GCP| ENHEDERNE
God klinisk forskning

The Danish GCP Units guide to the Clinical Trials Information System (CTIS)

Content

Abbreviations

AR = Assessment report

AxMP = Auxiliary medicinal product

CT = Clinical Trial

CTA = Clinical Trial Application

CTIS = Clinical Trial information System

CTR= Clinical Trial Regulation

EMA = European Medicines Agency

GCP = Good Clinical Practice

(s)IMPD = (simplified) Investigational Medicinal Product Dossier

MSC = Member states concerned

OMS = Organisation Management System

RFI = Request for information

RMS = Reporting member states

RSI= Reference Safety Information

SM = Substantial modification

SmPC= Summary of Product Characteristics

SAE=Serious Adverse Event

SAR=Serious Adverse Reaction

1 Introduction

1.1 What is CTIS?

The Clinical Trials Regulation, CTR (Regulation (EU) No 536/2014) came into force on 31 January 2022 and submission of clinical trials with medicinal products shall no longer be submitted directly to the Health Authorities and Ethics Committees, but instead the submission will take place via a **Clinical Trial Information System (CTIS)**. CTIS is the **single entry point** for submitting clinical trial information in the EU. All communication including final decision from the authorities will be 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. Link for sponsors workspace in CTIS

- 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 submit, complete and maintain a clinical trial application (CTA) in Denmark or in EU as a sponsor, using the **trial-centric approach**, as well as management of relevant notifications and information throughout the life-cycle of clinical trials.

Any feedback and questions to the Danish GCP unit´s Guidances is welcome:
GCP unit at Aalborg University hospital: gcp@rn.dk
GCP unit at Aarhus University hospital: gcp-unit@clin.au.dk
GCP unit at Odense University hospital: GCP-enheden@rsyd.dk
GCP unit at Copenhagen University hospital: gcp-enheden.bispebjerg-frederiksberg-hospitaler@regionh.dk

This guidance is based on and can be used as a supplement to the following:

CTIS training guides:

- Clinical Trials Information System (CTIS): online modular training programme | European Medicines Agency (europa.eu) - How to create a CTA – see module 10
- Clinical Trial Information System (CTIS) – Sponsors Handbook
- Quick guide for sponsors – Regulation 536/2014 in practice
- How to access CTIS: Step by step guide to access CTIS
- How to search and create organisations in CTIS: Step by step guideline
- Guide for CTIS common features
- EMAs help desk for CTIS: Service Now - *Before submitting a ticket to Service Desk, please check information available on the EMA CTIS Support page*
  Help desk: Non-commercial sponsors can submit their question now by raising a ticket and indicating their status as a "Non-commercial Sponsor" in the mandatory field "User affiliation".
- EMA CTIS Support page
- Heads of Medicines Agencies: Clinical Trials Coordination Group (hma.eu) (See: Key documents list)

Q&As for CTR and CTIS:

- Regulation CTR Q&A (Question and answer document – Regulation Eudralex vol. 10, Chapter V - Additional documents)
- EMA Questions and answers – Clinical Trials Information System (CTIS) and Clinical Trials Regulation (CTR)
- Danish Medicines Agency Q&A and general information from DMA
- Danish Ethics Committee Q&A

1.2 Sponsor is responsible for the application via sponsors workspace

The sponsor workspace provides clinical trial sponsors with functionalities for submission of CTA's, notifications and clinical trial results to Member states authorities and the public and management of information throughout the life cycle of clinical trials.

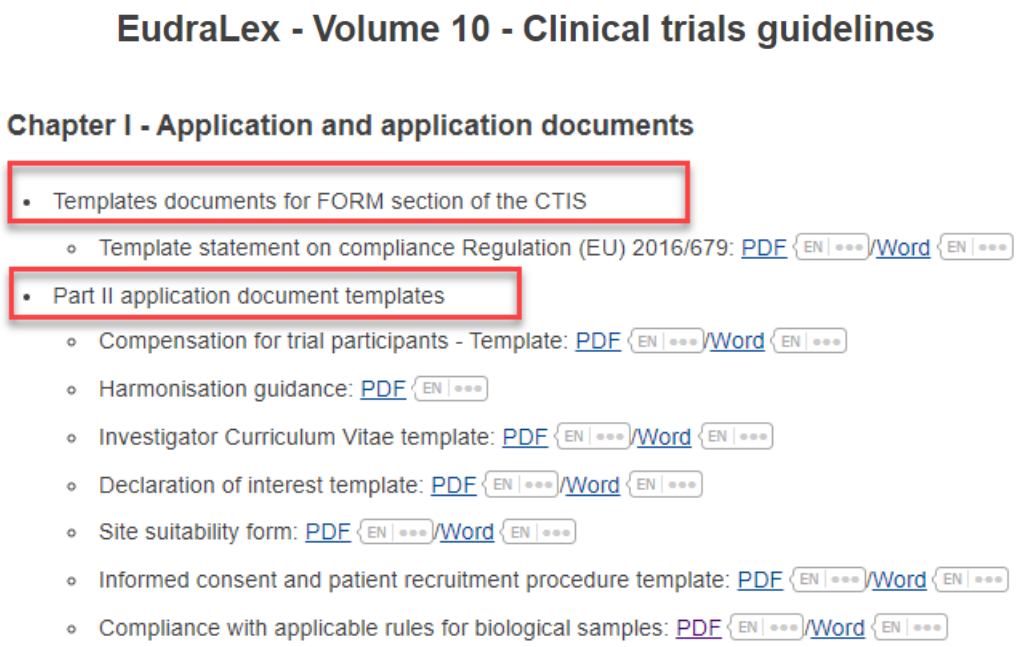
2 How to Create, Submit and Withdraw an initial Clinical Trial Application (CTA)

2.1 Application dossier for the initial application

Link to the CTIS database. For first time log-in see section 3.2 in the "The Danish GCP Units guide – User access, roles and responsibilities in CTIS"

The documents for the Clinical Trial Application dossier is described in Annex I of the CTR.

Info box:
Templates for some documents can be found in
EudraLex - Volume 10 - Clinical trials guidelines
GO TO: Chapter I - Application and application documents



EudraLex - Volume 10 - Clinical trials guidelines

Chapter I - Application and application documents

- Templates documents for FORM section of the CTIS
  - Template statement on compliance Regulation (EU) 2016/679: PDF EN /Word EN
- Part II application document templates
  - Compensation for trial participants - Template: PDF EN /Word EN
  - Harmonisation guidance: PDF EN
  - Investigator Curriculum Vitae template: PDF EN /Word EN
  - Declaration of interest template: PDF EN /Word EN
  - Site suitability form: PDF EN /Word EN
  - Informed consent and patient recruitment procedure template: PDF EN /Word EN
  - Compliance with applicable rules for biological samples: PDF EN /Word EN

Info box:
Please avoid any kind of signatures, both digital and wet ink signatures, in all documents, as they can be copied, when the documents are made public. Be aware not to include personal information (e.g. CPR numbers, private addresses and telephone numbers) in investigators CV.

Overview of documents and information that are made public in CTIS public database: Revised CTIS Transparency Rules

Info box:
Language requirements (Part I): CTR Q&A Annex II
National requirements (Part II) CTR Q&A Annex III (CTR Q&A: *Eudralex Vol. 10: Chapter V)*
List of all documents: CTR ANNEX I - APPLICATION DOSSIER FOR THE INITIAL APPLICATION

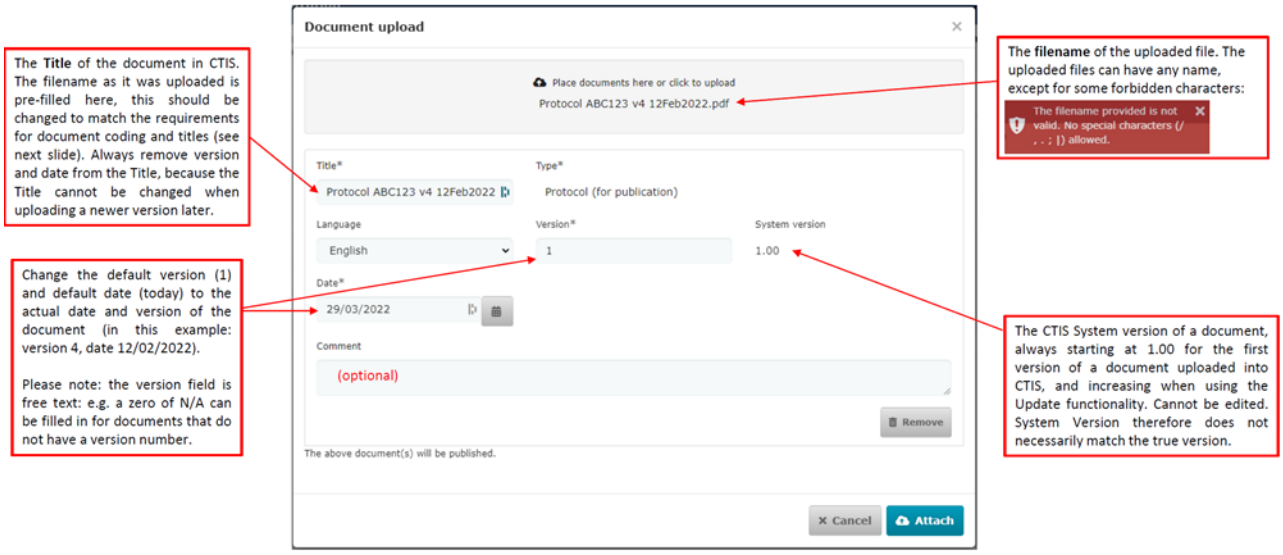
The asterisk * in CTIS indicates mandatory fields. Some separate documents (e.g. recruitment) must be uploaded even though the same text is already mentioned in other documents e.g. the protocol.
Documents can be in Danish for trials running in Denmark only.

Part I	Part II
➢ Cover letter (content, Annex 1, section B in the Regulation) – cover letter must be uploaded in the section "Form" in CTIS. Template: Clinical Trials Coordination Group (hma.eu) , CTCG "Key documents list") ➢ EU Application form (structured data entered directly in CTIS) ➢ Protocol and protocol synopsis (synopsis can be part of protocol or separate document) (CTR Q&A, section 5.8 for synopsis guidance) ➢ Patient facing documents (questionnaires, diary) that are linked to the endpoints of the clinical trial shall be uploaded with the protocol in Part I - *you can upload several documents with the protocol* ➢ Investigators Brochure (IB)/SmPC ➢ IMPD quality, safety and efficacy/ Simplified IMPD with reference to the valid SmPC ➢ Content of labelling of IMPD ➢ Template statement on compliance with Regulation (EU) 2016/679 (GDPR) (template in Volume 10) – must be uploaded in the section "Form" in CTIS	➢ Informed consent and patient recruitment procedure template (template in Volume 10) ➢ Subject information and informed consent form ➢ Patient facing documents (e.g. recruitment) ➢ Investigator CV (template in Volume 10) – it is not mandatory to use this template ➢ Site suitability form (template in Volume 10) - one form per site ➢ Proof of insurance cover or indemnification (Insurance: non-commercial sponsors can upload a document stating that the trial sites in DK are covered by "Patienterstatningen") ➢ Financial and other arrangements ➢ Proof of payment of fee ➢ Compliance with applicable rules for biological samples (template in Volume 10)

Info box:

Documents in CTIS **must not contain DATE and VERSION in the file name** 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 , also in case of substantial modifications. Or you can rename your documents in CTIS after upload.

1. Uploading documents into CTIS: filename, CTIS title, version number and date



Document codes and titles in CTIS (version 1.4, dd 7 September 2022)

Please adhere to the structure of CTR Annex I for document codes and titles when uploading files in CTIS, as shown below (Part I: section B-J; Part II: section K-S). Please fill in the requested information in the marked grey fields. Make sure that all documents have self-explanatory titles including relevant identification when applicable as mentioned below and include "redacted" in the file name in case a separate document for publication is uploaded. Please note that the files uploaded into CTIS can have any filename, but do not include special characters ()/,.;|[]. The coding and naming applies to the document name in CTIS (the field 'Title' in the upload window). The original filename is pre-filled in the field 'Title' but can be adapted. Version number and date should not be in the document title, instead indicate the correct version number and date in the corresponding fields in the upload window.

B. Cover letter
B1_ Cover letter EU CT number

D. Protocol
D1_ Protocol EU CT number
D1_ Protocol synopsis_ENG EU CT number
D1_ Protocol synopsis_NL EU CT number (*include MS in title, example is for NL*)
D2_ Protocol modification nr number EU CT number (*in case of SM as separate doc.*)
D3_ DSMB Charter EU CT number
D4_ Patient facing documents e.g. questionnaire or diary (*if applicable*)
D5_ Master protocol EU CT number and name and sub-protocol name and specific number/ID (*applicable for complex CT*)

E. Investigator's Brochure
E1_ IB product name

F. Documents GMP compliance (if applicable)
F1_ GMP declaration abbreviated name manufacturer/importer
F2_ QP declaration abbreviated name manufacturer/importer
F3_ Other statements/licences (*e.g. import license*) abbreviated name manufacturer/importer

G. Investigational Medicinal Product Dossier
G1_ IMPD_Q product name
G1_ IMPD_E-S product name
G2_ SmPC product name

H. Auxiliary Medicinal Product Dossier
H1_ AxMPD product name

I. Scientific advice and pediatric investigational plan (PIP)
I1_ Scientific advice name organization
I2_ PedCo opinion
I3_ PIP decision name agency

J. Labeling
J1_ Label IMP_NL product name (*include MS in title, example is for NL*)
J1_ Label IMP_ENG product name
J2_ Label AxMP_NL product name (*include MS in title, example is for NL*)
J2_ Label AxMP_ENG product name

K. Recruitment arrangement
K1_ Recruitment arrangements
K2_ Recruitment material description

L. Subject information sheet, informed consent form, other subject information material
L1_ SIS and ICF description (*e.g. SIS and ICF adults, SIS and ICF 12-16 yr*)
L2_ Other subject information material description (*e.g. information leaflet adults*)

M. Suitability investigator
M1_ CV Investigator name investigator and clinical trial site (*use abbreviations*)
M2_ DoI Investigator name investigator and clinical trial site (*use abbreviations*)

N. Suitability facilities
N1_ Site suitability form name clinical trial site

O. Proof of Insurance or indemnification
O1_ Trial participant insurance certificate
O2_ Proof of coverage sponsor or investigator name sponsor/trial site (*if not covered by O1*)

P. Financial and other arrangements
P1_ Compensation trial participants, investigator, funding and other arrangements

R. Compliance GDPR
R1_ Compliance on the collection and use of personal data

S. Biological samples
S1_ Compliance on the collection, use and storage of biological samples

[CTCG best practice guide naming of documents, version 2.01, 9 March 2023]

2.2 Fill in the trial title and sponsor organisation in CTIS

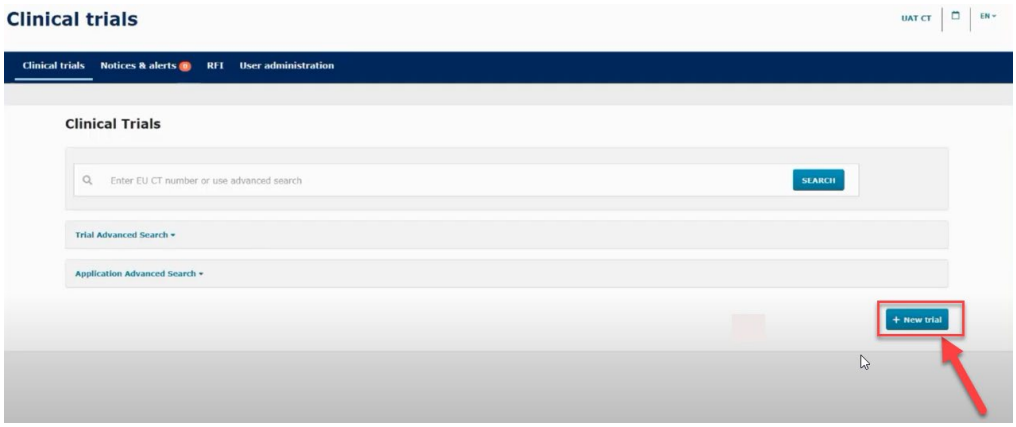
Info box:

The padlock 

needs to be **locked** to enter data. Remember to unlock after uploading data in each tab. Save the data before going to the next tab.

CTIS should be completed in English. Remember to click **Save** on the top of the page. This should be done often as there will be no automatic savings.

When you are logged into CTIS, click on the tab "New Trial":



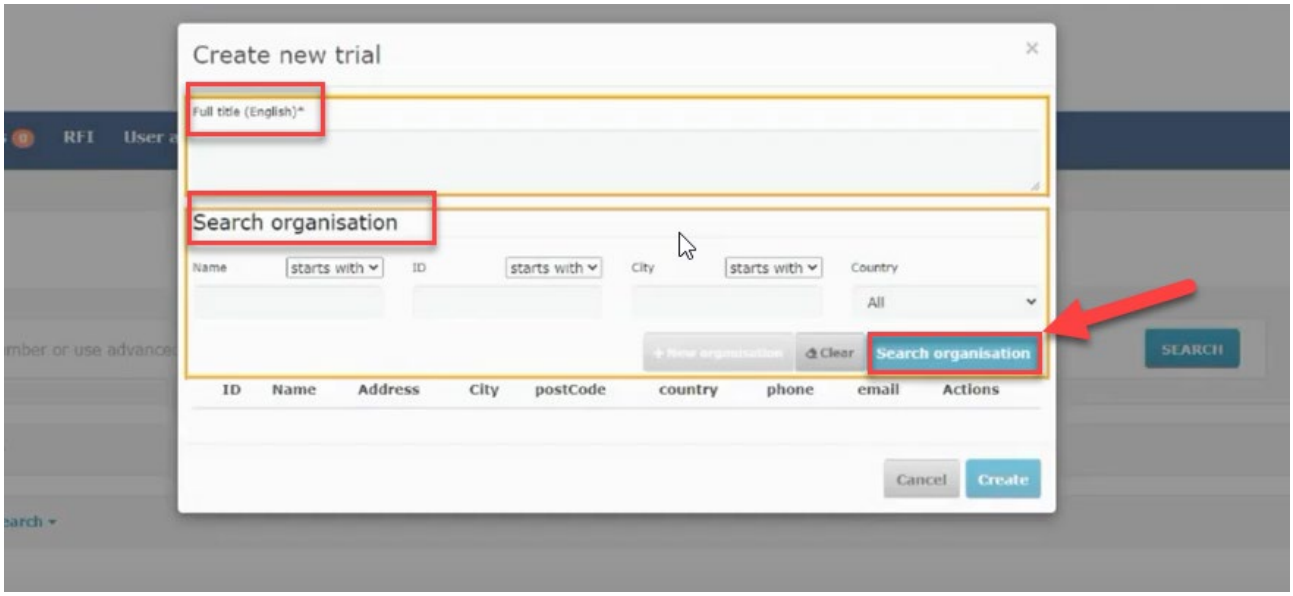
Type the full title of the trial.

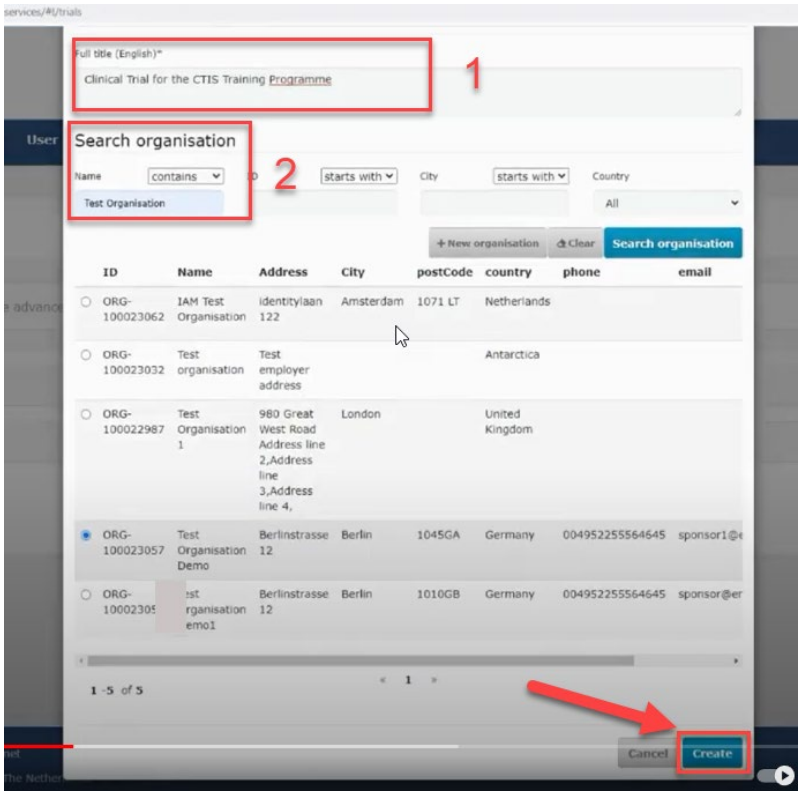
Click on the "Search organisation" to search for the sponsor which must be registered in the Organisation Management System (OMS) before the CTA is created. It is important to choose the organisation where sponsor is located if it is different from where you are located. It is not possible to correct afterwards.

Be sure you choose the right address for the specific organisation. This can be the address of the hospital, university etc., where sponsor is located.

If the specific address of sponsor location, is not registered in OMS, then you must choose the overall address of the hospital/university.

Some hospitals are mentioned in OMS as "Region Hovedstaden" and "Region Midtjylland" etc. Be aware to choose the right location (street address) of the hospital.

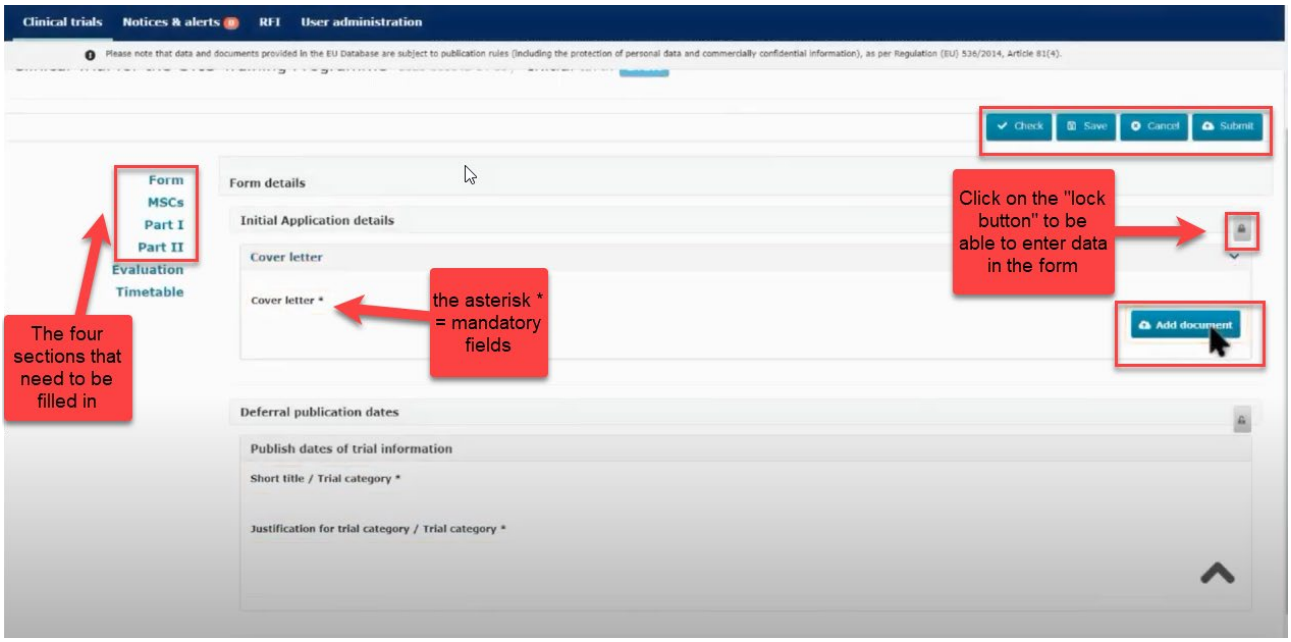




When the two fields are filled in, click on the create button and the draft of the CTA will be created. On the following picture on the top right side there are four buttons:

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

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.



Info box:

The ”Check” button 

can as well be used to validate for missing sections at all times during completion.

The asterisk * in CTIS indicates mandatory fields to be filled in and/or mandatory upload of documents.

See also check list of required fields/documents:

List of required fields per CTA (europa.eu).

2.3 Fill in the Form and Member states concerned (MSCs) section

Video on this topic in EMA training module 10:

Training video: Fill in the Form and the MSC sections

Form: Add the cover letter and category of the trial. To select the trial category you must use the drop down menu. The category can be from 1- 3.

Category 1: Pharmaceutical development clinical trials:
First trials conducted with new medicines or new pharmaceutical forms or routes of administration of existing medicines as well as generic or biosimilar medicines. Includes **phase 0 and I clinical** trials in healthy volunteers or patients. **Bioequivalence and bioavailability trials** are also in this category 1.

Category 2: Therapeutic exploratory and confirmatory trials:
Carried out for treatment, diagnosis or prevention. Include the **phase II and III and phase I+II (integrated)** trials carried out during clinical development of a new product or during exploration of new indications, pharmaceutical forms, strengths and routes of administration for an existing product that already has a marketing authorisation.

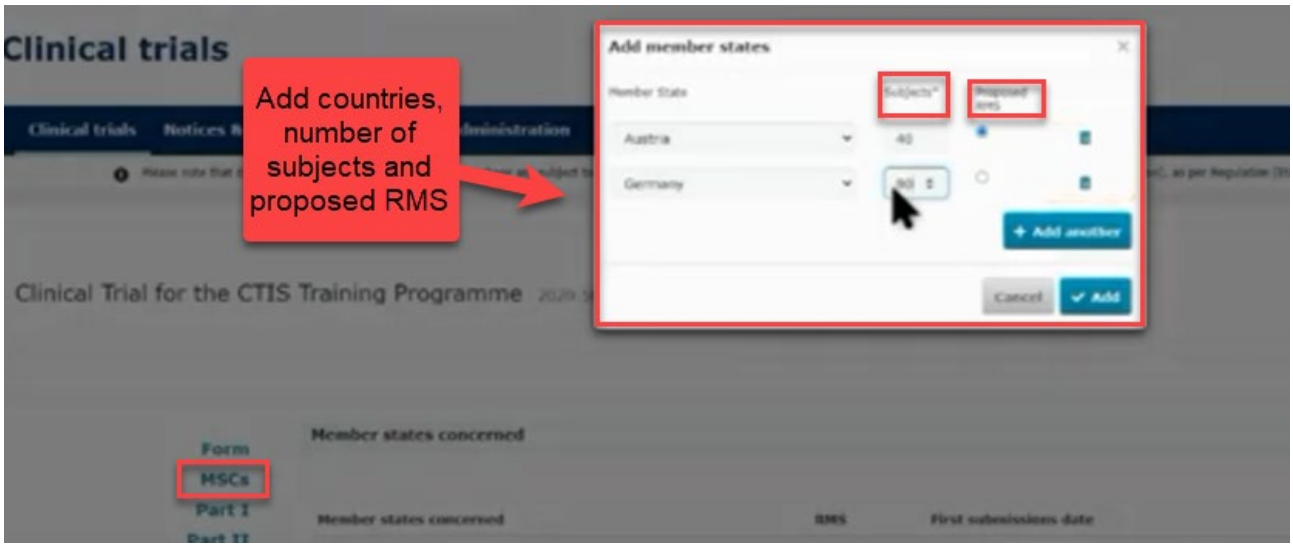
Category 3: Therapeutic use clinical trials:
The study drug is in routine use in medical practice. Includes **phase IV trials and phase III+IV (integrated)** that are post marketing studies to delineate additional information including the risk, benefits, and optimal use of the study drug. They are carried out in accordance with the terms of the marketing authorisation (indication, route of administration and pharmaceutical form and strength).
Low-intervention clinical trial is also a category 3 trial.

More information about categories, see guideline: Revised transparency rules, Annex 1

Thereafter you need to add the “justification for the trial category”.

Info box:
The protocol will automatically be accessible in the public workspace (Category 2 and 3 trials).
In case of sensitive information in the protocol according to GDPR, it is also possible to upload a second edition of the protocol not for publication. The first document you upload is always for publication so be sure to choose the document without sensitive information first.
If you afterwards want to upload a document not for publication click on the ´Add´ button (+) and upload a second protocol (not for publication)

MSCs: Member states concerned. Add the countries (member states) where the trial application should be submitted. Add the number of subjects that are expected to participate in each country. If there are more than one country participating in the trial, you can suggest a country as RMS (reference member state) which is the country that are responsible for the overall scientific assessment.



2.4 Fill in the Part I section

Videos on this topic in EMA training module 10:

Training video: Fill in the Part I section

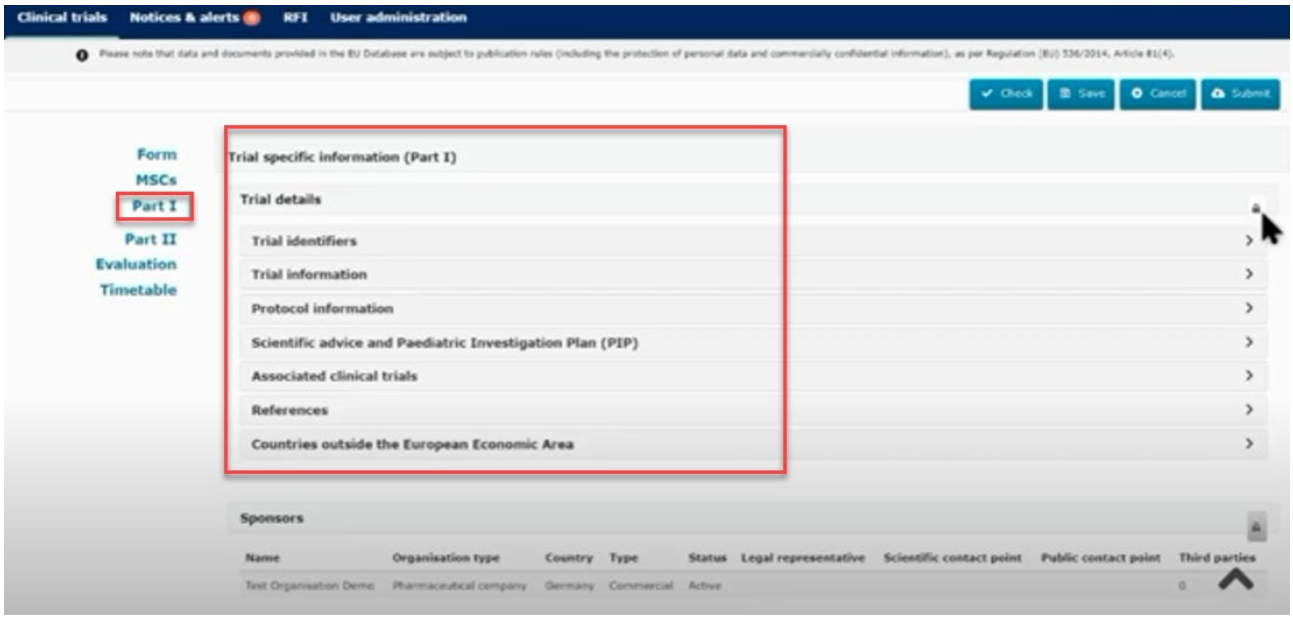
Training video: Fill in the trial details of Part I section

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

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

Part I: This section contains information mainly to be assessed by the Medicines Health Authorities in each country.

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

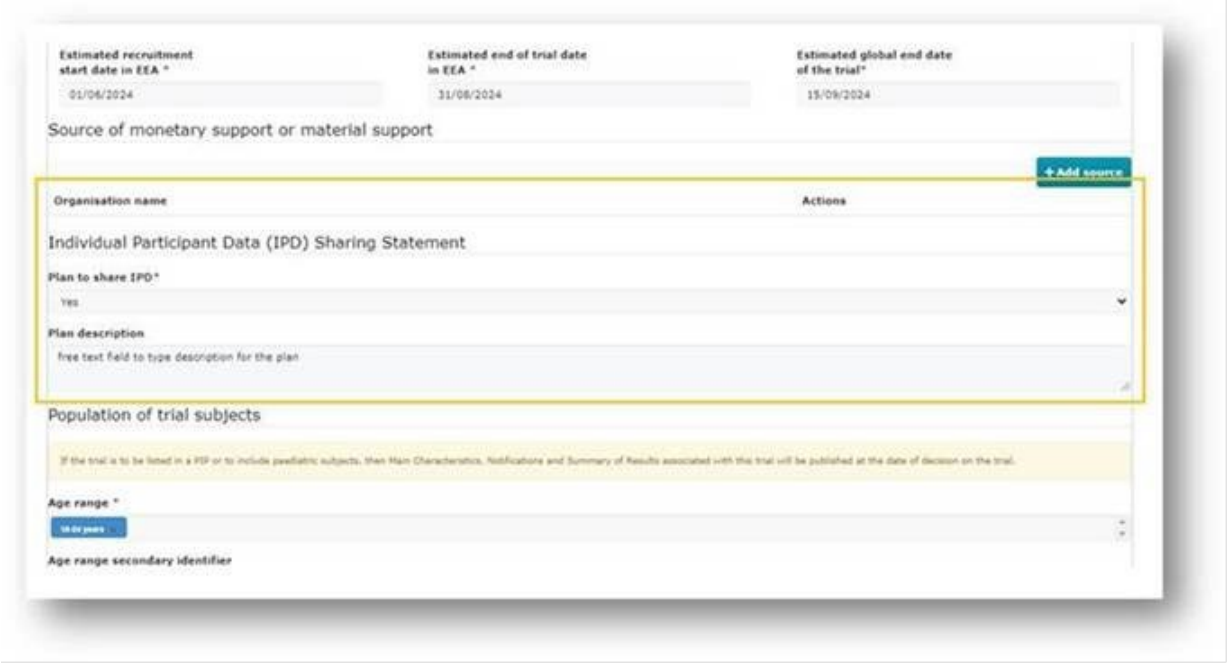


For the main objective you can choose several “trial scopes” that are relevant for the trial.

Trial Information
Two new fields have been added in the Part I section of the application form in CTIS, above the fields for the population of trial subjects. The first new field, ‘Plan to share IPD’, is mandatory. Users need to select a response from a drop-down list of pre-defined values (Yes/No/Undefined). We recommend that sponsor users select “Yes” or “No”, to meet the requirements of the International Committee of Medical Journals Editors (ICJME).

The second field, ‘Plan description', is optional. It allows users to describe the plan in detail, in free text, using up to 1000 characters.

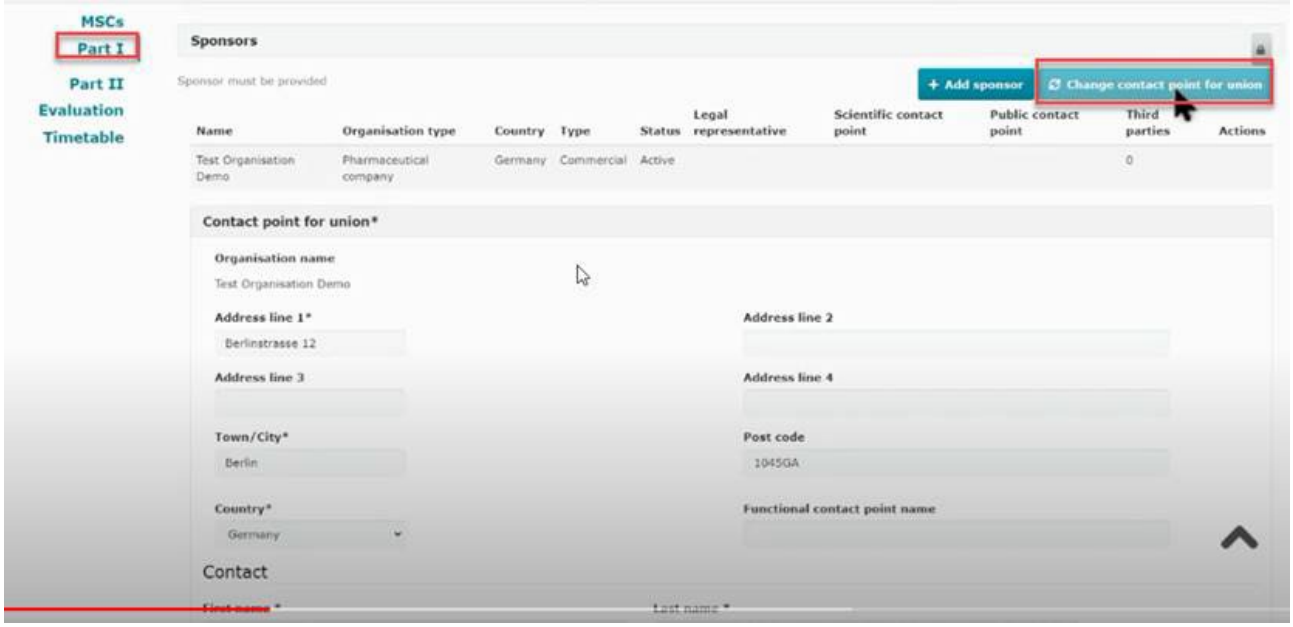
The field ‘Individual Participant Data (IPD) Sharing Statement’ collects information on how this data will be made available to other researchers. Sponsor users in CTIS can now record in a structured way how IPD will be shared in the future.

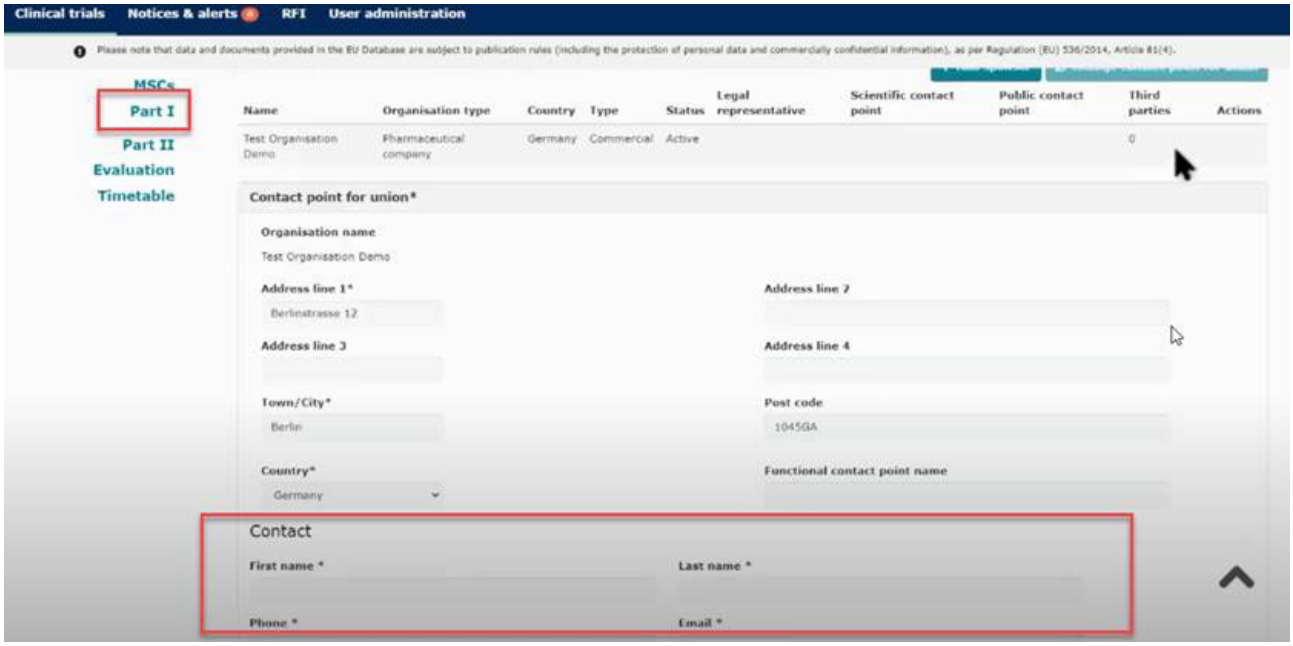


Important note: If you are working on a draft application (initial, SM, NSM, RFI response) with Part I in scope, please ensure that you populate the mandatory field “Plan to share IPD” before submitting, otherwise the technical validation will flag this field and prevent the submission.

Sponsor details

Includes sponsor information which was added when the application was first created.





Click on the sponsor line and add:

- The legal representative (an EU contact that only need to be added if sponsor is located outside EU),
- Scientific contact point and public contact point (must be added for all trials and can be the same person) – The organization (including its email address) where the general public may obtain information about the clinical trial - in academic/non-commercial trials this person will often be the sponsor contact point (the contact point for union).
- Contact point for union – this is the **sponsor representative from the sponsor organisation**. This contact is used by the Union in case of required **contact to the sponsor** - in academic/non-commercial trials this person will often be the same as the scientific contact point.
- Third party (only if tasks or functions in the trial have been delegated to third parties). This is e.g. On-site monitoring, Safety reporting, E-data capture (for example, if agreed with the GCP units) or

laboratory facilities. If the third parties are not already registered in OMS, they can also be registered directly in CTIS without the need to register them in OMS (please refer to section 2.7).

- **To search for a third party in OMS you need to use the organization number (ORG) or location number (LOC) – it is not possible to search for the GCP-unit or a specific laboratory facility.**

Only the coordinating GCP unit in Denmark needs to be added as third party.

The organisation numbers (ORG) and location numbers (LOC) for the four Danish GCP units are mentioned below.

It is important that you choose the right ORG and LOC number. Each GCP-unit is registered only with hospital addresses and the name "GCP-unit" is not mentioned.
Phone no. and E-mail are mandatory fields and must also be added in CTIS.

Info box:
Please contact the GCP-unit in your Region
to inform about the trial
when you submit a CTIS application
where you mention the GCP-unit as third party.
https://gcp-enhed.dk/kontakt/

GCP-enheden ved Københavns Universitetshospital:

ORG-100028217
Organisation name: Frederiksberg Hospital
Address: Nordre Fasanvej 57
Location ID: LOC-100045259
Tel. phone: +45 38 63 56 20
E-mail: gcp-enheden.bispebjerg-frederiksberg-hospitaler@regionh.dk

GCP-enheden ved Odense Universitetshospital:

ORG-100007716
Organisation name: Odense University Hospital
Address: J B Winsloews Vej 4
Location ID: LOC-100053630
Tel. phone: +45 51 25 14 13
E-mail: OPEN@rsyd.dk

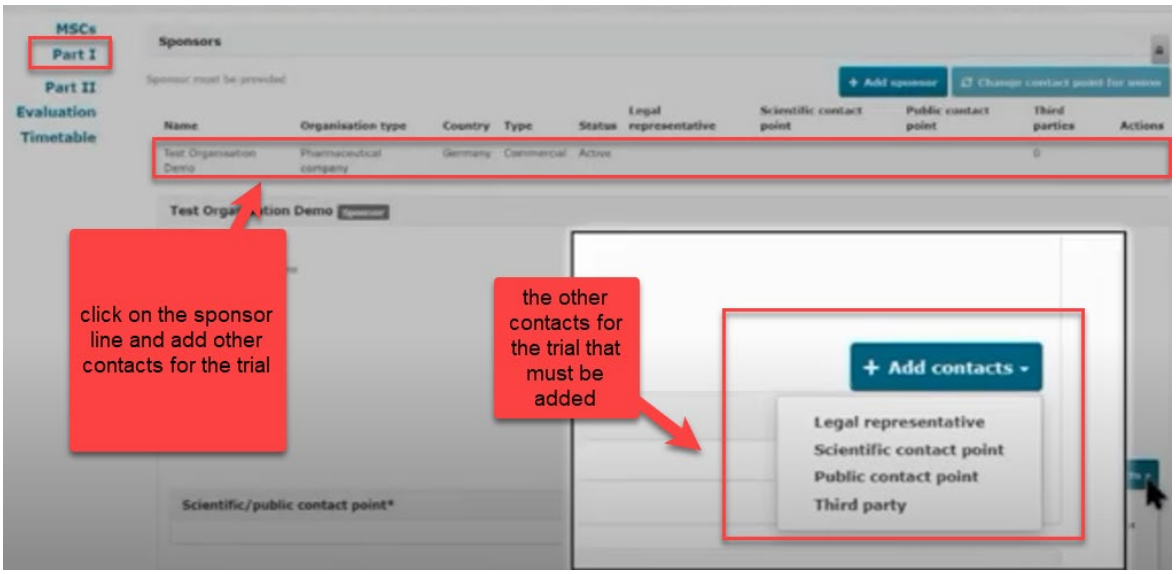
GCP-enheden ved Aarhus Universitetshospital:

ORG-100028380
Organisation name: Aarhus Universitet
Address: Palle Juul-Jensens Boulevard 11
Location ID: LOC-100079923
Tel. phone: +45 78 41 39 50
E-mail: gcp@clin.au.dk

GCP-enheden ved Aalborg Universitetshospital:

ORG-100022335
Organisation name: Aalborg Universitetshospital
Address: Søndre Skovvej 15
Location ID: LOC-100047716
Tel. phone: +45 21 53 13 49
E-mail: gcp@rn.dk

When adding a third party remember to update information about the third party (duties, phone number and email) using the pencil.

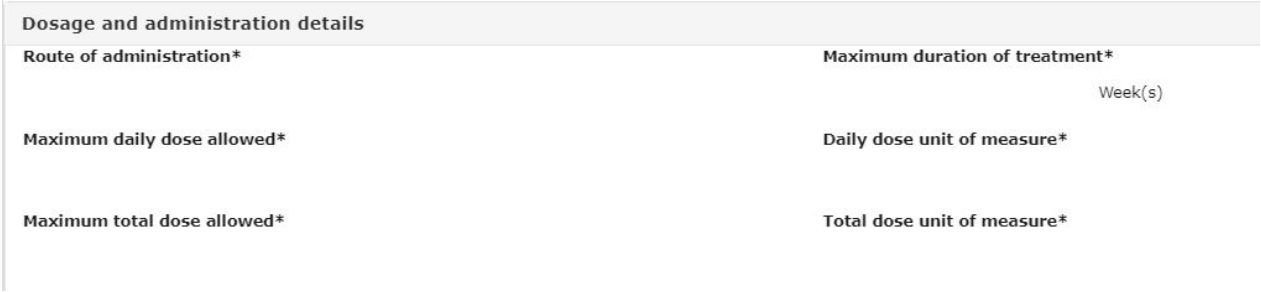


Product details

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

An authorised product or active substance can be added by searching per product details, active substance, or ATC code, as applicable.

When a substance is added further information must be entered. Be aware that if you tick the selected substance, there will reveal further sub-sections that contain mandatory fields to be populated.



It is mandatory to fill in "Information about the modification of the Medicinal Product" and "Dosage and administration details" for each product in CTIS. Dosage and administration details must be thoroughly and correct described in the protocol, this is very important. Therefore when you fill in "Dosage and administration" in CTIS you must use a safety perspective. If you don't know maximum daily dose allowed (e.g. because the product is administrated on a weekly basis) then you can estimate or calculate maximum daily dose.

Non authorised medicinal products must now be registered in the Extended Eudravigilance Medicinal Product Dictionary (XEVMPD), if not already done. For IMPs not registered in XEVMPD there is no EU MP number. Please contact the manufacturer (e.g. pharmacy) regarding registration of the product in the XEVMPD database.

For sponsors in the Capital Region: Please contact "Reg H Sygehusapotek Herlev" to get your product registered in XEVMPD, mail: kliniskeforsoeg.region-hovedstadens-apotek@regionh.dk or Tel: 44577803.

For IMPSs that are not authorised in the EU and do not have a marketing authorisation from a third country that is party to ICH, and are not manufactured in the EU, an authorisation referred to in article 61(1) and a QP declaration of GMP equivalence is required. In the latter case, if a Mutual recognition Agreement (MRA) covering also clinical trials is in place with the particular country, the latter declaration is not required if the MRA provides for GMP equivalence already.

In case IMP is still under development and the sponsor of a clinical trial is not the product owner (PO) of the IMP and should not have access to the quality IMPD (IMPD-Q) or associated considerations/RFI in order to protect commercially confidential information, the PO can submit the IMPD-Q to CTIS via an initial application for Part I only ("IMPD-Q-only application"). The "IMPD-Q-only application" must be submitted at the same time as the initial application of the trial for which the IMP is intended ("sponsor trial"). It is recommended that both submissions are not more than 24 hours apart.

GMP and quality of IMP (In Danish only, laegemiddelstyrelsen.dk)

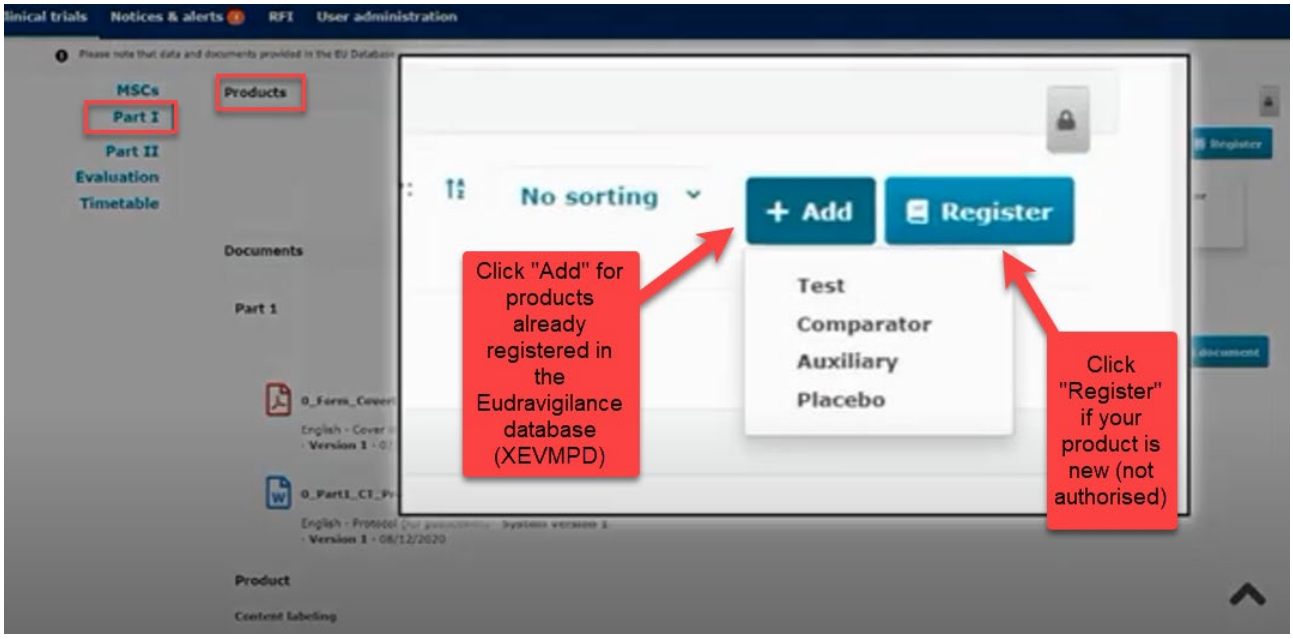
All medicinal products that are marketed in EU are registered in XEVMPD and can therefore be found in CTIS. Blinding, including re-encapsulation and re-packaging, of a marketed medicinal product does not need to be re-registered in XEVMPD. You can also read more about the registration in XEVMPD at the DKMA homepage (in Danish only).

The field "Excluded MSC"
This field is only relevant for multinational trials and should not be used for national trials. It must only be used if it is described in the protocol (and cover letter), that some products (Test, Auxilliary, Comparators), drug forms or strengths, *will not be used* in all Member States concerned.

Example: A multinational trial with MSCs Denmark, France and Netherlands with paracetamol as the test product. In France and Netherlands their sites will be using specifically Paracetamol Zentiva and in Denmark their sites will use Pamol. Hence, DK is added as "Excluded MSC" in the Paracetamol Zentiva tab, and FR and NL in the Pamol tab.

Placebo

If the IMP is a placebo, the information requirements shall be limited to quality data, a simplified IMPD (sIMPD) must be submitted. No additional documentation is required if the placebo has the same composition as the tested IMP (except the active substance), is manufactured by the same manufacturer, and is not sterile. In this case placebo must be added as an "Authorised Substance" followed by a search for *placebo*, remember to give the correct pharmaceutical form and route of administration as given for the test product. The strength for placebo must be "0 mg" and the pharmaceutical form must be added.



Documentation requirements in the application dossier
As a general rule, the documentation requirements in the application dossier for IMPs also apply to non-authorised AxMPs and authorised AxMPs which are modified while such modification is not covered by the marketing authorisation. Regulation (EU) No 536/2014 Annexes I and II set out the requirements of the application dossier for initial applications and substantial modifications, respectively. Registration in CTIS is only mandatory for non- authorised AxMPs and for authorised AxMPs for which such modification is not covered by the marketing authorisation.

In the section "**Investigator brochure for the medicinal product"** either the Investigators Brochure (IB) or the SmPC must be uploaded. The labelling must only be uploaded if the IMP has a special label.

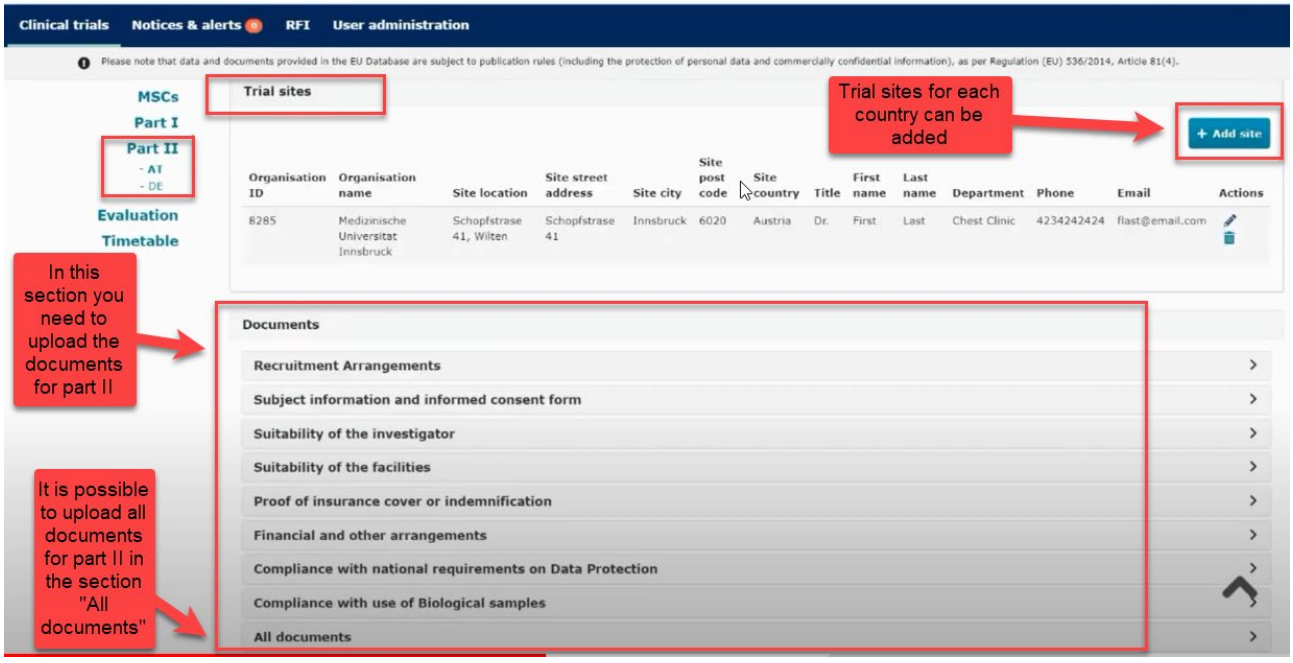
If you scroll down to the end you see all the uploaded documents for Part I.

2.5 Fill in the Part II section

Video on this topic in EMA training module 10:

Training video: Fill in the Part II section

Part II: Individual information for each country, mainly to be assessed by the Ethics Committees in each country. Local documents from each country needs to be uploaded.



Documents listed and uploaded in chronological order is recommended in the section "All documents".

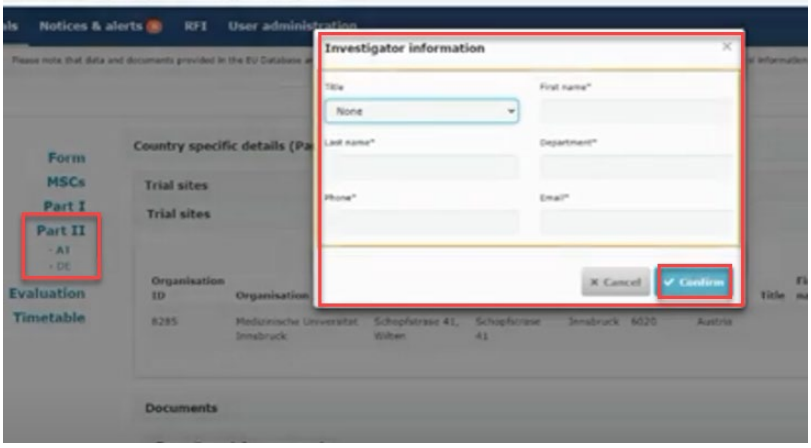
Trial sites must be added: Name, address and e-mail of trial sites and principal investigators at the trial sites.

Info box:
Please be aware not to include personal information (e.g. CPR numbers, private addresses and tel. numbers) in investigators CV and in the structured data in CTIS. The investigator name, mail and phone no. will be public available in "CTIS Public", when the trial is approved.
It is recommended to use a mail address and tel. phone no., created for the specific trial or from the department (site).

Please note: For some trials the trials and investigators will be listed in the Danish database "Nationalt Forsøgsoverblik". Only applicable for cancer trials. The website is driven by the Danish Region Zealand and the GCP-units are not involved in this website.

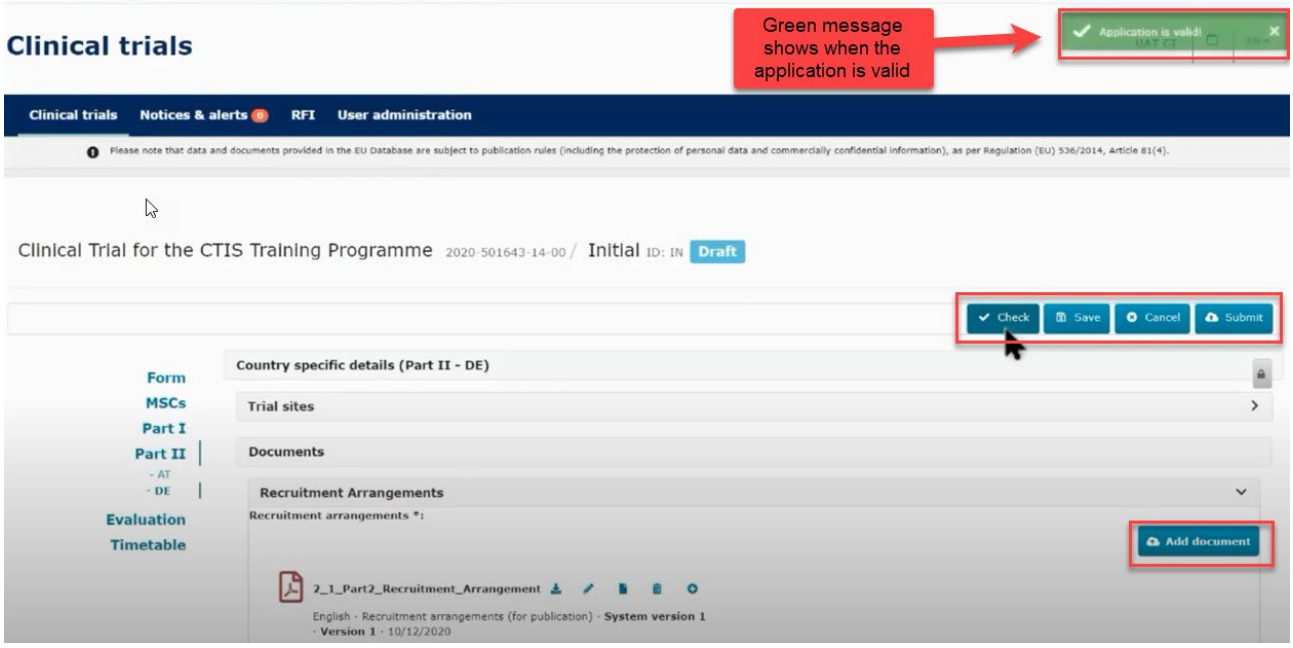
The name and address of the university/hospital organisation must be registered in OMS/CTIS before you can search and add the organisation (site) to the application form. If the specific address of investigator location, is not already registered in OMS or CTIS you can add the site – please refer to section 2.7.

When the organisation is found or registered in CTIS, the details of the principal investigator at each site must be added (first and last name, department, email address, phone).

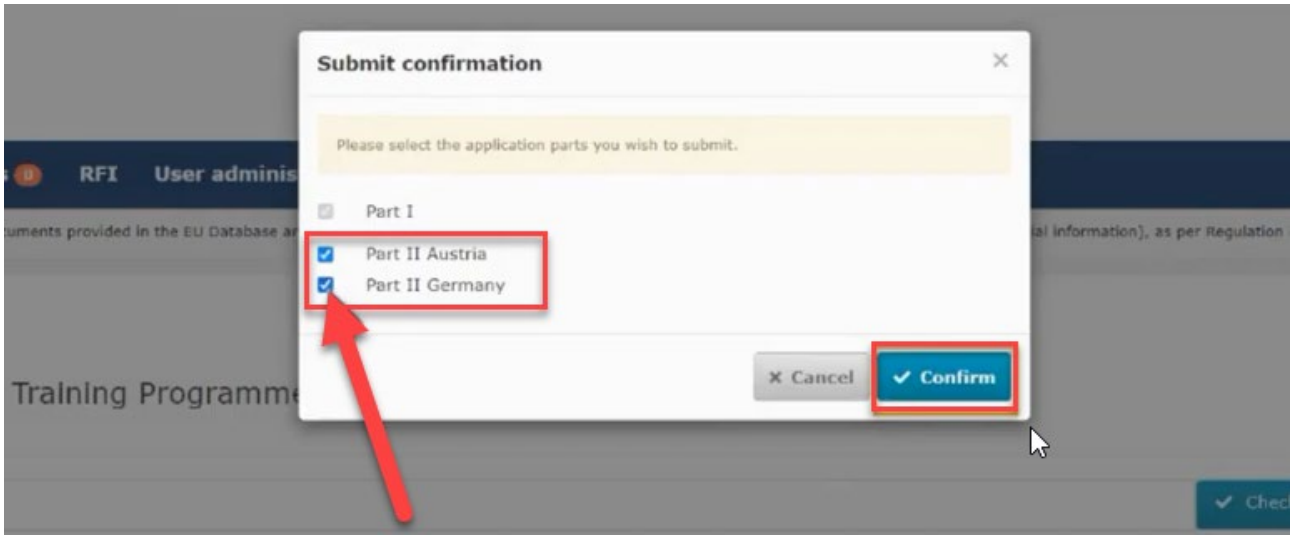


Supporting documents: Upload documents in each separate section or upload all the documents in the section "All documents" and specify in the document title what the document contains.

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.



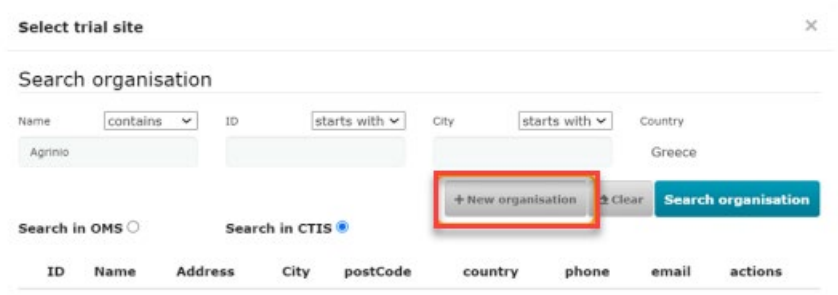
Remember to upload the Part II information relevant for each country. Part I is always included by default in the submission for all countries.



2.6 Site and third party registration directly in CTIS

Sites and third parties can also be registered directly in CTIS without the need to register them in OMS.

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



If users do not find the site in CTIS (red message will be displayed on the upper right corner), or if it is not listed in the search results, they can create the site in CTIS by clicking the button 'New Organisation', which will now appear enabled.

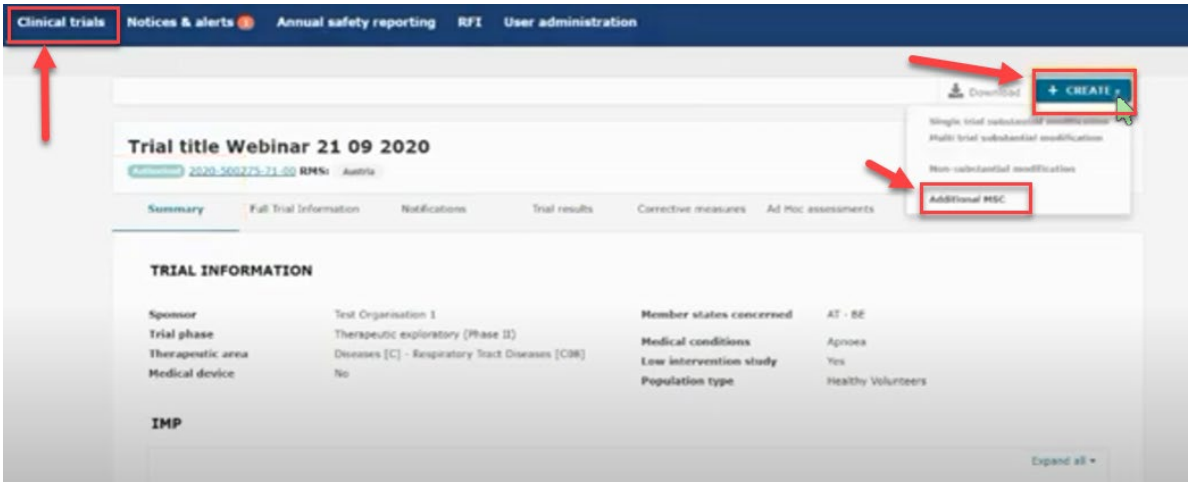
For more details of site registration in CTIS, please refer to EMA module 03 step by step guide.

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

Video on this topic in EMA training module 10:

Training Video: How to submit an additional MSC application in the CTIS Sponsor workspace

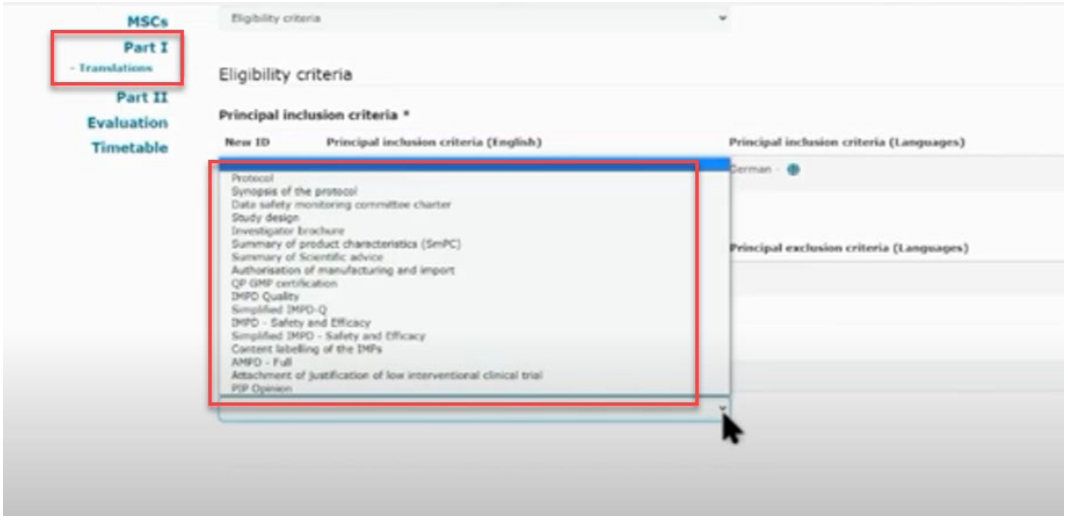
To add a new member state (MSC) to an already approved application. In the page of the authorised clinical trial click on the "create" button and choose "Additional MSC".



In the next pop-up window you can select one or several MSCs to add on 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 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.

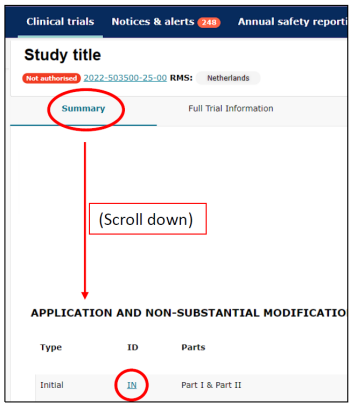
2.8 Withdrawal of an application

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

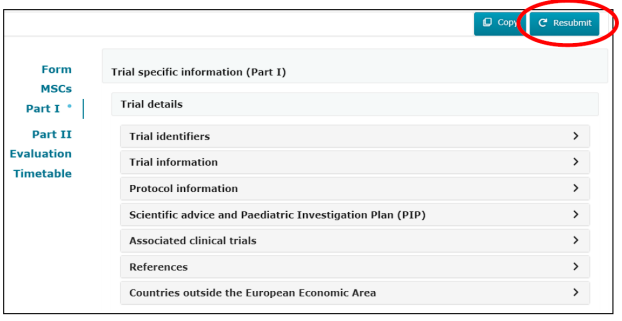
2.9 Resubmission of a trial

Resubmission of a trial

CT applications can lapse (e.g. when the sponsor misses a response due date), be withdrawn by the sponsor, or rejected by the authorities. Lapsed, withdrawn and rejected CT applications can be resubmitted.
On the CT page, in the Summary tab, scroll down to the application section. Click the application you want to resubmit: IN = initial application



Then, in the top-right corner, click Resubmit



The documents of the original submission will be copied to the resubmission. Documents can be replaced if necessary (e.g. cover letter). Please note: the version and date of all documents is reset to v1 and today, so click Edit (pencil icon) to enter the correct version and date for all documents. The resubmission will keep the original CT-number, but ending with -01.

3 Validation, Request for Further Information (RFI) and Authorisation

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

Videos on this topic in EMA training module 11:

Training Video: How to access and view a request for further information (RFI) in CTIS (Sponsors)

Info box:
Please be aware to regularly check for Request for Information (RFI) from the authorities **in CTIS**. It is not possible to receive any mails or reminders in your mail box.

RFI: Questions from authorities to sponsor.

Sponsor must check for Request for Information (RFI) from the authorities during both validation and assessment. As some RFIs can have a very short deadline for responding, the GCP units recommend that sponsors or delegated personal check for RFI on a daily basis.

Info box:
In case the sponsor does not respond to a RFI before the given deadline, it will cause the lapse of the application - there is no second change. RFI must be answered within the specified deadline for each RFI. Sponsors do only have one change to answer each RFI. When sponsor submits the answer to RFI, all questions from the authorities must be answered.

If the application is rejected, use the “re-submission”.

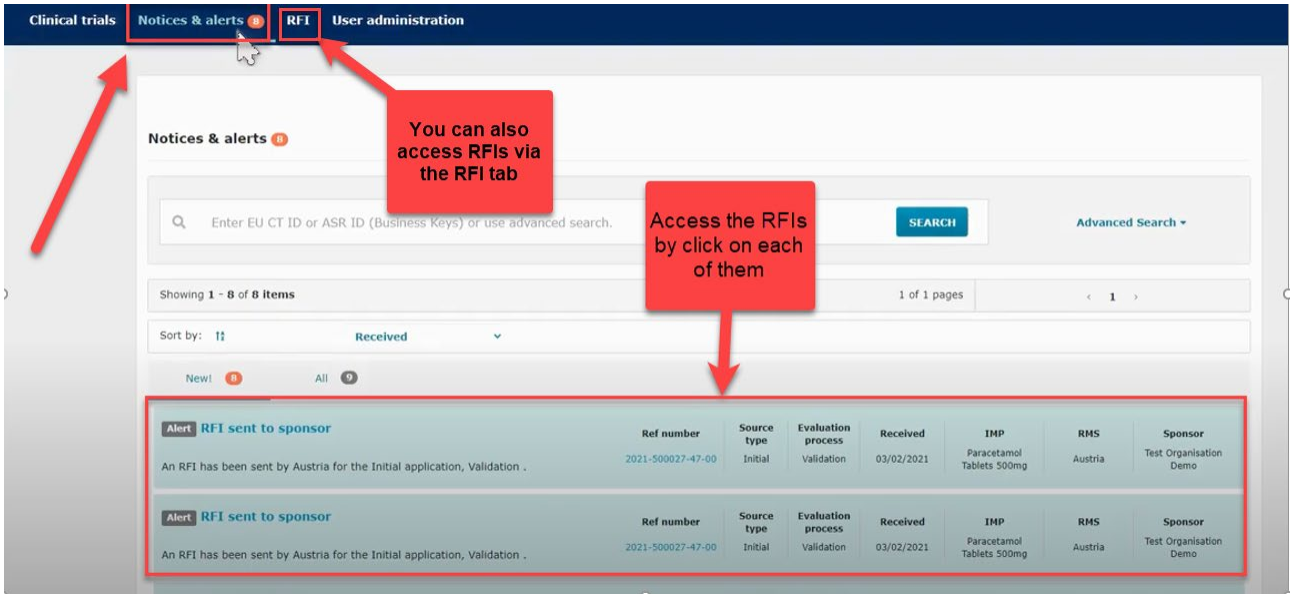
If in doubt about anything – call the Danish Medicines Agency or EC before submitting the answer to the RFI.

A timetable (see section 3.4) for estimated timelines will be generated and available in CTIS for each CTA, but it is important for sponsors to notice that the workflow in CTIS is dynamic. This means that the timelines shown in CTIS correspond to the maximum deadlines foreseen for each task/action. If a task/action is completed before its deadline, the corresponding deadlines for the following tasks/actions are recalculated.

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. The RFI can also be accessed from the RFI tab next to the “Notices and alerts” tab, this is a more direct path to respond to each RFI.

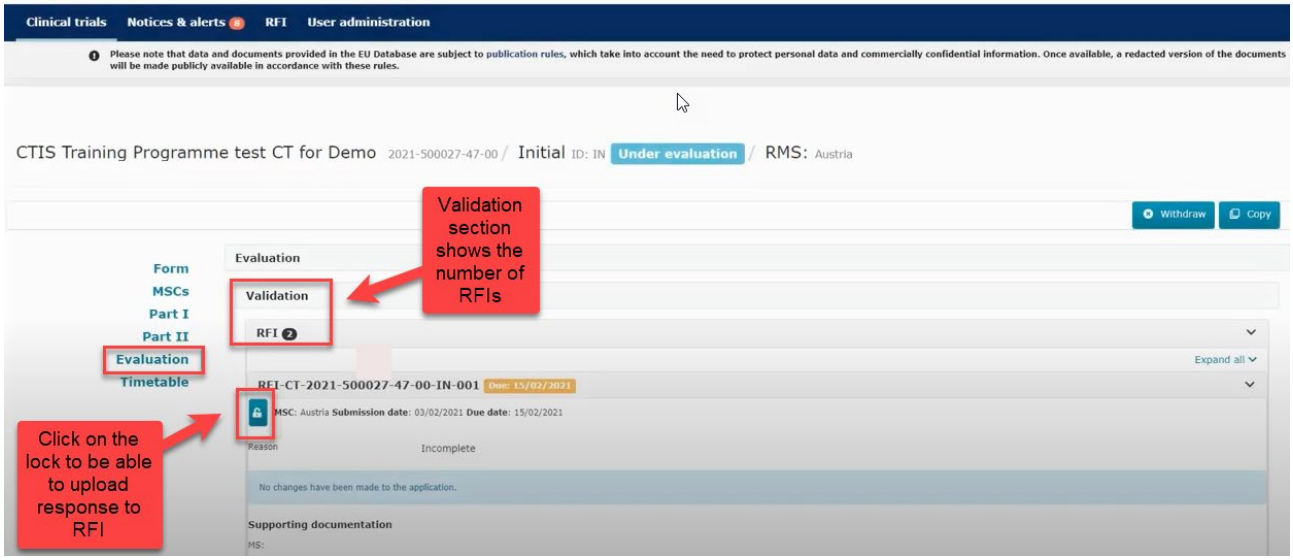
It is possible to download the RFI’s – see section 3.7



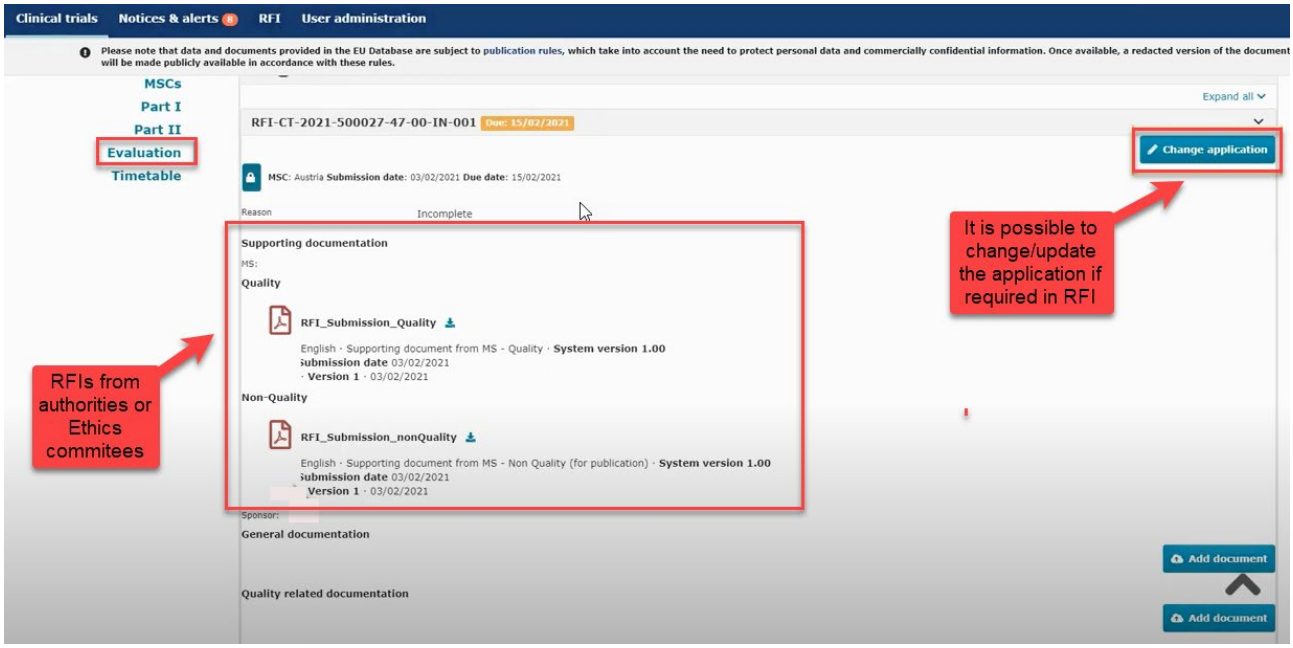
Every single RFI must be opened by clicking on ´RFI- CT-xxxx-xxxxxx-xx-xx-IN-001 IN´ (black text):

In most cases there will be several RFIs and often in both Part I and Part II. The due date for responding to each RFI is stated in “Due” column in the RFI tab.

Click on the RFI and you will be redirected to the “Evaluation” section where the Request for further information (RFI) is shown.



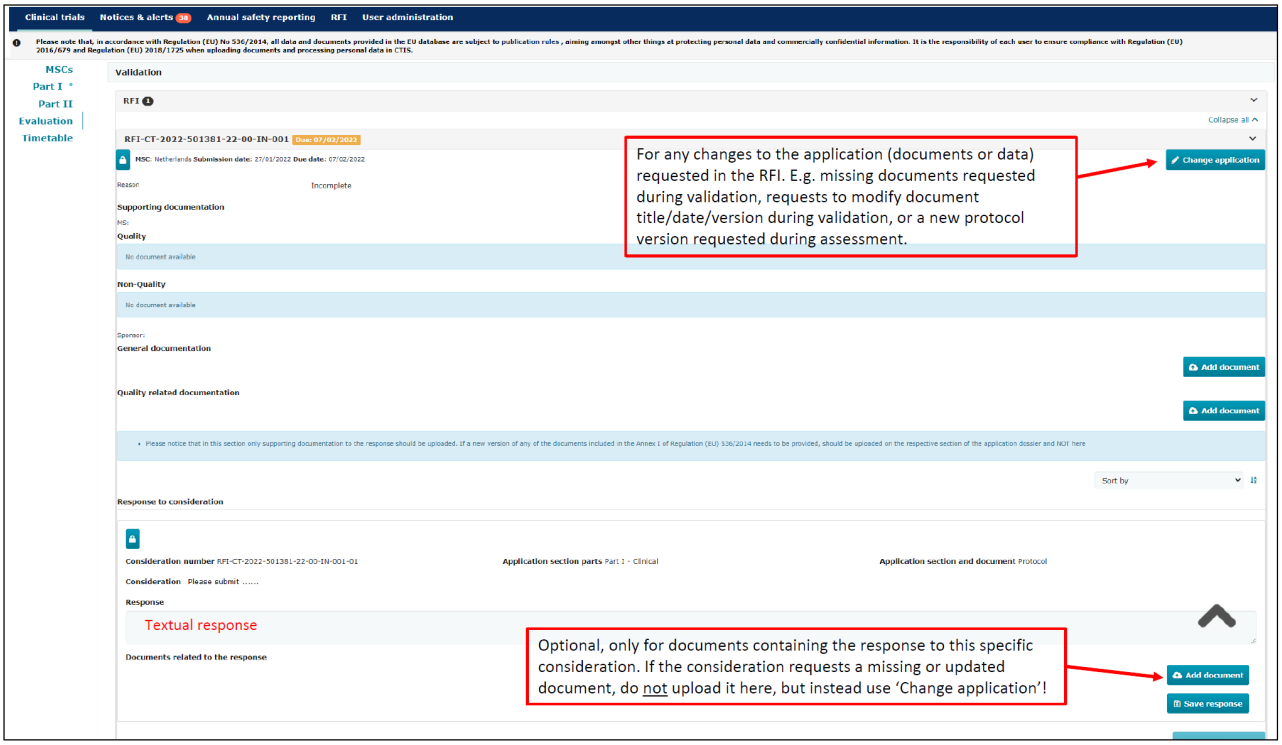
When you have clicked on the padlock button you can see the documents that the authorities have attached to the RFI. The RFI can be related to “quality” or “non quality”.



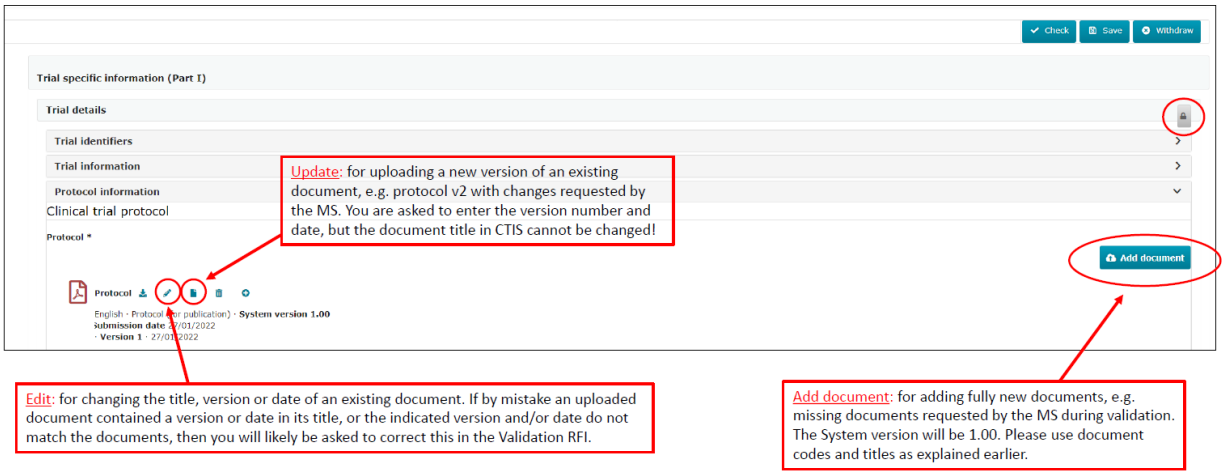
In the "Add document" tab you can upload supporting documentation to the RFI. You must as well click on the "Change application" and then change information in documents that have previously been uploaded or entered for the CTA. Be aware that besides responding to each RFI, changes to the CTA is most often required as revised documents like for example an edited protocol with a new version must be uploaded.

Remember to upload both a **clean protocol** (as an updated version of the current document in trial dossier in part I in CTIS) and a **protocol with track changes**, (as supportive documentation to the RFI response in CTIS). Please refer to the info-box in section 2.4 to see how to upload a document "not for publication".

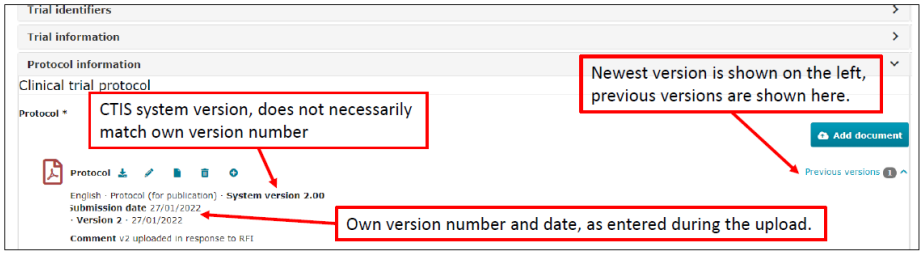
3.2 How to upload documents into CTIS in response to an RFI: change application



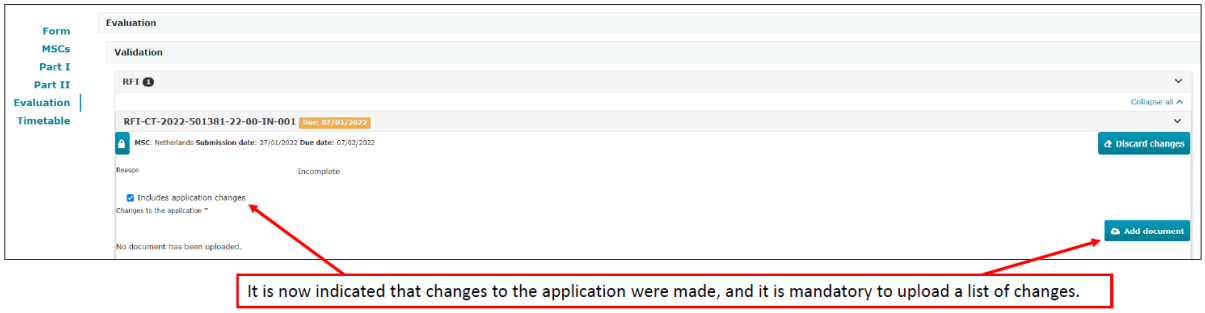
Clicking 'Change application' and confirming it, leads you back to the dossier, where documents can be added similarly to the initial submission. Click the lock and navigate to the location of the dossier where the change should be made.



Uploading a new version of an existing document using the **Update**-button, creates System Version 2.00



When finished adding new/changed documents to the application, navigate back to the RFI response.



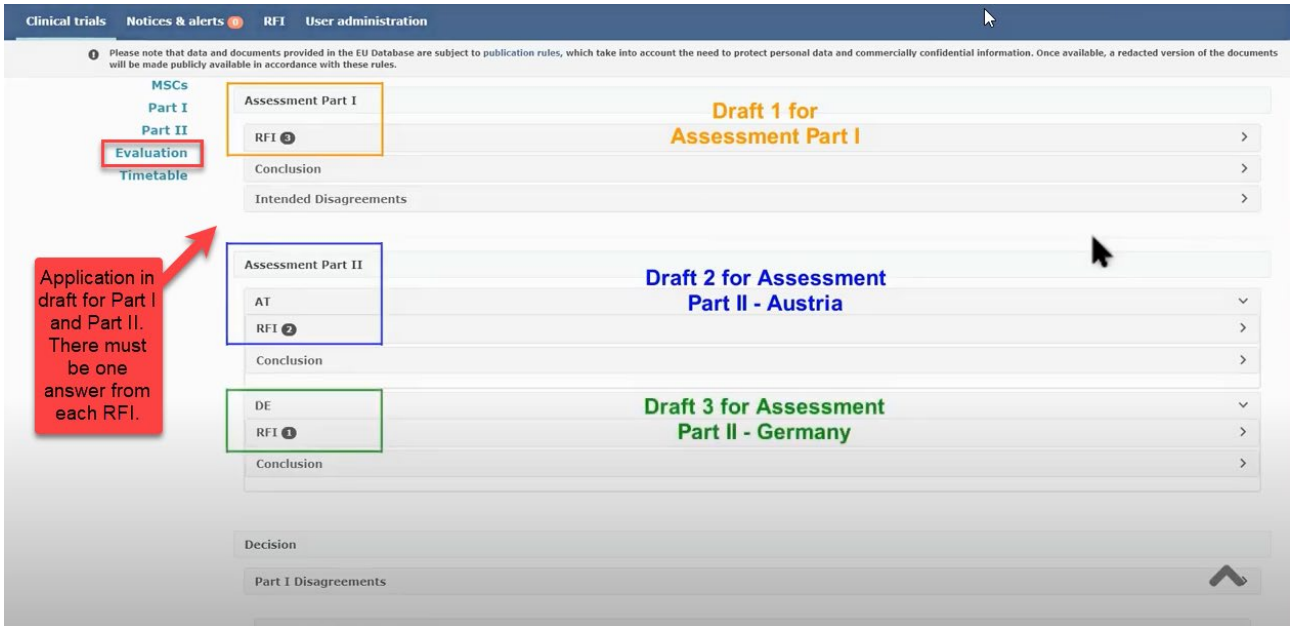
3.3 How to change a Clinical Trial Application as part of a RFI response (Sponsors)

Videos on this topic in EMA training module 11:

Training Video: How to change a Clinical Trial Application as part of an RFI response (Sponsors)

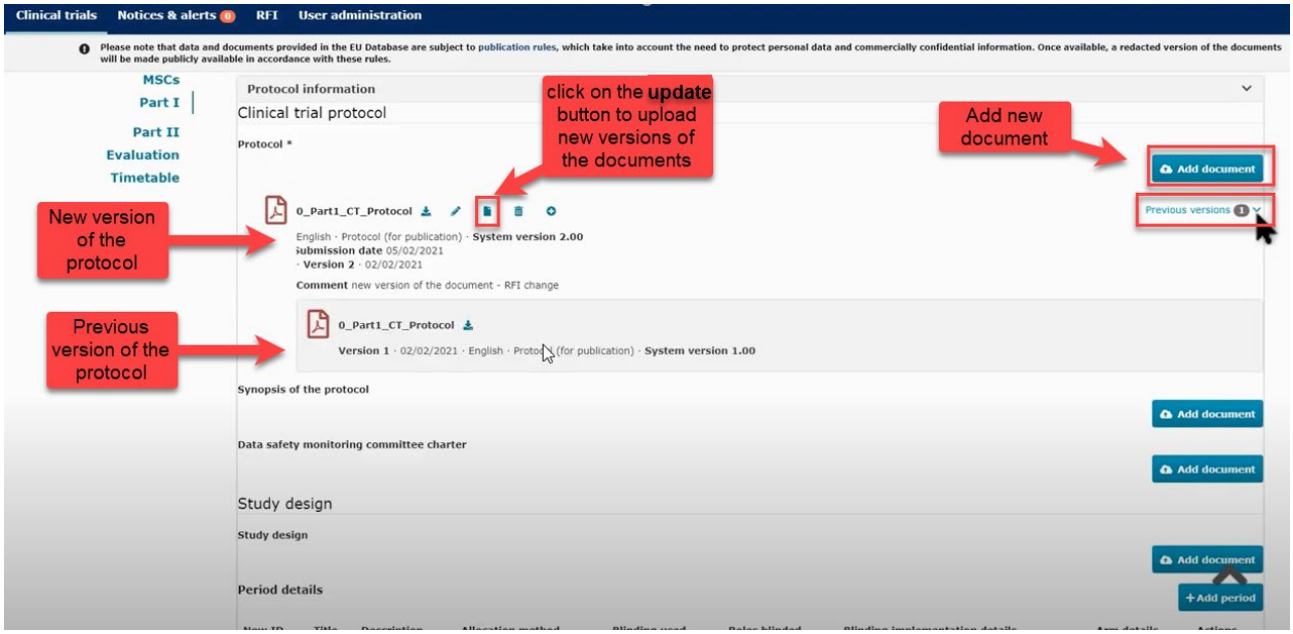
If the RFI requires changes to the application you must click on the change application button. Then a new version of the application has been drafted. Each RFI must be answered separately. You can make changes in the sections Form, Part I and Part II.

If there are RFIs from different countries it is necessary to make a draft application for each RFI. There can for example be one RFI for Part I and one RFI for Part II from each member state.



If a document (e.g. protocol) needs to be changed, this should be done from the correct placeholder (by the original document) by using the "update" button. This will ensure correct versioning of approved documents and publication in accordance with deferral/transparency rules.

The "add document" button next to the response to RFI, should only be used in case you have supportive documentation to justify your response.



Remember to unlock each section when you are done answering the RFI and uploading new documents.

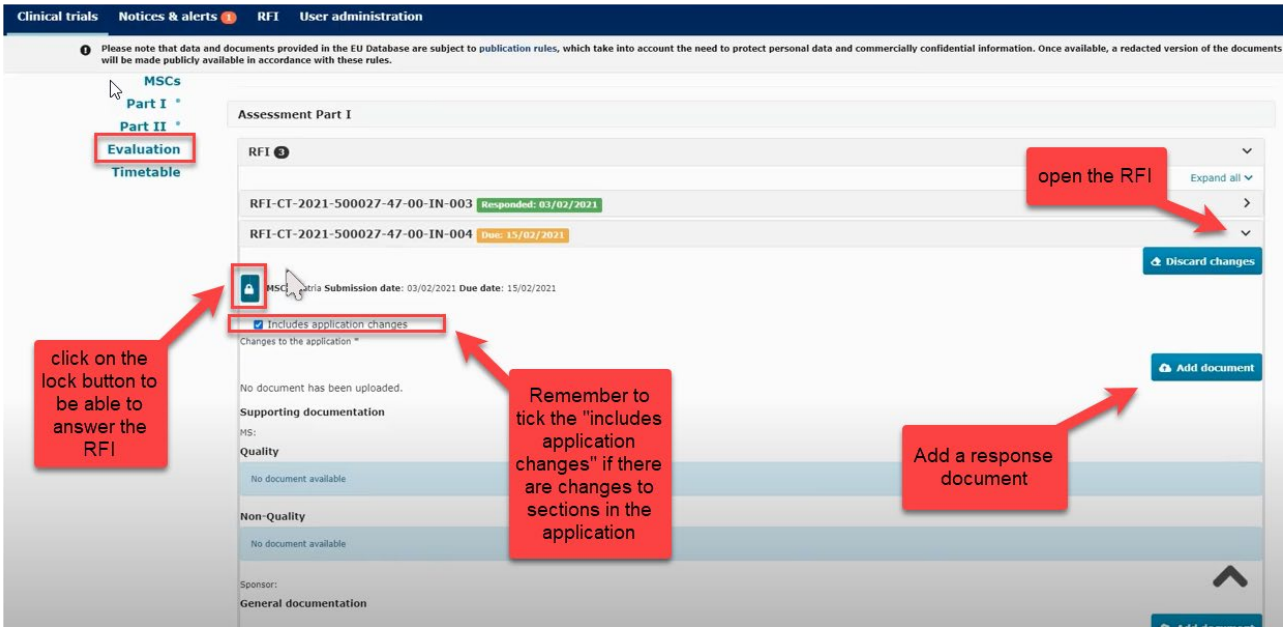
3.4 How to respond to RFI considerations and submit an RFI response

Videos on this topic in EMA training module 11:

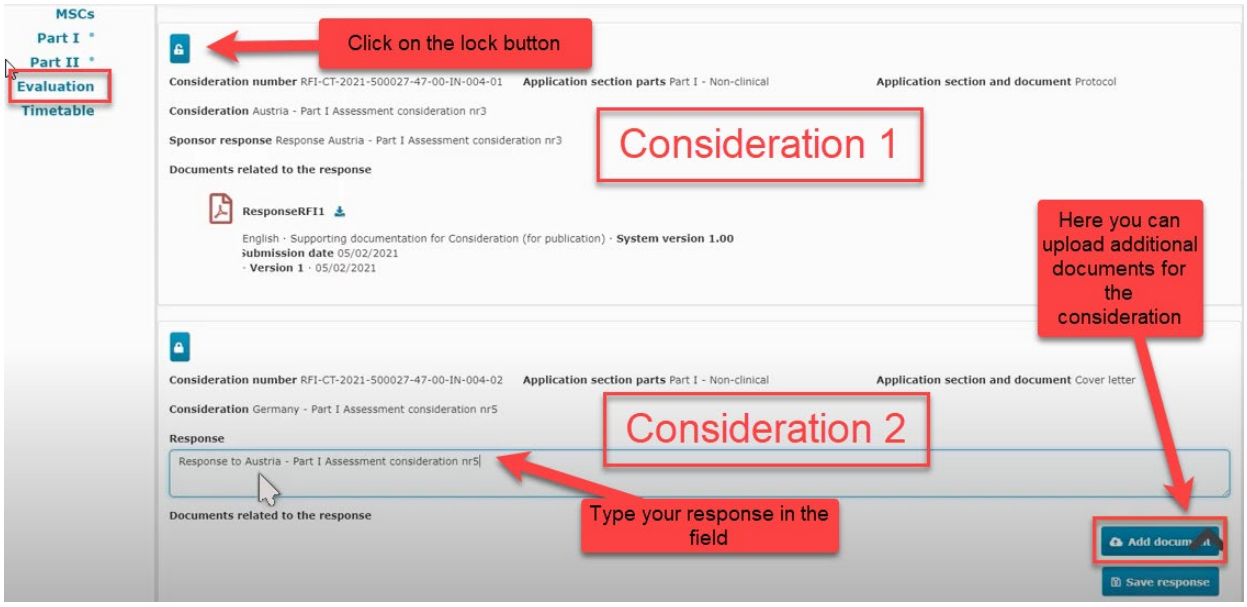
Training Video: How to respond to RFI considerations and submit an RFI response (Sponsors)

Sponsor must reply to each of the RFI received from the authorities.

When making changes to the application, a document listing the changes has to be uploaded at the RFI response and the box with "includes changes to the application" has to be ticked off.



Below the RFI, there can be considerations which also must be answered. You can respond separately to each consideration.



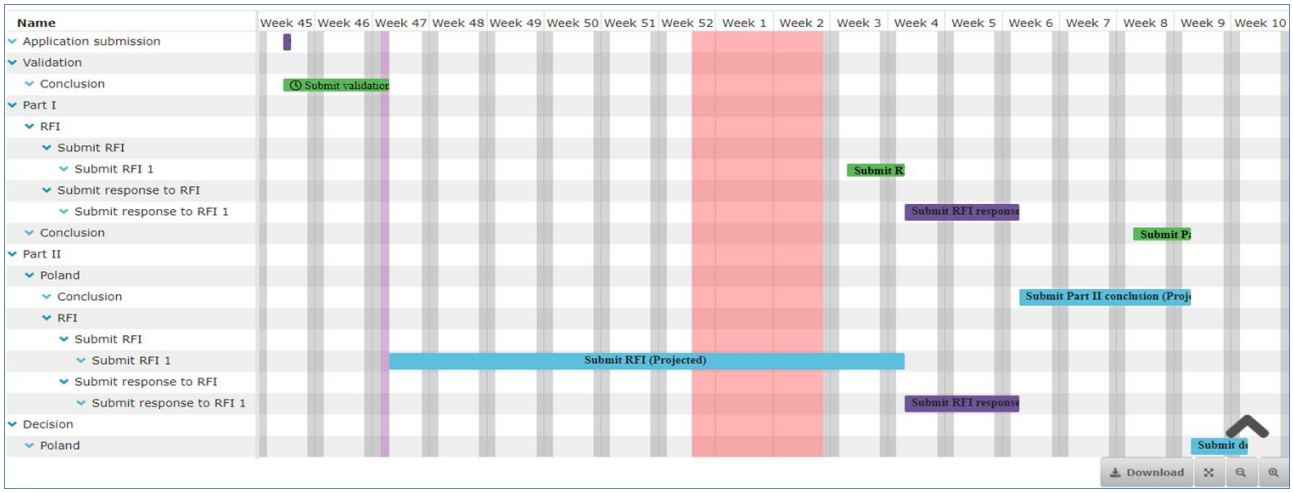
The “Submit response” button will be active when the changes have been saved on “save response”.

Important to remember to be able to click on “submit response”:

- All response fields should be answered
- It is mandatory to upload a list of changes
- Pad locks to each consideration should be closed and the pad lock to the RFI should be open

3.5 Timetable

In the timetable tab on the left side of the page in CTIS it shows the dates for the assessment schedule. All timelines will be in calender days, however the due dates must never fall on a weekend or official holiday. A time period will not be shorter than two consecutive working days. It is important for sponsors to notice that the workflow in CTIS is **dynamic** which means that timelines can be changed.



The figure below shows an overview of the general timetable and deadlines for authorities and sponsors. [CTIS Evaluation Timelines]

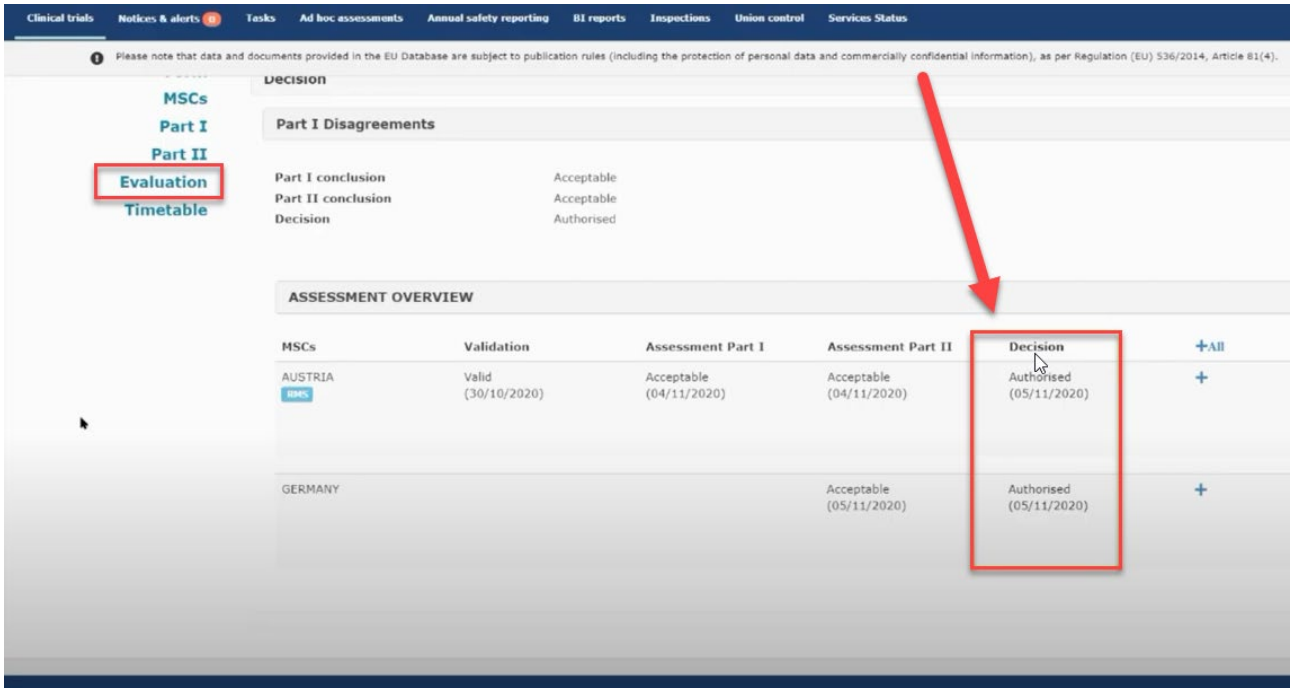
Process	Task	Timers for an initial application	Shorten the due date of the next workflow if completed earlier?
Validate Application	Submit validation conclusion	Day 10 + 15	Yes
Assess Part I	Submit part I conclusion	Day 45 + 31	Yes, if the assess part II is also completed earlier
Assess Part II	Submit part II conclusion	Day 45 + 31	Yes, if the assess part I is also completed earlier
Submit Decision	Submit decision	Day 5	-

3.6 Authorisation

Info box:
The trial must include patients in the member state within 2 years from authorisation date in order to keep the trial authorised in that member state.

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

There must be a conclusion and a final assessment report (FAR) from both Health Authority and Etichs Committee. If you receive a “No conclusion” it means that the authorities have not answered within the deadline (60 days), which is a mistake.



An overview of all documents and the approval date is shown at the end of ”full trial information”. Some countries do send “approval letters” but Denmark is not, and the approval date can only be seen in CTIS “Decision – authorised”.

ALL DOCUMENTS

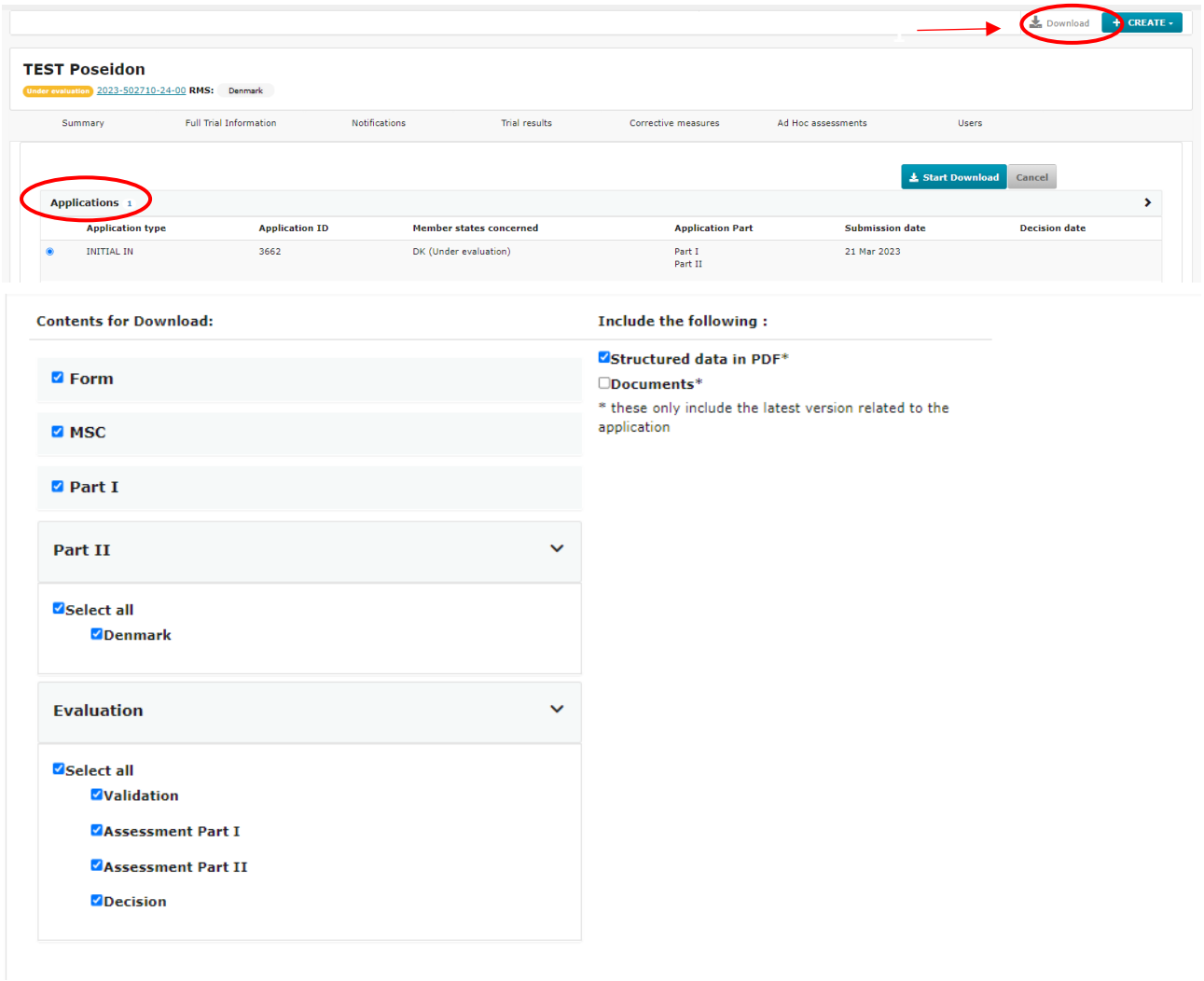
Section	Document type	Document Title	Document Version	Document Comment	Document Submission Date	System version	Language	Authorisation date	Application	Download
Part I	Cover letter (for publication)	Cover letter	1		17/01/2022	1.00	English	17/01/2022	INITIAL - IN	
Part I	Protocol (for publication)	Protocol for publication	1		17/01/2022	1.00	English	17/01/2022	INITIAL - IN	
Roles: Test Name:DENUBIL 250 mg/180 mg solución oral	Summary of Product Characteristics (SmPC) (for publication)	SmPC - NaCl 09 - Braun Melsungen DE	1		17/01/2022	1.00	English	17/01/2022	INITIAL - IN	
Part I	Content labelling of the IMPs (for publication)	Labelling	1		17/01/2022	1.00	English	17/01/2022	INITIAL - IN	
Part I	Compliance with Regulation (EU) 2016/679 (for publication)	Compliance with Reg 2016_679	1		17/01/2022	1.00	English	17/01/2022	INITIAL - IN	

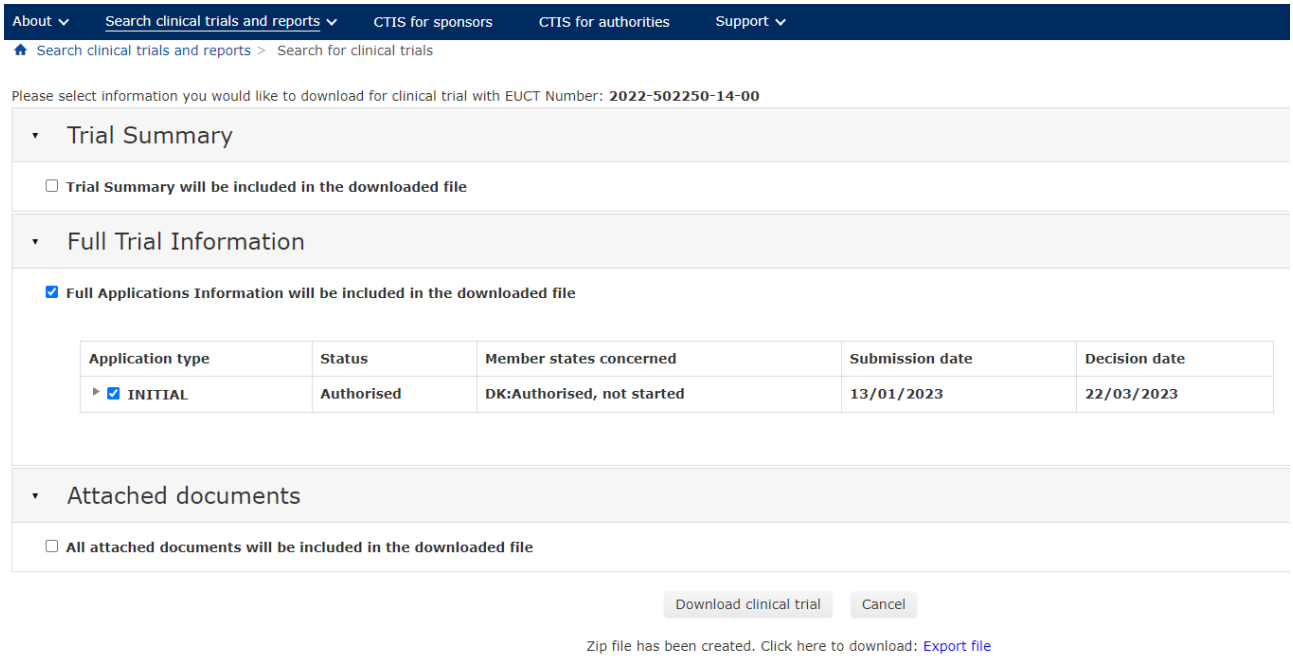
3.7 How to find the "Report for the Application Evaluation Decision" in CTIS:

Go to front page -> "Summary" -> 1 ("Download") -> "Applications " -> mark "Initial" -> mark "Form, MSC, Part 1, Part 2 and Evaluation" select all -> mark "structured data in PDF"

Click the Start download button. Will be downloaded as a ZIP file.

Go to evaluation and then decision.





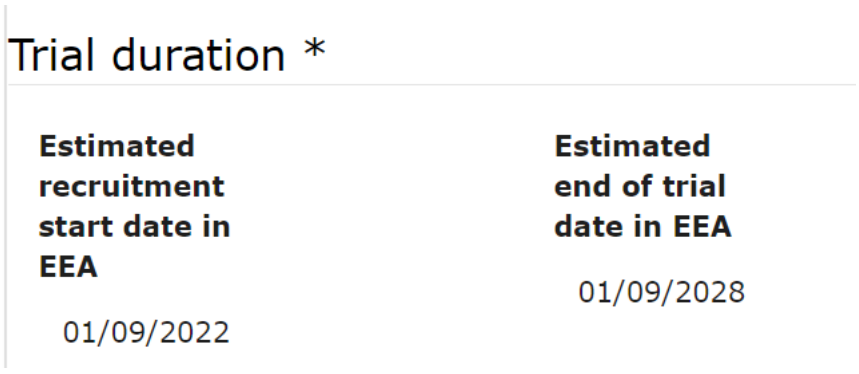
How to see in CTIS how long the trial is approved: Go to ”Full trial information” -> “Trial details” -> “Trial information” -> “Trial duration”.

The extension of trial duration is a non-substantial modification and require no approval from the authorities

The sponsor must describe the extension and new date in a comment (free text) when creating a Non substantial modification (NSM) in CTIS and thereafter submit the change. It is not possible for sponsor to change the date manually in CTIS as it is a NSM.

Sponsor can only change the date next time the sponsor submit a substantial modification (SM).

Date for “estimated end of trial” is the expected date for last patient last visit (LPLV). EEA: European Economic Area.



4 15 days notifications from start to end of trial

Video on this topic in EMA training module 5:

Training Video: How to manage a CT in the CTIS sponsors workspace – Trial and recruitment periods notifications

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:

Notifications that need to be submitted for every clinical trial:

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

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

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

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

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

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

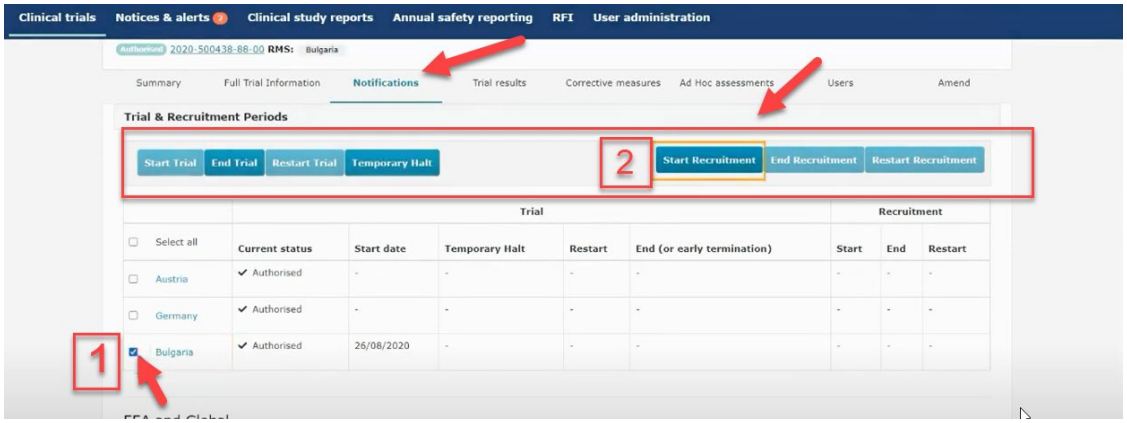
• **Restart trial:** The act of restarting the trial, after a temporary halt or after a suspension of the CT as part of a corrective measure by an MSC.

• **Restart recruitment**: The act of restarting the recruitment of subjects. The trial must have been restarted to be able to restart the recruitment.

The **deadline** for reporting these notifications in CTIS is **15 days** after the date of the specific event has taken place.

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.

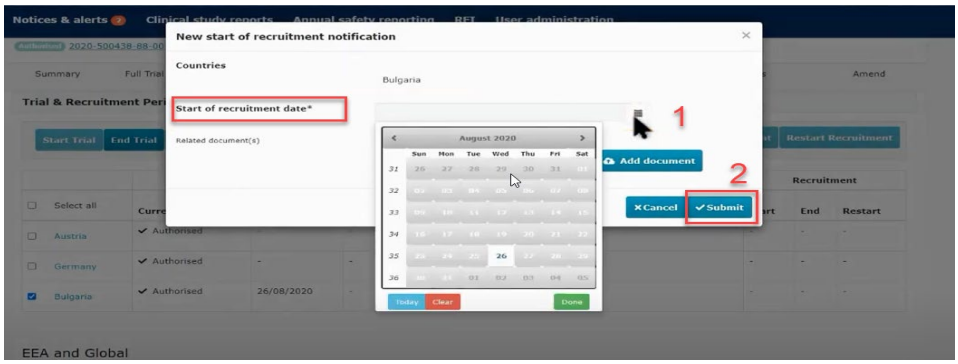


Select the specific country where you want to make a notification.

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.**

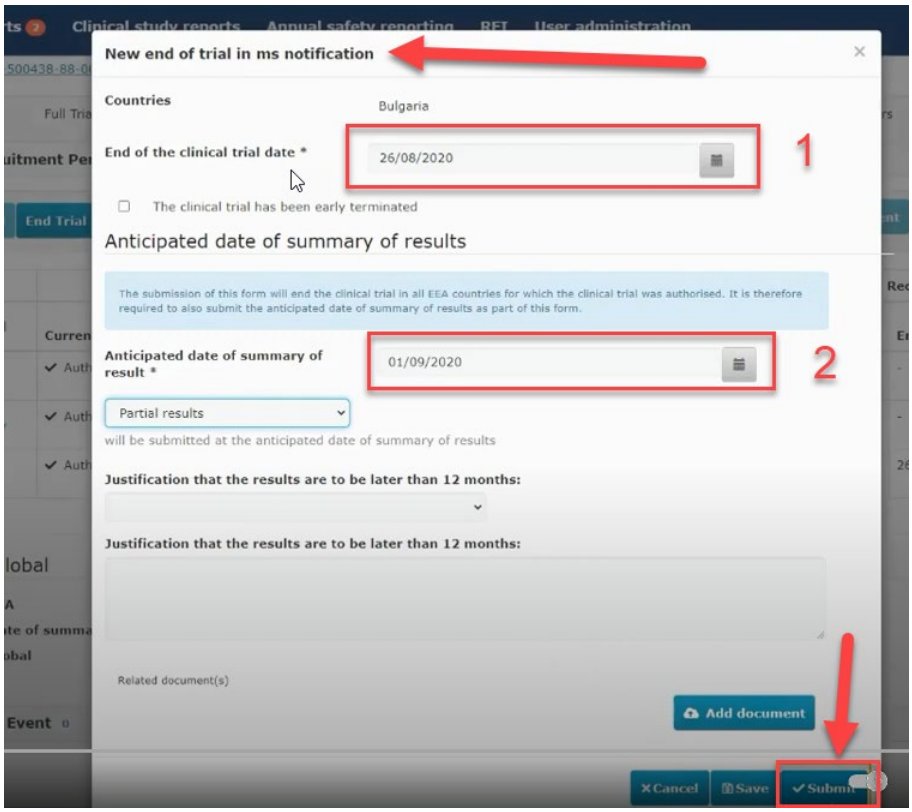
Examples:

Start of recruitment notification at the latest 15 days after start:



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

End of trial notification at the latest 15 days after the trial ended:

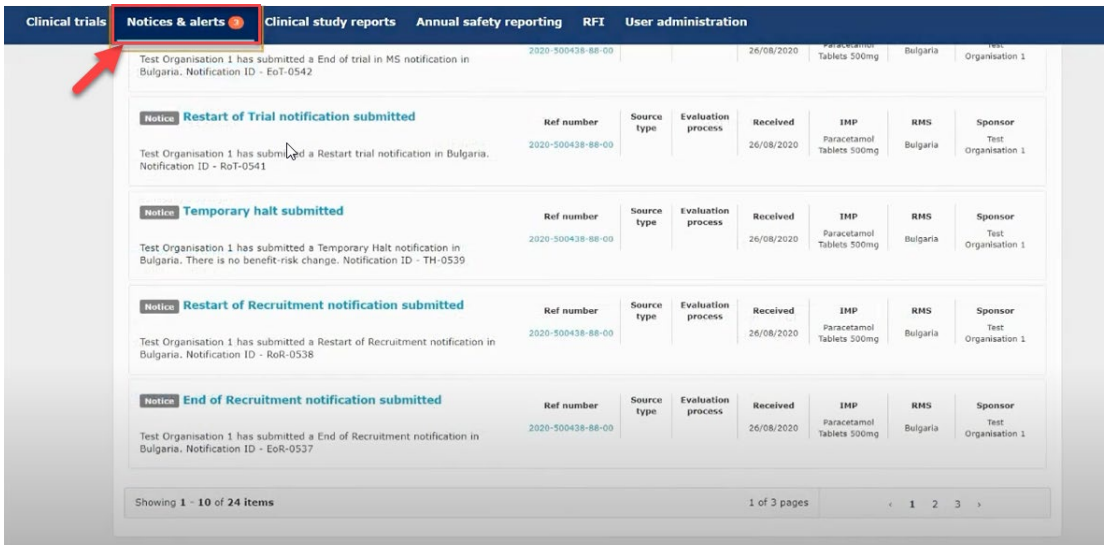


Enter the date where the clinical trial ended according to the protocol or if it was terminated early.

Enter the anticipated date of where the summary of results will be available.

By clicking on the country link you can go to the notification history for that specific country.

Each time you submit a notification a notice is created on the “notices & alerts” tab.



Info box:
To be able to see the "**Annual safety reporting tab"** and to perform ASR related activities, the CT administrator should assign the "ASR submitter role" to him/herself.

Please refer to **The Danish GCP Units guide - Submission of Annual Safety Report (ASR) in CTIS** for more information.

5 How to create and submit a Substantial Modification (SM)

Video on this topic in EMA training module 10:

Training Video: How to submit a substantial modification in the CTIS sponsor workspace

Step-by-step guide "Create, submit and withdraw a clinical trial application and nonsubstantial modification": CTTM10 - Step-by-step guide (europa.eu)

There are three types of changes to a clinical trial:

1. Substantial Modification (SM)
2. Non Substantial Modifications (NSM)
3. 81.9 Non Substantial Modification (81.9 NSM)

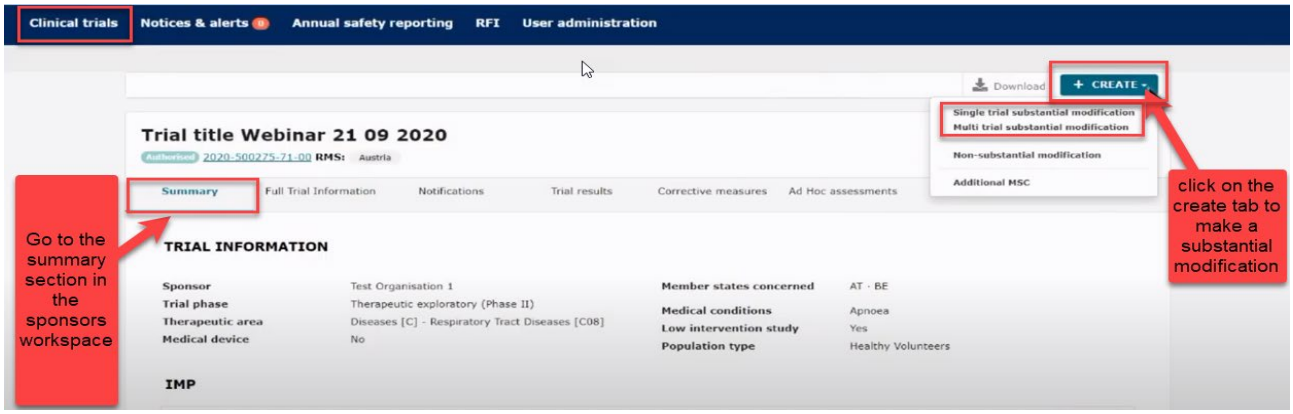
Classification of changes to ongoing trials can be found in CTR Q&A, Annex IV: "Classification of changes to ongoing clinical trial".

All non substantial changes, both 81.9 NSM and NSM, do not require an approval before implementation.

The 81.9 NSMs must be updated by sponsor regularly in CTIS during the trial period. These are changes that are relevant to the member states concerned.

Other NSMs must be updated in CTIS with next SM or latest at end of trial, if no SMs have been submitted meantime.

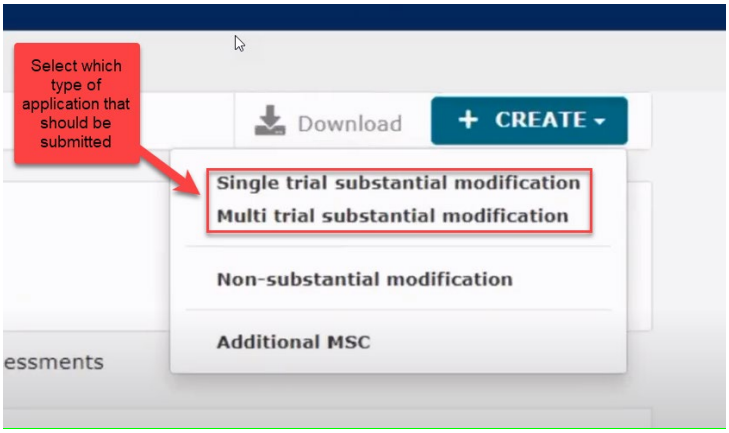
To create and submit a substantial modification after the clinical trial has been authorised, users can select the '+ CREATE' button in the sponsors workspace at the top-right corner of the Clinical Trial page.

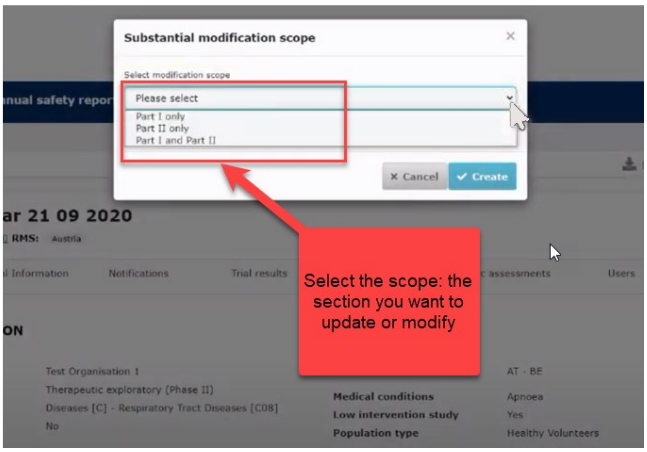


This will enable you to select which type of modification you want to submit:

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

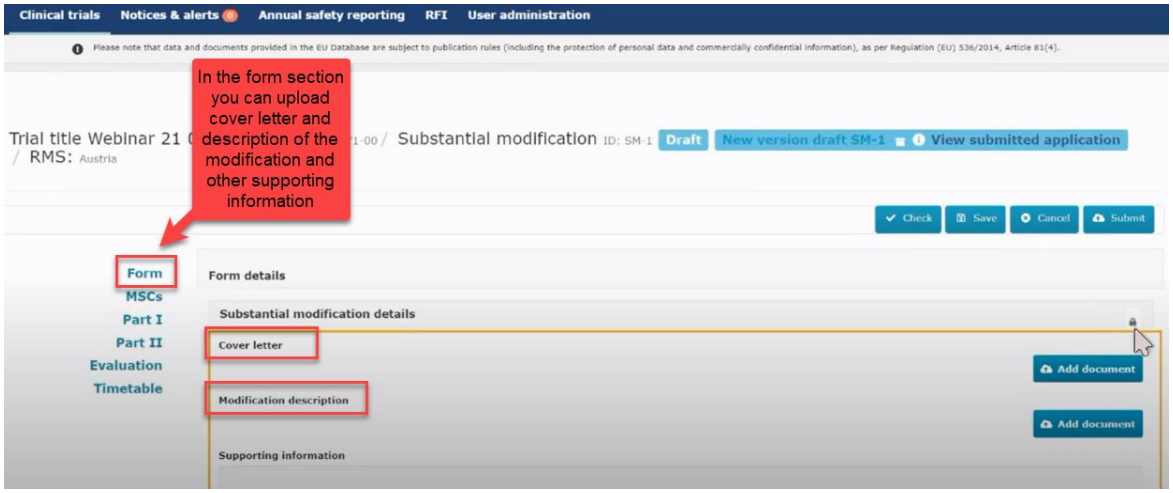
Multi trial substantial modification: to update information for trials that have the same investigational medicinal product (IMP) and the same sponsor. In this case it is possible to submit *a single application covering several trials.*



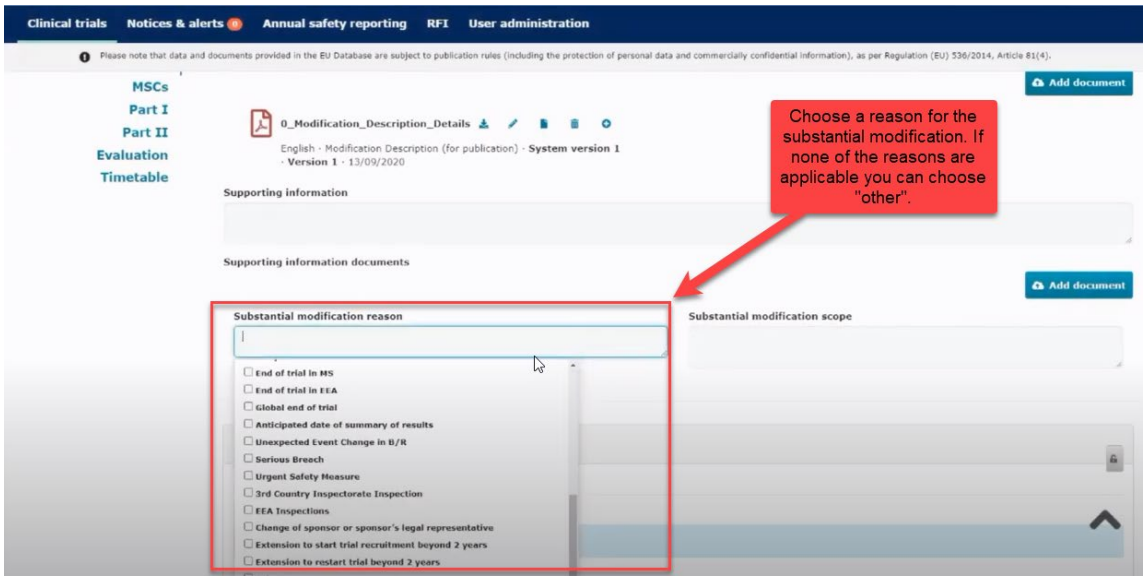


If you click on the **"Single trial substantial modification"** you will be redirected to a window where you need to enter the scope of the substantial modification. Thereby you will define the part which will be modified (Part I and/or II).

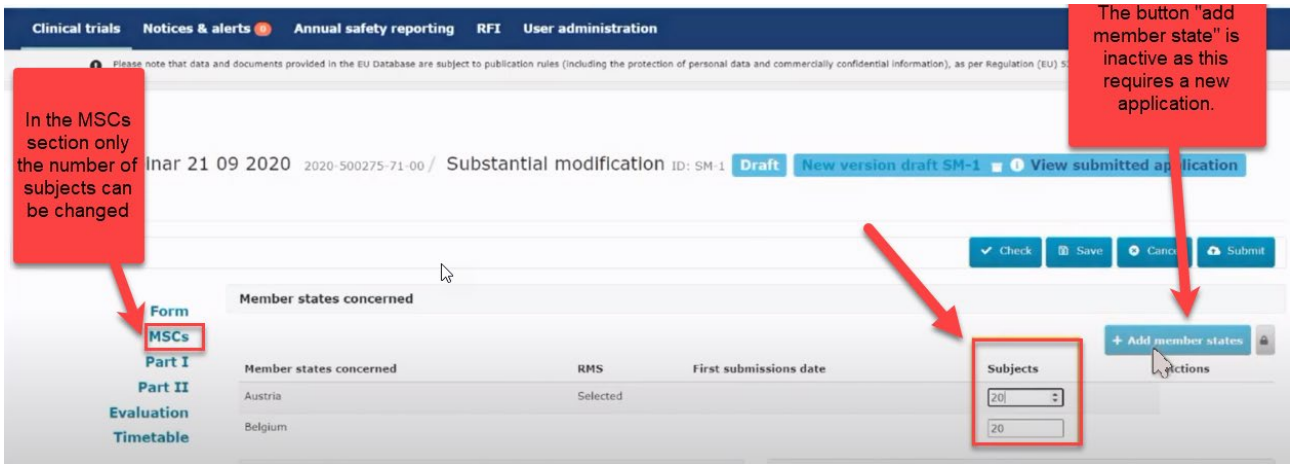
In the **"Form" section**, cover letter etc. should be uploaded and you can add details about the substantial modification.



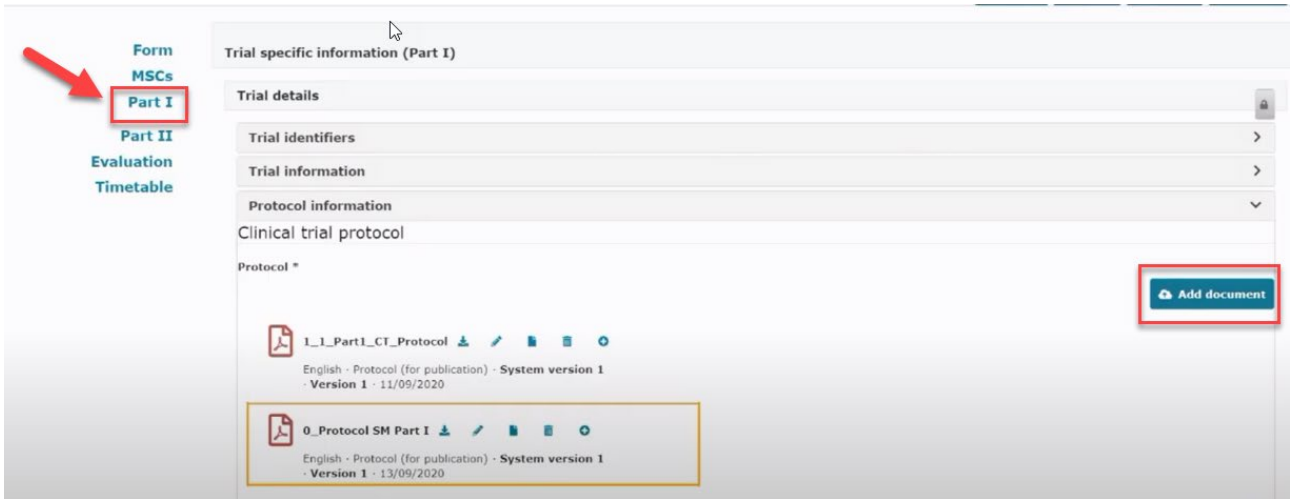
If you scroll down, the reason for the substantial modification must be added here.



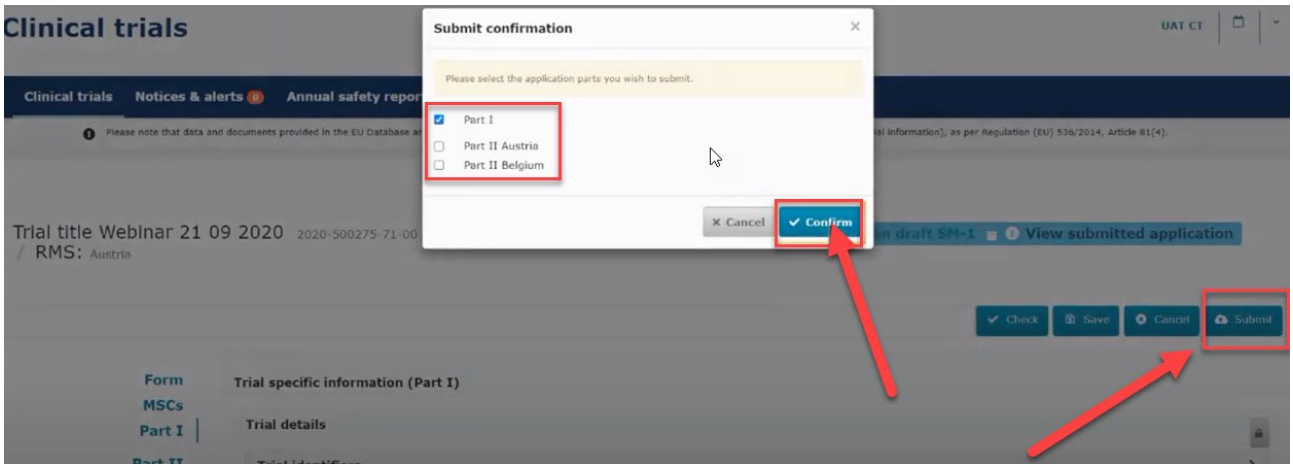
In the "**MSCs section"** only subject numbers (number of planned trial subject) can be modified.



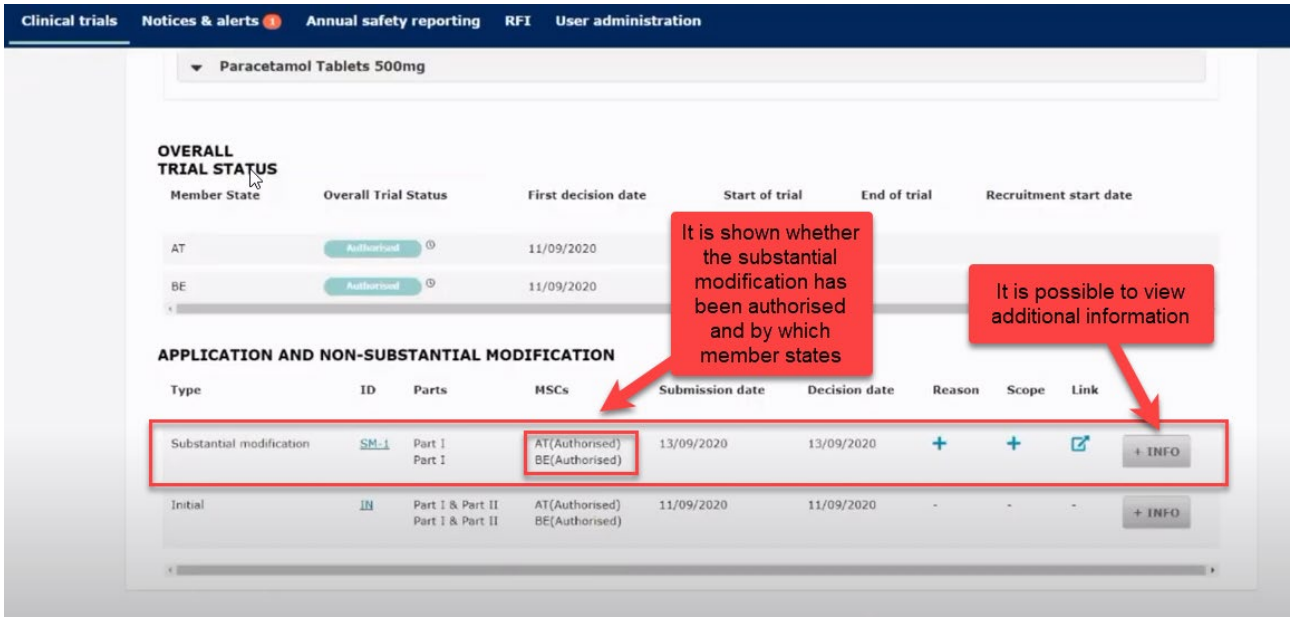
In the "**Part I or Part II" section** you can upload the relevant documents with changes.



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.



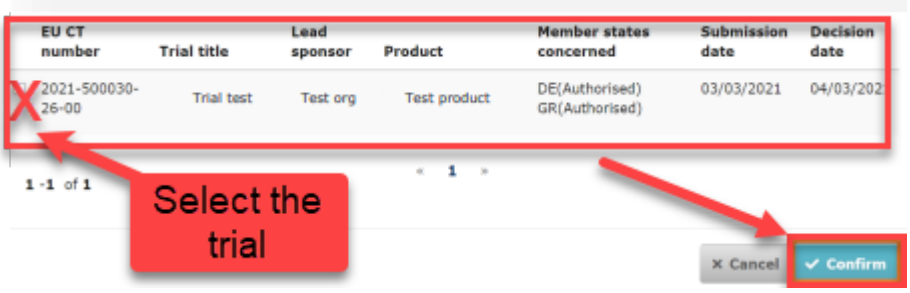
6 Summary of Results and Summary for Layperson

The sponsor shall submit a summary of the results of the Clinical Trial. The deadline for uploading the results in CTIS is 1 year after end of trial.

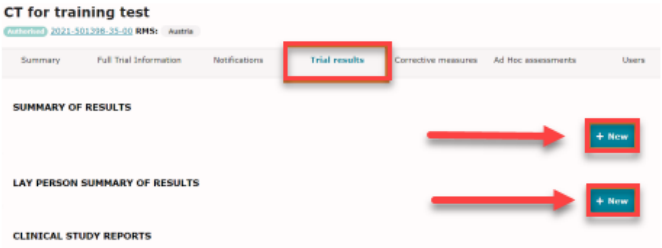
The content of the summary of results is set out in Annex IV of the regulation. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of lay person summary of results is described in Annex V of Regulation.

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

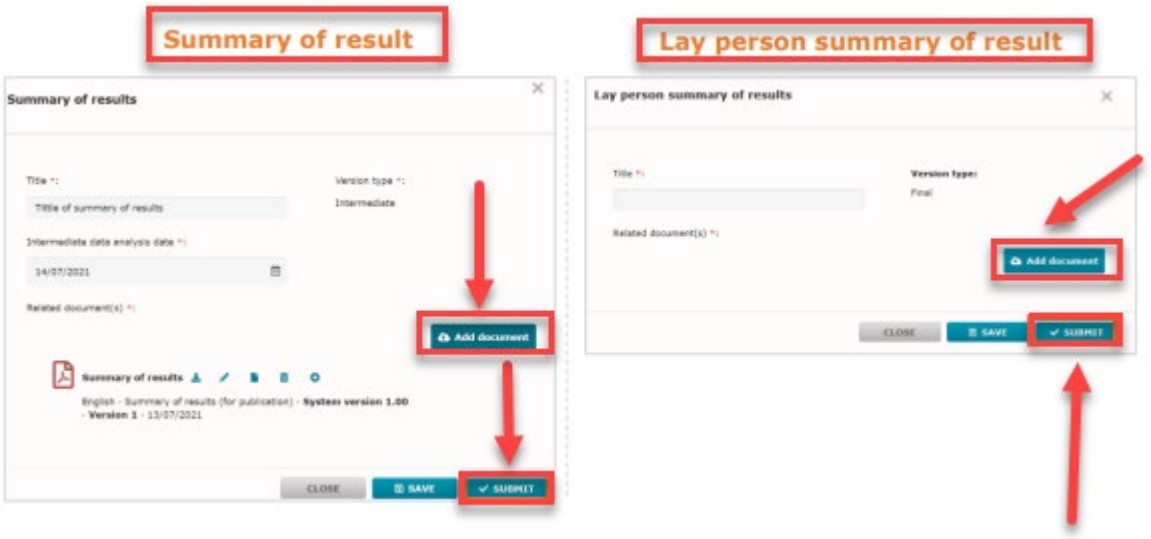
Select the trial from the results page and click on the 'Confirm' button.



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



Select the "Add document". Then "Save" and "Submit".



7 Changes log

Version 1.0

Version 1.2 Links corrected.

Version 1.3 Updated according to comments from users.

Version 1.4 Updated with new experiences from authorities and users and links corrected.

Version 1.5 Updated with information of resubmission and other small corrections.

Version 2.0 Updated section on how to respond to RFI, removal of section on how to create an EMA account, roles and responsibilities and ASR.

Version 2.1 Updated with information of sponsor, third party and site registration directly in CTIS, updated list of documents and templates and new links.

Version 2.2 Updated according to comments from users and how to find and download Report for evaluation decision in CTIS and in public space. Location number is updated for the GCP-unit in Aalborg and Aarhus.

Version 2.3 Added comment from Trial Nation regarding the first mentioned investigator in CTIS will be named “coordinating investigator” in the database Danish National Trial Overview (Nationalt Forsøgsoverblik).

Version 2.4 Further explanation about log in to CTIS.

Version 2.5 Updated according to comments from users and new/updated guidelines.

Version 2.6 Updated according to comments from users, authorities, and new/updated guidelines.