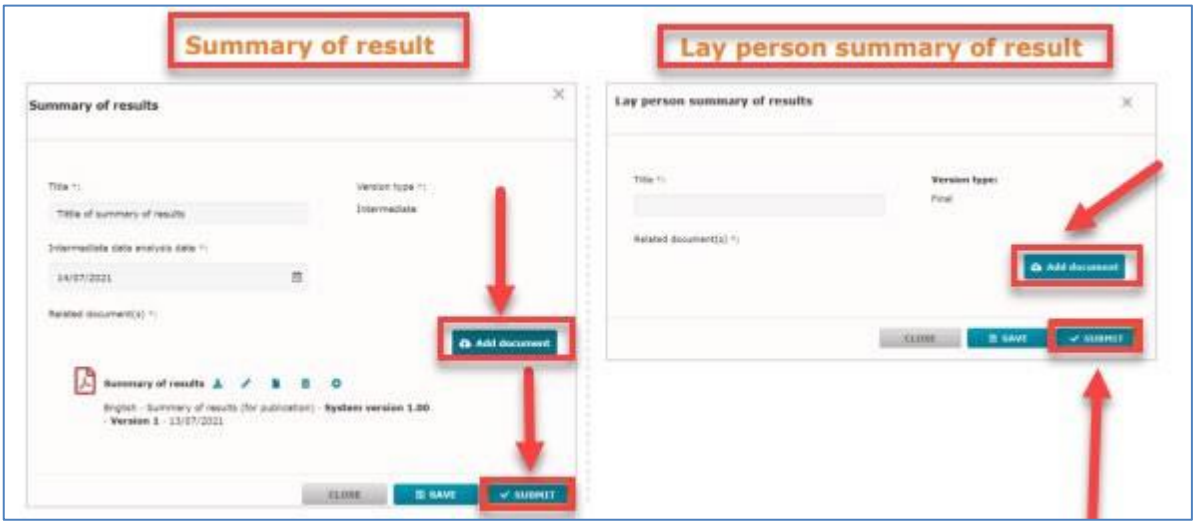
To submit the summary of results, go to Clinical Trials page and search for the clinical trial by entering the "EU CT number" or use advanced search.

Select the trial from the results page and click on the **Confirm** button.



When the trial is selected a window will show where the "summary of results" and "layperson summary of results" can be uploaded.

Select **Add document**. Then **Save** and **Submit**.

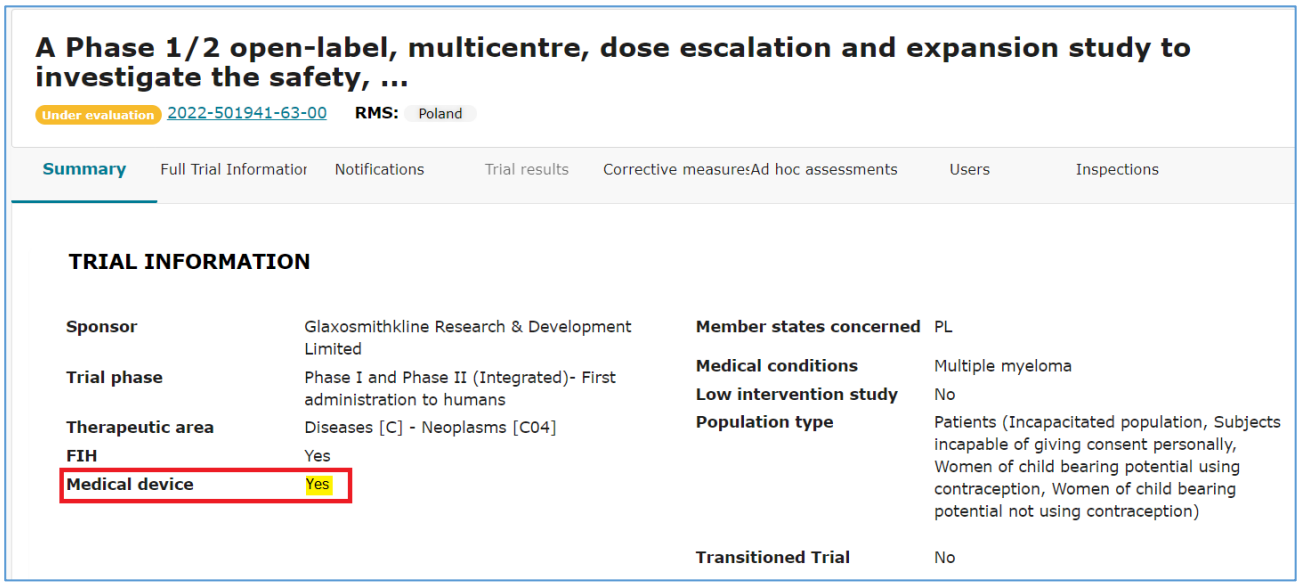


For further information on this topic please see this step-by-step guide in EMA training Module 5, and this training video.

Annex I. Instructions for clinical trials with medical devices

Clinical trials with medicinal products and medical devices without CE marking

In clinical trials whith medical devices to be investigated but which are not a part of the investigational medicinal product or products, and are not CE-marked for the intended use, documents listed in Annex I of the CTR must be submitted through CTIS. The statement of the use of the medical device must be included in the cover letter (CTR, Annex I, B.i). In the Medical device structured field of CTIS, the sponsor has to indicate "Yes".



The documents required for the authorization of a clinical investigation with a medical device or a performance study for in vitro diagnostics must be submitted through the general electronic registry of the General Spanish Administration, attaching additionally in this submission the clinical trial protocol. In case the electronic submission is not available for the sponsor, these documents can be physically submitted (on paper or on CD/USB) through the General Registry of the AEMPS: C/ Campezo, 1; edificio 8; 28022 Madrid.

Both applications must be simultaneously submitted for their assessment, that will be performed in paralell. The Ethics Committee appointed in Spain must be the same.

The sponsor has to pay two different fees: one regarding the clinical trial application, and other regarding the clinical investigation with a medical device or the performance study for in vitro diagnostics.

Two separate authorizations will be granted. To start the clinical trial, it is essential that the sponsor has both authorizations.

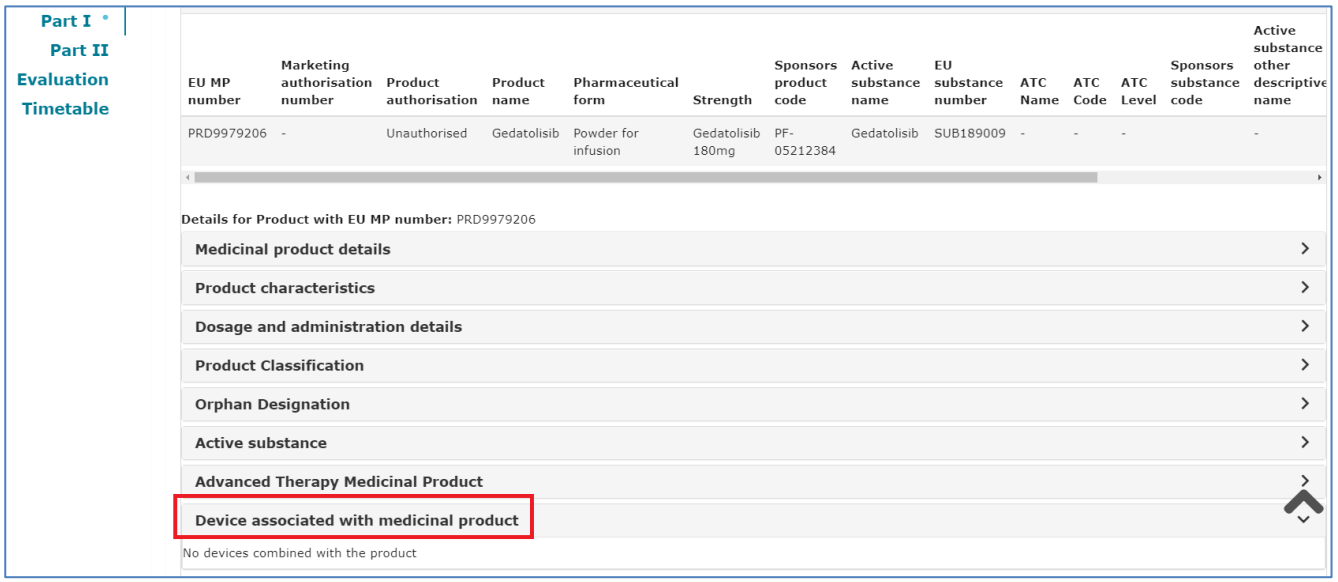
Clinical trial with an integrated product

In clinical trials investigating an integrated product that has components which, used separately, could be considered a medical device or a medicine, two situations can be differentiated:

a) In case the main action is due to the medicinal product, the sponsor should submit a CTA through CTIS,

marking "Yes" in the Medical Device section of the general information of the trial and indicating this in the cover letter.

It should also be specified that a medical device associated with the investigational medicinal product is used in the structured field of CTIS (Part I - Products):



In this case, it is not necessary to submit an application to the Medical Devices Department, and only the fee for the clinical trial with medicinal products has to be paid.

The part of the product that separately could be considered a medical device must comply with the safety and performance requirements set out in Annex I of Regulation 2017/745 on medical devices.

b) In case the main action is due to the medical device, it would be a clinical investigation with medical devices that must comply with the provisions of its legislation. The application must be sent through the General Register of the AEMPS addressed to the Department of Medical Devices and only the fee corresponding to clinical investigation involving medical devices shall be paid.

Annex II. How to register sites in CTIS

It is possible to create organisations locally in CTIS, without the need to register them in OMS, in the following five areas of the system:

- Part I: Sponsor section - “Third-party organisations”
- Part II: “Trial sites”
- Serious Breach Notification: “Details of the site where the serious breach occurred”
- Third Country inspectorate Notification: “Third country inspection site”
- MS Inspections: “Inspected site”

The registration only requires the population of structured data as per the process explained below. There is no validation required apart from the completion of the mandatory fields and users can add the new site as soon as it has been registered in CTIS.

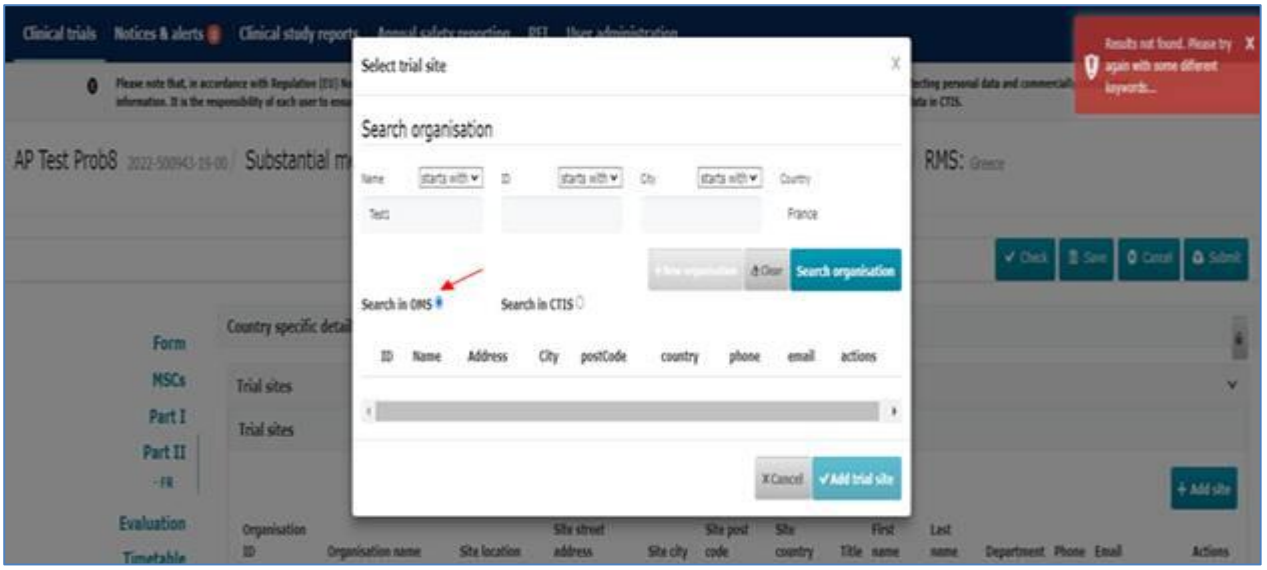
Organisations created locally in CTIS behave and function in the same way as the ones sourced from the Organisation Management Service (OMS) and can be searched and selected once they have been registered in CTIS.

Step-by-step instructions: How to register sites in CTIS

The following example refers to the registration of an investigational site. Please note the process is also applicable to the other four CTIS areas where this functionality has been enabled (see above).

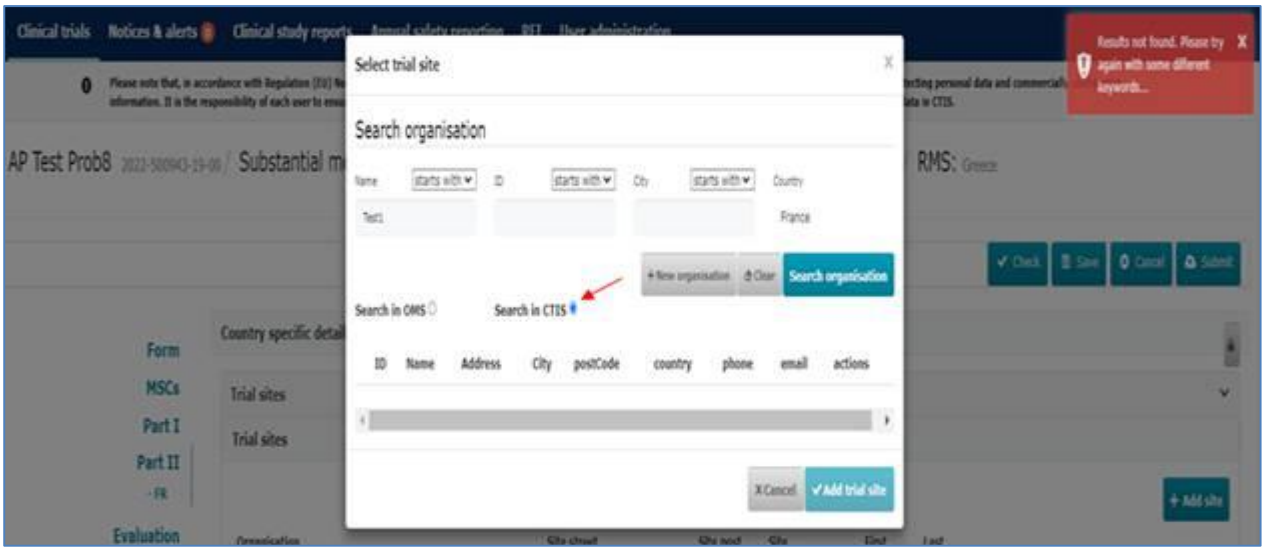
Step 1

The user must first search OMS, as the “Search in OMS” radio button is ticked by default.



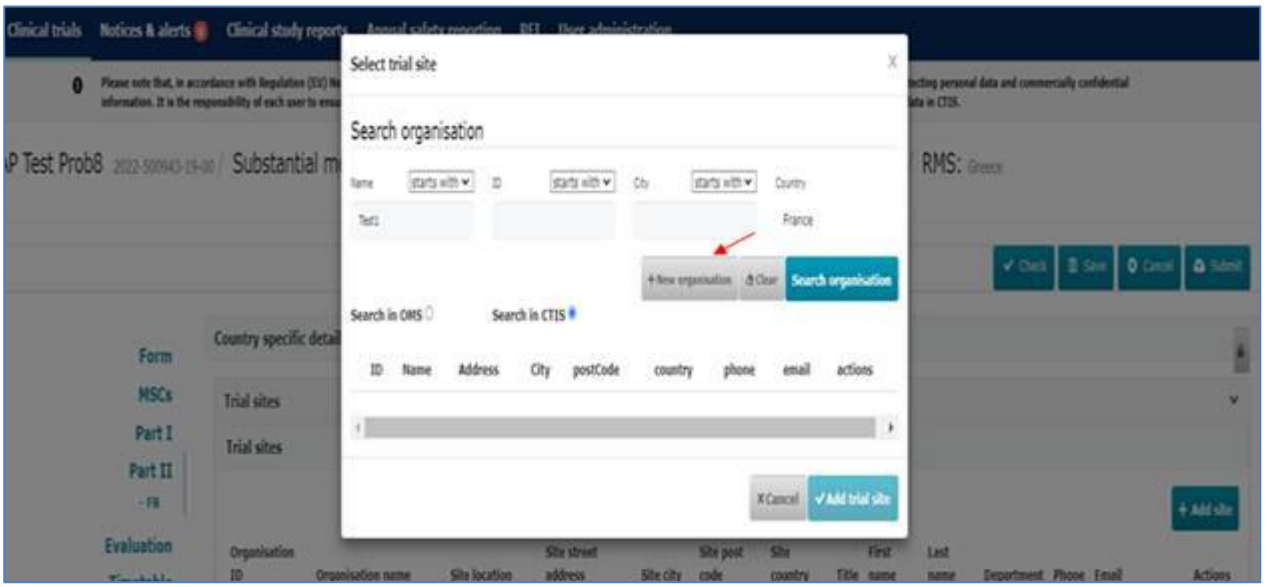
Step 2

If the user does not find the site in the OMS (red error message displayed) or the organisations displayed are not the ones the user is looking for, the user should then search for the site in CTIS by selecting the second radio button “Search in CTIS”.



Step 3

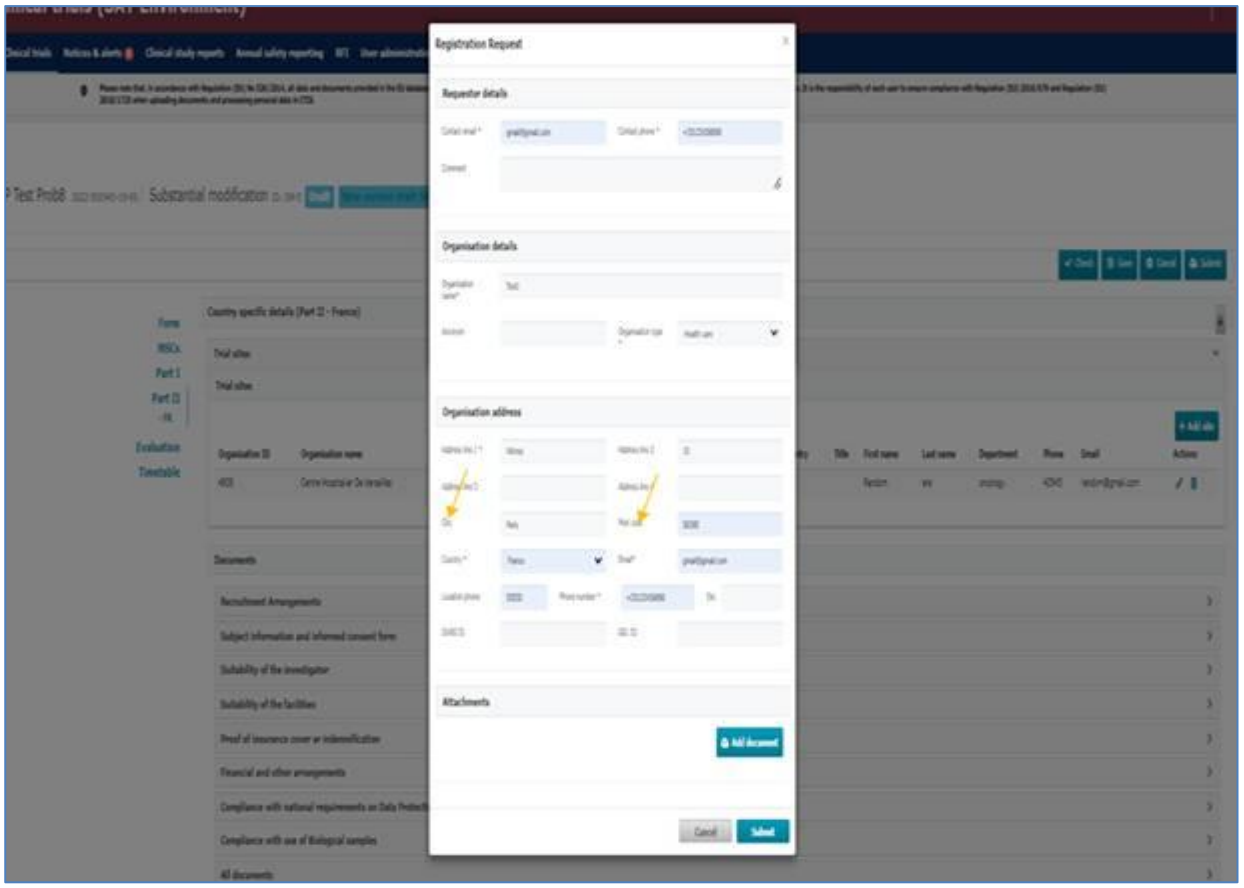
If the user does not find the site in CTIS (red error message displayed) or the organisations displayed are not the ones the user is looking for, the user can opt to create the site in CTIS by clicking the button “New Organisation”, which will now appear enabled.



Step 4

The user completes the displayed form.

IMPORTANT: Users are advised to enter the city and post-code, although these fields are not highlighted as mandatory, to ensure notifications that include sites registered in CTIS pass the technical validation. Moreover, in the case of investigational sites/third party vendors, this is relevant information for inspections.



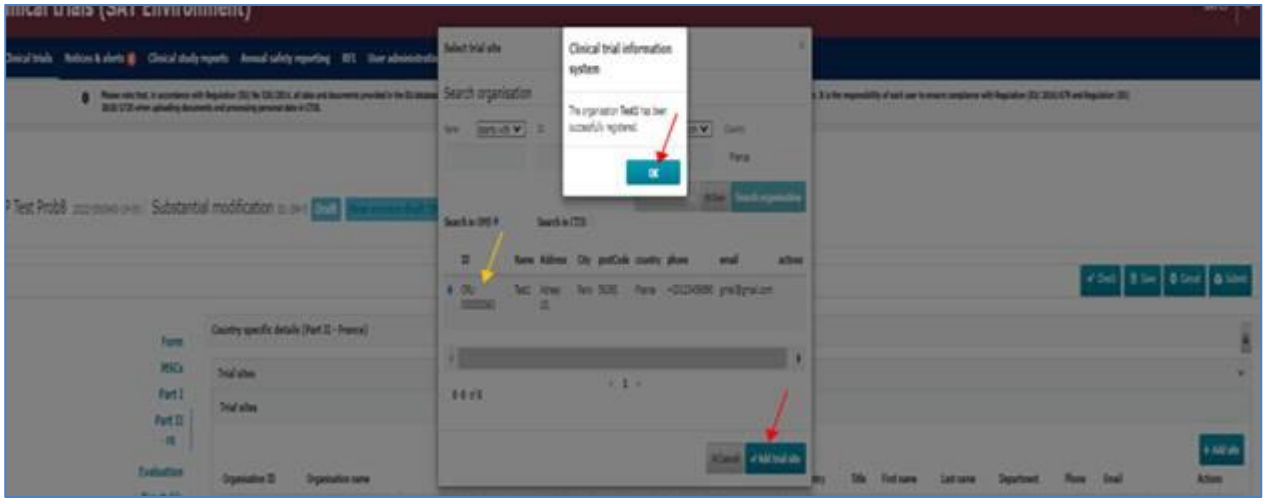
Step 5

The user then clicks submit and a pop-up confirmation window appears.

Please note that organisation IDs for organisations registered in CTIS will start with ORL. Users may wish to take note of this “Organisation ID” for future reference, although they are always able to search using the Organisation name.

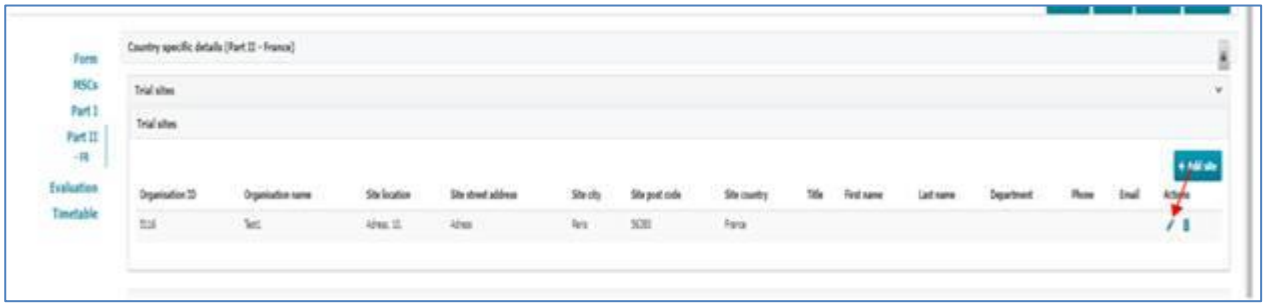
Step 6

The user should confirm and click the “Add trial site” button.



Step 7

The trial site is displayed. In this particular case, for trials sites, the user can edit the additional pending information by using the pencil.



Important notes

1. The user is given ample options to search (i.e., first in OMS, then in CTIS), with a view to prevent duplication and ensure better quality of data.

2. Once the user has registered an Organisation in CTIS, it will remain in DRAFT status. The draft Organisation will be visible only within the scope of the draft CTA or draft notification, i.e. it will not appear when other sponsors search in CTIS.

3. Once the CTA or notification, which contains this Organisation registered in CTIS in DRAFT status, is submitted, the locally registered site in CTIS is changed from DRAFT status to ACTIVE status. This implies that the site is now searchable by other users, including users from different organisations such as other sponsors. This also implies that the local site is no longer editable. If the user now wishes to change or remove the site from the Clinical Trial application or Notification, the user will have to raise a modification or update the notification, respectively.

For further information on this topic, please see the step-by-step guide in EMA training Module 3.