EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Step-by-step guide

Create, submit and withdraw a clinical trial application and non-substantial modifications

CTIS Training Programme – Module 10
Version 1.0 – November 2021

Learning Objectives

- Understand the different types of CTAs and Non-substantial modifications.
- Understand the process of creating, submitting, and cancelling a CTA.
- Understand the process of withdrawing a CTA.
- Understand the key differences of other types of applications, compared to an Initial CTA.

The European Medicines Agency developed this training material to enhance public access to information on the Clinical Trial Information System (CTIS). This material describes a preliminary version of CTIS and may therefore not entirely describe the system as it is at the time of use of this material. The Agency does not warrant or accept any liability in relation to the use (in part or in whole) or the interpretation of the information contained in this training material by third parties.

Clinical trial applications and non-substantial modification

The CT Regulation introduced a harmonised procedure for the submission of Clinical Trial Applications (CTAs) regarding Clinical Trials (CTs) to be conducted in the EU (whether they are mono-national or multinational). Three types of applications can be submitted in CTIS for a trial:

- **Initial CTA:** Request to conduct a CT that includes comprehensive information about the CT for the evaluation by the Member State Concerned (MSC).
- **Additional MSC CTA:** Request by the sponsor of extending an authorised CT to one or more MSC.
- **Substantial modification CTA:** Request by the sponsor for a change of a CT that is likely to have a substantial impact on the subjects' safety or rights or on the reliability/robustness of the generated data.

The CT Regulation also establishes that sponsors can submit **non-substantial modifications** during an ongoing CT. These are not considered as applications as they are not subject to the evaluation by the MSCs.

This Step-by-step guide includes:

Initial CTA

This section outlines the steps that sponsor users should follow to create, submit, withdraw and copy an Initial clinical trial application.

Additional MSC CTA

This section outlines the steps that sponsor users should follow to create and submit an Additional MSC application.

Substantial modification CTA

This section outlines the steps that sponsor users should follow to create and submit a Substantial modification.

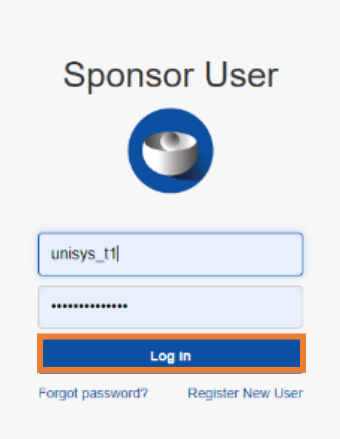
Non-substantial modification

This section outlines the steps that sponsor users should follow to create and submit a Non-substantial modification.

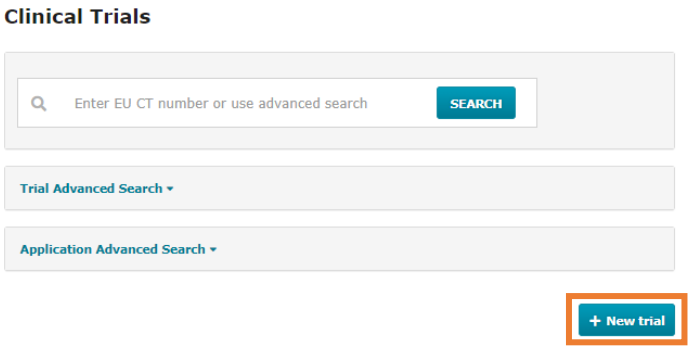
Initial CTA

Create and submit an Initial CTA

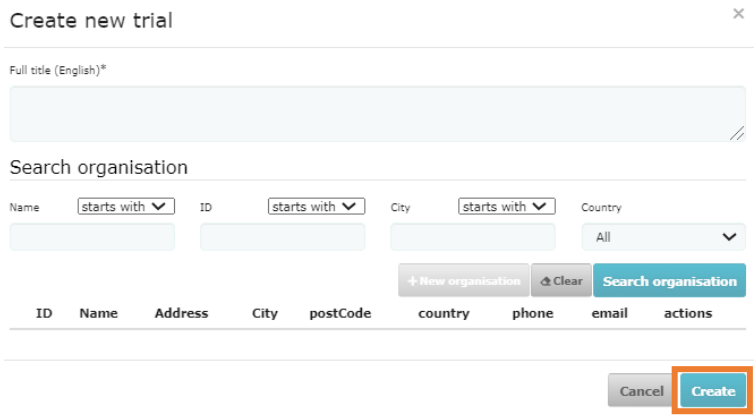
1. Users can populate the credentials and select the **'Log in'** button.



2. In the **Clinical trial** tab, they can select the '+ **New trial**' button.



3. After populating all fields 'trial title' and 'sponsor organization' from the pop-up window they can select the **'Create'** button.



#CTIS insights

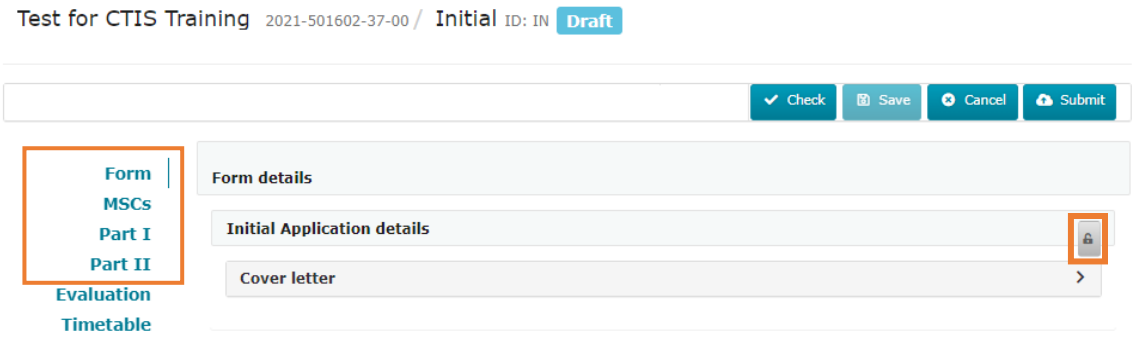
Users can **search for the sponsor organisation information** by clicking on the 'Search Organisation' button. This information is retrieved from the Organisation Management Service (OMS).

If the **sponsor organisation is not registered**, users need to do so in the OMS website https://spor.ema.europa.eu/omswi

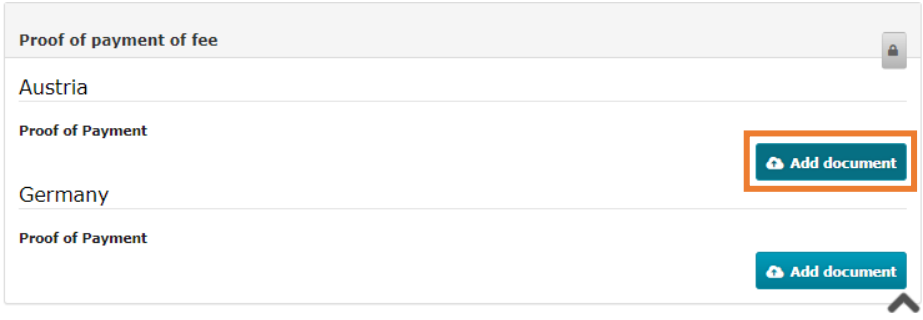
Initial CTA

Create and submit an Initial CTA

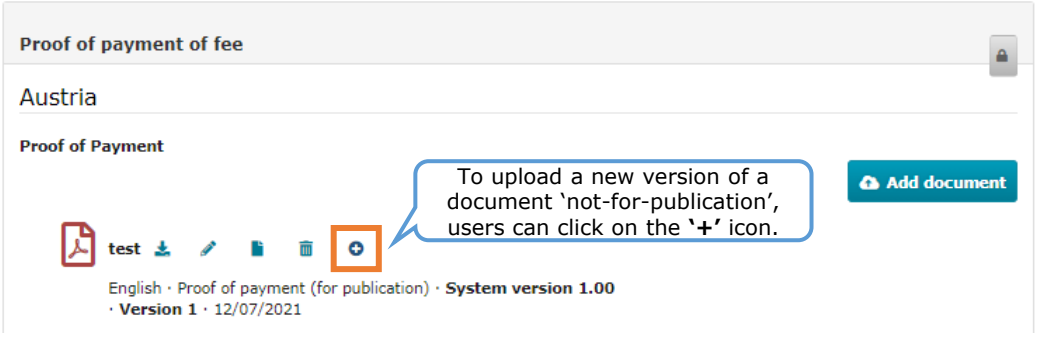
4. Users can start to populate the required fields of the sections 'Form', 'MSCs', 'Part I' and 'Part II'. In order to populate a field, users can select the **padlock** button in each subsection.



5. Users can upload documents by selecting the **'Add document'** button in each section.



6. CTIS allows users to upload **two versions** of a same document: one for publication and another one not for publication. Documents not for publication are used to protect personal data and/or to commercially confidential information, provided that the data minimisation principle is observed *(refer to Module 12: Data protection in CTIS for more information).*



#CTIS insights

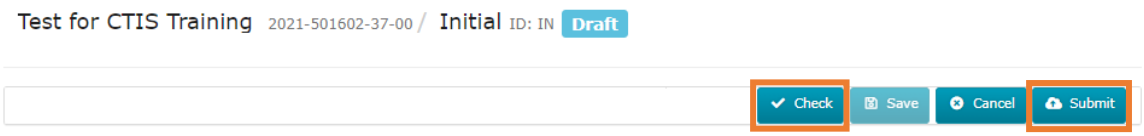
Users can **save the CTA as a draft before submitting it**. To continue editing the CTA users can access it in the CT page.

A list of **required fields per application type** can be found in Module 10: How to create, submit and withdraw a CTA.

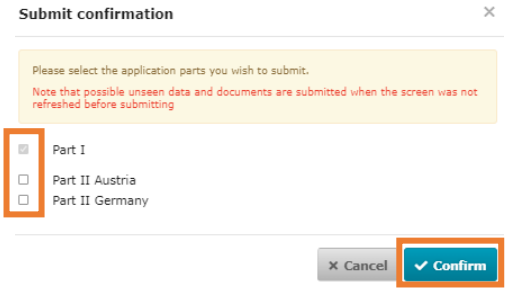
Initial CTA

Create and submit an Initial CTA

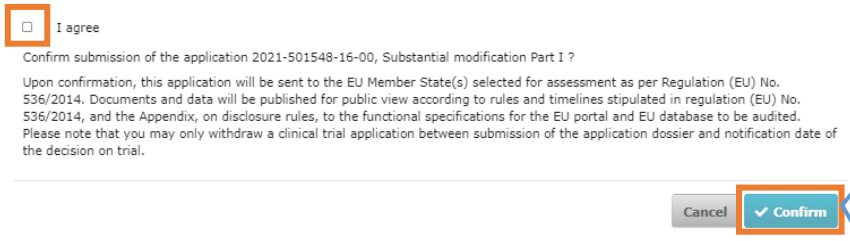
7. After populating all the fields, they can select the '**Check**' button on the top-right corner of the CTA page to see if any required field has not been populated (the missing fields will appear marked in red). After all the required fields are populated, they can select the '**Submit**' button.



8. Users can select the **application parts** that are to be submitted and click on the **'Confirm'** button.



9. After reading the confirmation text, they can select the **'I agree'** box and then click on the **'Confirm'** button.



After the sponsor submits the Initial CTA, the MSC will start the **evaluation process.** Therefore, the **state of the CT** will change from 'draft' to **'under evaluation'.**

#CTIS **insights**

As per article 11 of the CT Regulation, **CTAs can be limited to the aspects covered by Part I.** However, **Part II of the application dossier** will need to be submitted within **two years.**

As per article 13 of the CT Regulation, **CTAs can be resubmitted following the refusal to grant an authorisation or the withdrawal of it.**

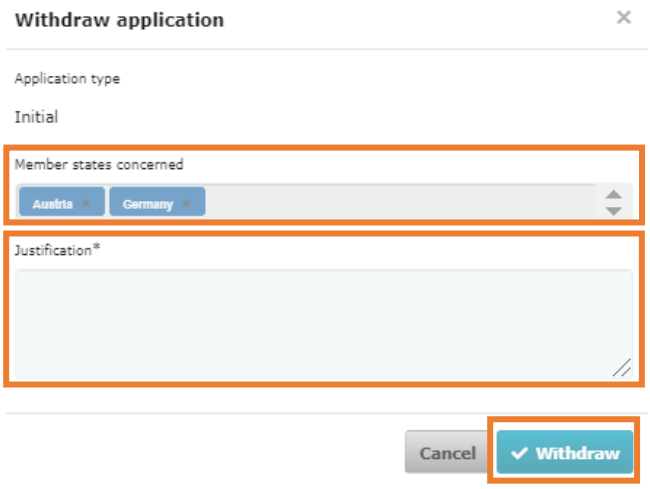
Initial CTA

Withdraw an Initial clinical trial application

1. Users can search for a clinical trial application in the **'Application and Non-substantial modification'** section and click on the **IN** of the application under the 'ID' column.

2. After opening the clinical trial application, they can select the **'Withdraw'** button.

3. In the case of withdrawal of an initial application before the reporting date (date of part I conclusion) the withdrawal will apply to all MSCs. In case of withdrawal after the reporting date, users need to select the **Member State Concerned** for which the application should be withdrawn. In case of SM withdrawal including part I, this will apply to all MSC. In any circumstance, a justification for the withdrawal should be provided.



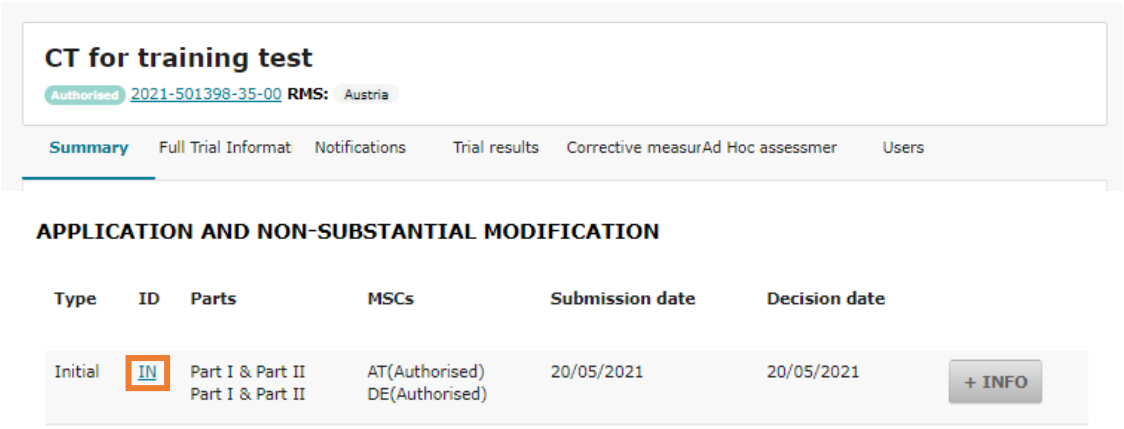
#CTIS insights

As per Article 12 of the CT Regulation, **a withdrawal of a multinational CTA for all MSC can be done until a conclusion on Part I** (reporting date) **is submitted.** After that date, it can be individually withdrawn from each MSCs.

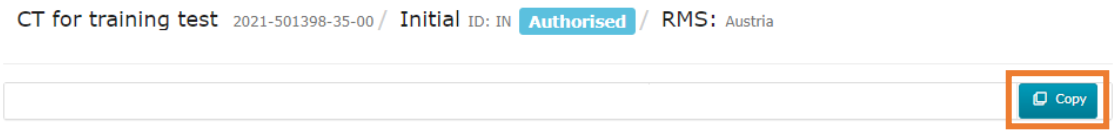
Initial CTA

Copy an Initial CTA

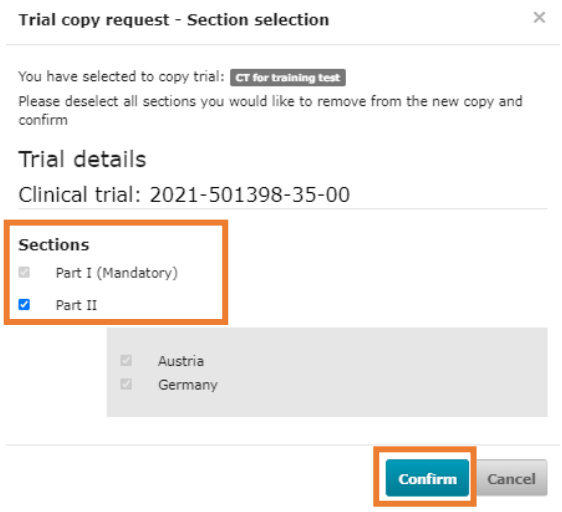
1. Users can search for a clinical trial application in the **'Application and Non-substantial modification'** section and click on the **IN** of the application under the 'ID' column.



2. After opening the clinical trial application, they can select the **'Copy'** button.



3. By default, Part I of the CTA to be copied is mandatory and users can select if they wish to copy Part II of a specific MSC. After, they can select the '**Confirm'** button.



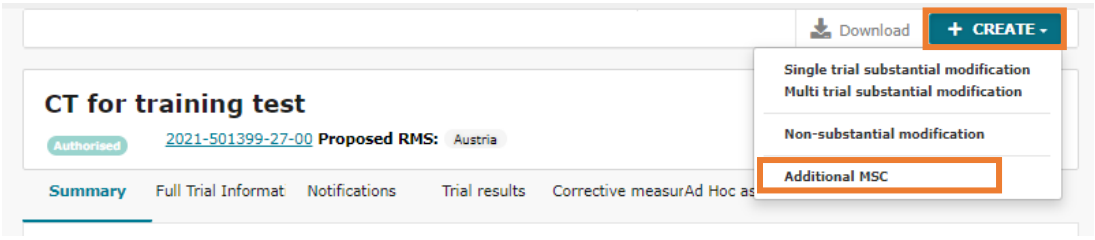
#CTIS insights

The copy functionality allows users to create a new initial CTA starting from an **already prepared application**, where, for example the same medicinal products were used. All the **data and document are automatically copied** and populated in the dossier. The various sections can then be modified according to the user needs.

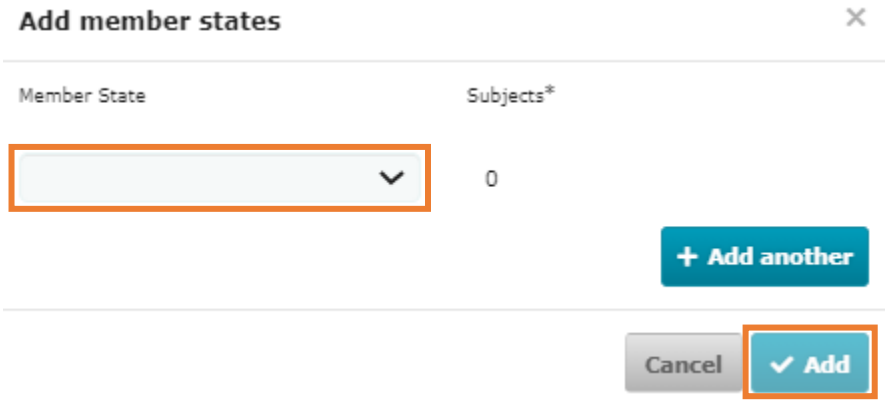
Additional MSC CTA

Create and submit an Additional MSC CTA

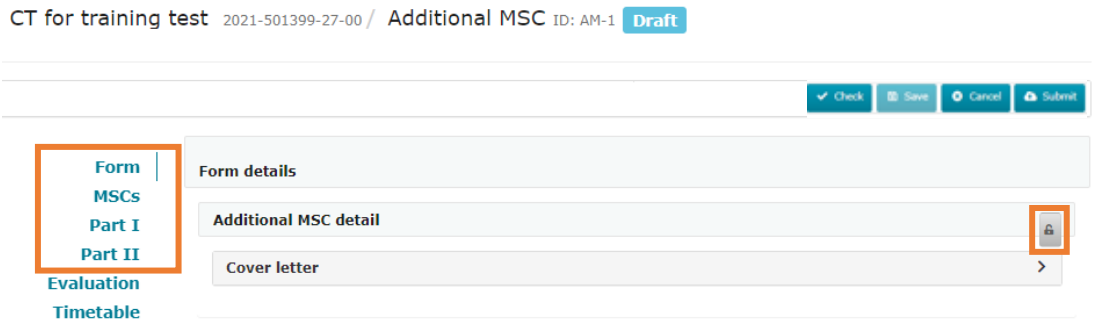
1. After an Initial application for the clinical trial has been authorised in at least one MSC, users can select the '**+ CREATE'** button, and select **'Additional MSC'** at the top-right corner of the CT page.



2. In the pop-up window, they can select the new Member State Concerned to which the sponsor wishes to extend an authorised clinical trial and populate the foreseen number of subjects for the trial in that MSC. After that, they can click on the **'Add'** button.



3. Users can start to populate all the required fields of the sections 'Form', 'MSC' and 'Part II' found on the left of the screen. Additionally, they can include translations of the data and documentation of Part I (click on Part I to add translations). In order to populate a field, users can select the **padlock** button in each subsection.



#CTIS insights

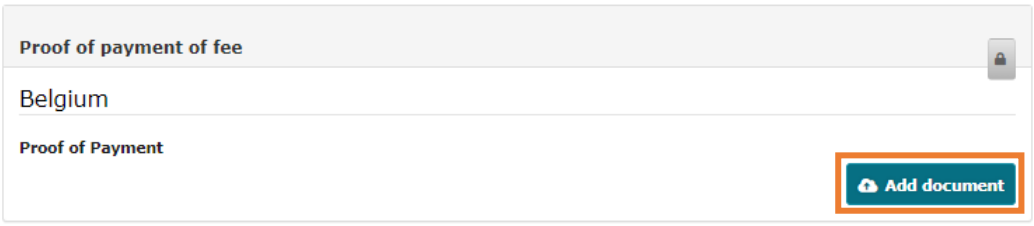
An **Additional MSC application** can only be submitted **once** the initial CTA has been **authorised** by at least one MSC.

Users can only **modify the documents and data** of the **Form, MSC and Part II sections** as Part I has already been evaluated. However, **translations** of the documents of Part I can be added.

Additional MSC CTA

Create and submit an Additional MSC CTA

4. Users can upload documents by selecting the **'Add document'** button in each section.



5. CTIS allows users to upload **two versions** of a same document: one for publication and another one not for publication. Documents not for publication are used to protect personal data and/or to commercially confidential information, provided that the data minimisation principle is observed *(refer to Module 12: Data protection in CTIS for more information).*

6. After populating all the fields, they can select the '**Check**' button on the top-right corner of the CTA page to see if any required field has not been populated (the missing fields will appear marked in red). After all the required fields are populated, they can select the '**Submit'** button.

7. After reading the confirmation text, users can select the **'I agree'** box and then click on the **'Confirm'** button.

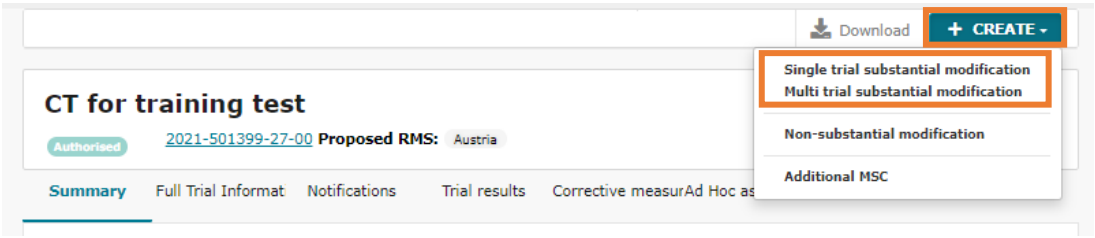
#CTIS insights

The sponsor can **withdraw an Additional MSC** by accessing the CTA and selecting the 'Withdraw' button. The sponsor must provide a justification. The withdrawal of an Add MSC can only be done before the MSC has **issued a decision**.

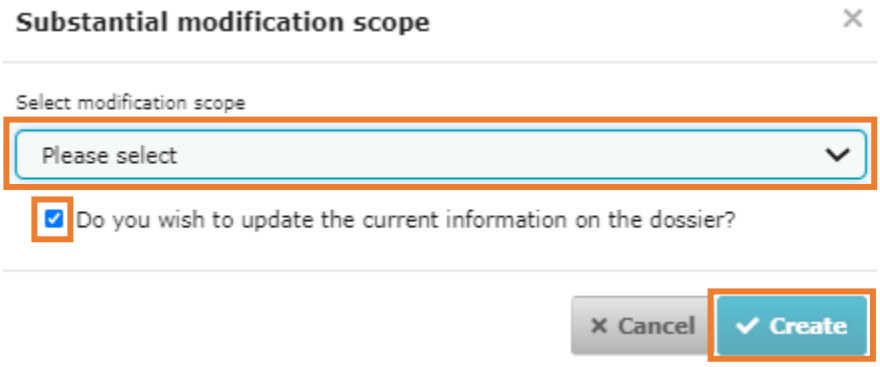
Substantial modification CTA

Create and submit a Substantial modification CTA

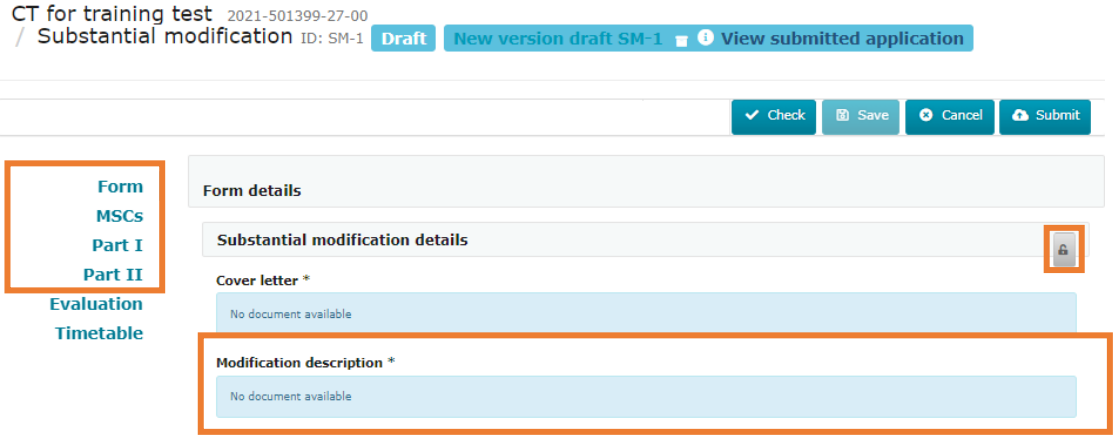
1. After an Initial application for the clinical trial has been authorised, users can select the '**+ CREATE'** button, and at the top-right corner of the CT page select '**Single trial substantial modification'** or **'Multi trial substantial modification'** depending on whether the modification corresponds to one or to more clinical trials.



2. In the pop-up window, users can select the **scope of the modification**, if it is for part I only, part II only, part I and II, and select the **checkbox** in case the current information of the application dossier needs to be updated. After that, they can click on the **'Create'** button.



3. In case users wish to update the current information in the dossier with a SM, they can populate the field **'Modification description'** and update the information required to modify the corresponding sections. In order to populate a field, users can select the **padlock** button in each subsection.



#CTIS insights

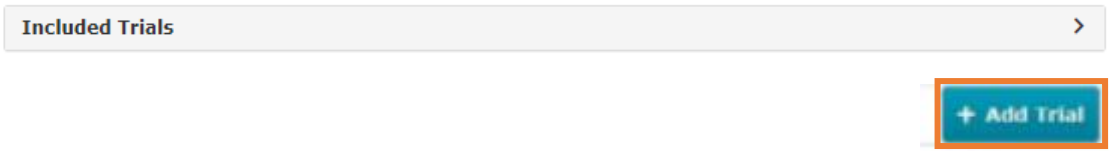
An **SM** allows users to modify aspects in the different sections of a CTA that might have an **impact on the subjects' safety, rights or the robustness and reliability of the data generated** in the CT.

A substantial modification will be **evaluated by the Member States Concerned** after it has been submitted.

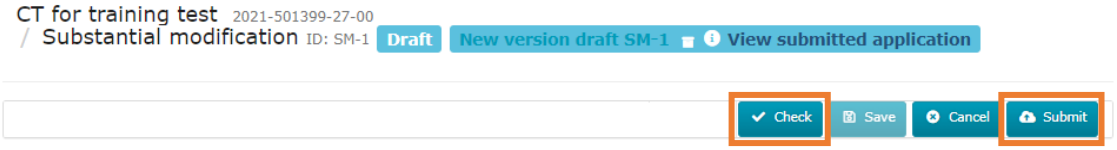
Substantial modification CTA

Create and submit a Substantial modification CTA

4. Users can select a multi trial Substantial Modification to apply modifications on trials with the same sponsor and the same product. To do so, they can populate the **EU CT Number** of the different CTs that the substantial modification applies to in the 'Included Trials' section, using the **'+ Add Trial'** button.

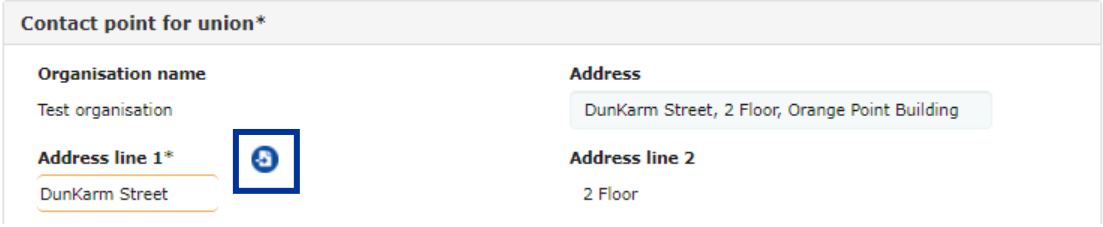


5. After populating all the required fields, including a new cover letter and a document explaining the substantial changes, they can select the '**Check**' button on the top-right corner of the CTA page to see if any required field has not been populated (the missing fields will appear marked in red). Lastly, they can select the '**Submit'** button.



6. After reading the confirmation text, they can select the **'I agree'** box and then click on the **'Confirm'** button.

7. After submitting the Substantial Modification application, the **changes** to the application will be **indicated with a blue icon**.



#CTIS insights

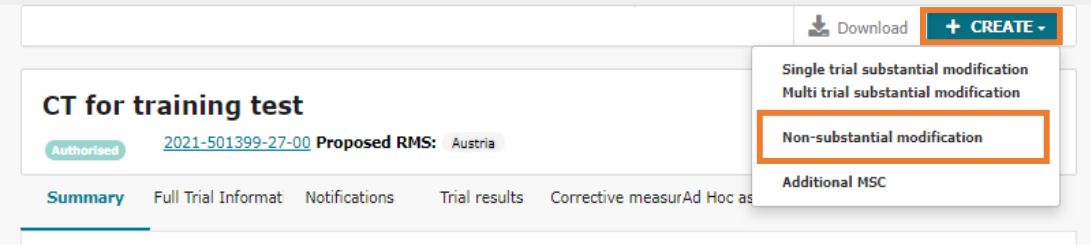
The **scope of a substantial modification** can be Part I only, Part II only, or Part I and Part II.

It is possible to **change the uploaded document** by clicking on the pencil icon.

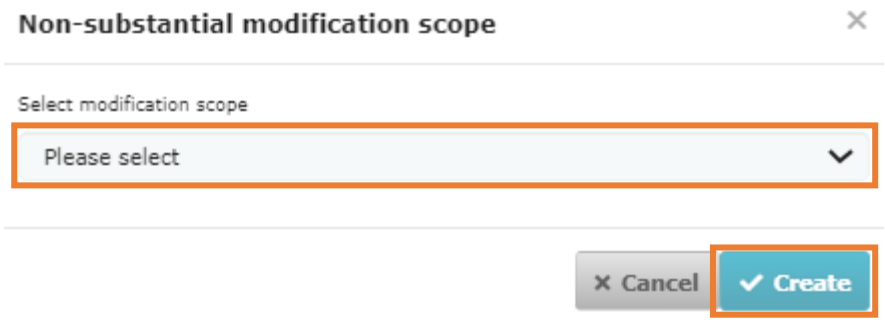
Non-substantial modification

Create and submit a Non-substantial modification

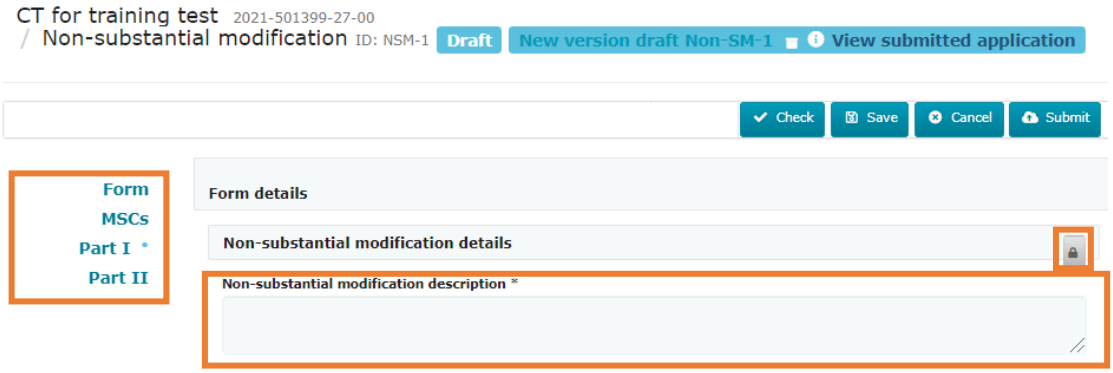
1. After an Initial application for the clinical trial has been authorised by at least one MSC, users can select the '**+ CREATE'** button, and at the top-right corner of the CT page select 'Non-substantial modification'.



2. In the pop-up window, they can select the **scope of the modification**. After that, users can click on the **'Create'** button.



3. Users can populate the field **'Non-substantial modification description'**. In order to populate a field, users can select the **padlock** button in each subsection.



#CTIS insights

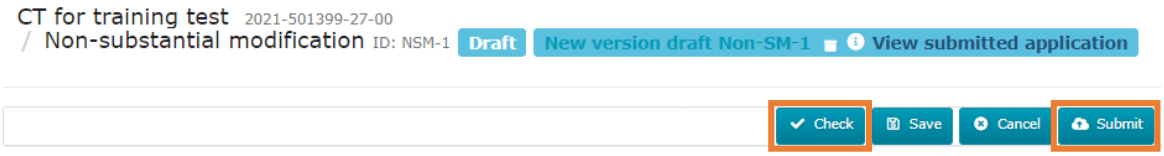
Non-SMs are **not considered clinical trial applications**.

A non-SM is **not subject to evaluation by the Member States Concerned**.

Non-substantial modification

Create and submit a Non-substantial modification

4. After populating the fields that users wish to modify, they can select the '**Check**' button on the top-right corner of the CTA page (e.g. in case any information has been unintentionally removed the missing fields will appear marked in red). Lastly, they can select the '**Submit**' button.



5. After reading the confirmation text, users can select the **'I agree'** box and then click on the **'Confirm'** button.

6. After submitting the Non-substantial Modification, the **changes** to the application will be **indicated with a blue icon**.

#CTIS insights

Non-SM allows users to modify aspects in the different sections of a CTA that **do not have an impact on the subjects' safety, rights or the robustness and reliability of the data generated** in the CT.

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Clinical Trials Information System (CTIS)
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