



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 1.1 – May 2024

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.

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Record of updated versions

Version	Version description	Date
1.1	Minor changes: Additional information in Step 6 (Page 5) and Step 5 (Page 10) .	May 2024

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 to extend 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.



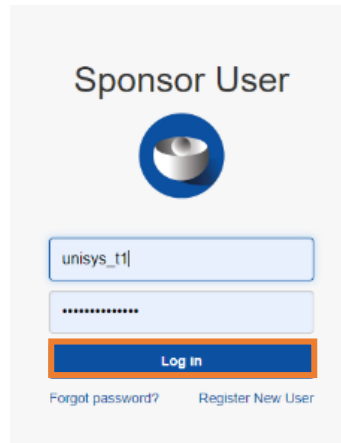
Non-substantial modification

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

Initial CTA

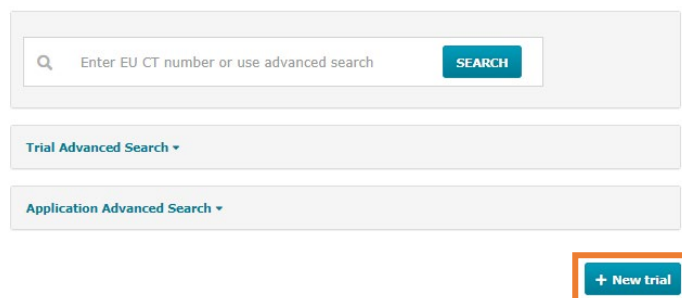
Create and submit an Initial CTA

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

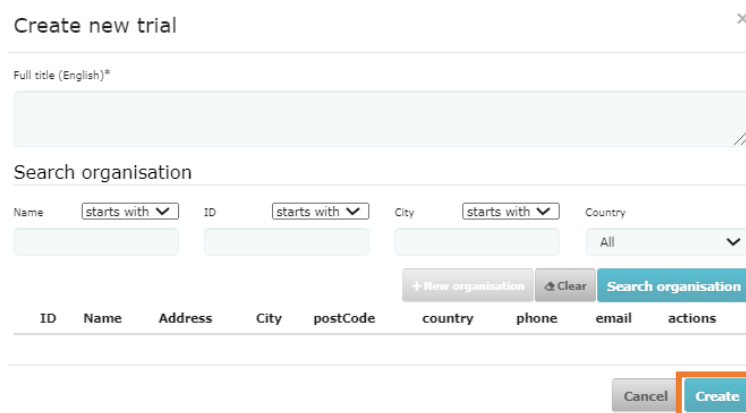


2. In the **Clinical trial** tab, they can select the '+ **New trial**' button.

Clinical Trials



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



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.

Test for CTIS Training 2021-501602-37-00 / Initial ID: IN **Draft**

✓ Check Save Cancel Submit

Form
MSCs
Part I
Part II
Evaluation
Timetable

Form details

Initial Application details

Cover letter

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

Proof of payment of fee

Austria

Proof of Payment

Germany

Proof of Payment

Add document

Add document

- 6¹. For most placeholders, documents are not published; however, for a few of them, **the initially uploaded versions are published**. The **Plus Icon** (available only for those placeholders) can be used by users to upload versions not intended for publication. **The Revised Disclosure Rules have been introduced to improve transparency and accessibility regarding the agency's operations.** (Refer to [Revised CTIS Transparency Rules](#), [Module 02: Guide on CTIS common features](#) and [Module 12: Data protection in CTIS](#) for more information).

Financial and other arrangements

Financial and other arrangements *:

Add document

Financial and other arrangements

English · Financial arrangements · System version 1.00
· Version 1 · 23/04/2024

Initial CTA

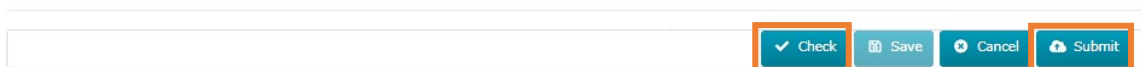
Create and submit an Initial CTA



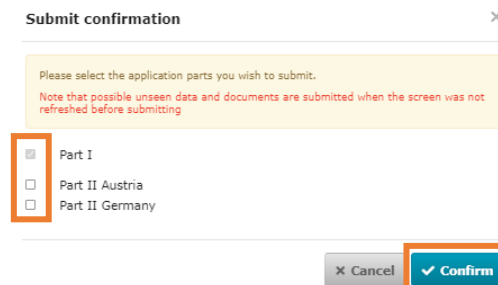
¹ Plus icon can be used by users to upload versions not for publication

- 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.

Test for CTIS Training 2021-501602-37-00 / Initial ID: IN **Draft**



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



- 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**'.

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.

CT for training test
Authorised 2021-501398-35-00 RMS: Austria

Summary Full Trial Information Notifications Trial results Corrective measures Ad Hoc assessment Users

APPLICATION AND NON-SUBSTANTIAL MODIFICATION

Type	ID	Parts	MSCs	Submission date	Decision date	
Initial	IN	Part I & Part II Part I & Part II	AT(Authorised) DE(Authorised)	20/05/2021	20/05/2021	+ INFO

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

CT for training test 2021-501399-27-00 / Initial ID: IN Under evaluation

✓ Check Save **Withdraw** Copy

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.

Withdraw application ×

Application type
Initial

Member states concerned
Austria Germany

Justification*

Cancel **Withdraw**



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.

CT for training test
Authorised [2021-501398-35-00](#) RMS: Austria

[Summary](#) [Full Trial Information](#) [Notifications](#) [Trial results](#) [Corrective measures](#) [Ad Hoc assessment](#) [Users](#)

APPLICATION AND NON-SUBSTANTIAL MODIFICATION

Type	ID	Parts	MSCs	Submission date	Decision date	
Initial	IN	Part I & Part II Part I & Part II	AT(Authorised) DE(Authorised)	20/05/2021	20/05/2021	+ INFO

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

CT for training test [2021-501398-35-00](#) / Initial ID: IN Authorised / RMS: Austria

 Copy

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.

Trial copy request - Section selection ×

You have selected to copy trial: **CT for training test**

Please deselect all sections you would like to remove from the new copy and confirm

Trial details
Clinical trial: 2021-501398-35-00

Sections
☐ Part I (Mandatory)
☒ Part II

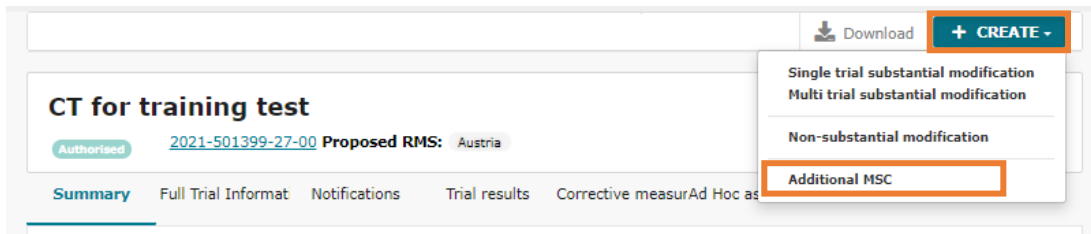
☒ Austria
☒ Germany

[Confirm](#) [Cancel](#)

Additional MSC CTA

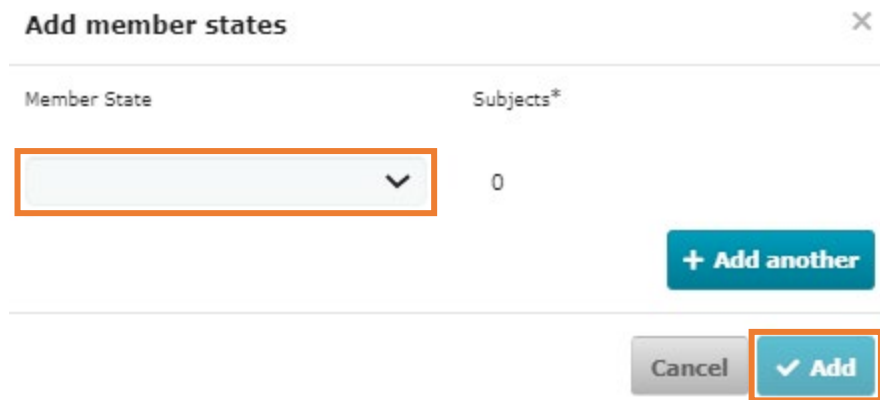
Create and submit an Additional MSC CTA

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.



The screenshot shows the 'CT for training test' page. At the top right, there is a 'Download' button and a '+ CREATE' button. A dropdown menu is open from the '+ CREATE' button, showing options: 'Single trial substantial modification', 'Multi trial substantial modification', 'Non-substantial modification', and 'Additional MSC'. The 'Additional MSC' option is highlighted with an orange box. Below the dropdown, there are tabs: 'Summary', 'Full Trial Information', 'Notifications', 'Trial results', 'Corrective measures', 'Ad Hoc', and 'Additional MSC'.

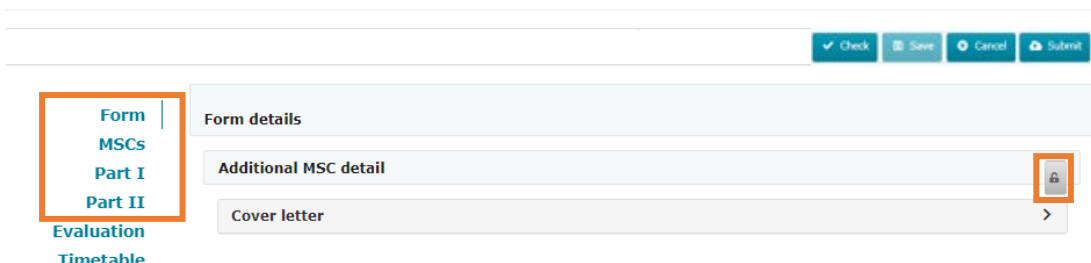
2. In the pop-up window, they can select the new Member State Concerned to which the sponsor wishes to extend an authorised clinical trial and populate the foreseen number of subjects for the trial in that MSC. After that, they can click on the 'Add' button.



The screenshot shows the 'Add member states' pop-up window. It has a title bar with a close button. Below the title bar, there are two columns: 'Member State' and 'Subjects*'. The 'Member State' column has a dropdown menu with a downward arrow. The 'Subjects*' column has a text input field with the value '0'. At the bottom right, there is a '+ Add another' button. At the bottom left, there are two buttons: 'Cancel' and 'Add'. The 'Add' button is highlighted with an orange box.

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.

CT for training test 2021-501399-27-00 / Additional MSC ID: AM-1 Draft



The screenshot shows the 'Form details' section. On the left, there is a sidebar with a list of sections: 'Form', 'MSCs', 'Part I', 'Part II', 'Evaluation', and 'Timetable'. The 'Form' section is highlighted with an orange box. In the main content area, there are three subsections: 'Form details', 'Additional MSC detail', and 'Cover letter'. The 'Additional MSC detail' subsection has a padlock icon in the top right corner, which is highlighted with an orange box. At the bottom right, there is a right arrow icon.



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. For most placeholders, documents are not published; however, for a few of them, the initially uploaded versions are published. The **Plus Icon** can be used by users to upload versions not intended for publication. The Revised Disclosure Rules have been introduced to improve transparency and accessibility regarding the agency's operations. (Refer to Revised CTIS Transparency Rules, Module 02: Guide on CTIS common features 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.



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.

The screenshot shows the 'CT for training test' page. At the top right, there is a 'Download' button and a '+ CREATE' button. A dropdown menu is open from the '+ CREATE' button, showing four options: 'Single trial substantial modification', 'Multi trial substantial modification', 'Non-substantial modification', and 'Additional MSC'. The page also shows 'Authorised' status, a reference number '2021-501399-27-00', and 'Proposed RMS: Austria'. Navigation tabs include 'Summary', 'Full Trial Information', 'Notifications', 'Trial results', and 'Corrective measures/Ad Hoc actions'.

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.

The screenshot shows the 'Substantial modification scope' pop-up window. It has a title bar with a close button. Inside, there is a section 'Select modification scope' with a dropdown menu currently showing 'Please select'. Below this is a checkbox labeled 'Do you wish to update the current information on the dossier?' which is checked. At the bottom right, there are two buttons: 'Cancel' and 'Create'.

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.

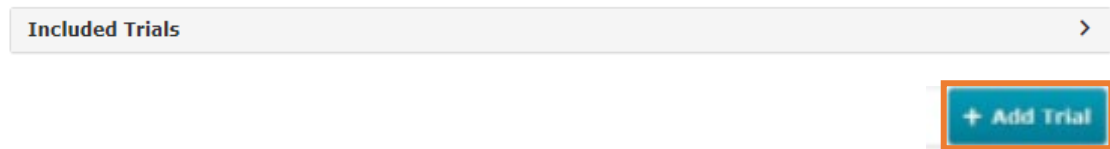
The screenshot shows the 'Substantial modification details' form. On the left is a sidebar with navigation links: 'Form', 'MSCs', 'Part I', 'Part II', 'Evaluation', and 'Timetable'. The main form area has a header with 'CT for training test 2021-501399-27-00' and 'Substantial modification ID: SM-1'. Below this are buttons for 'Draft', 'New version draft SM-1', and 'View submitted application'. The form has several sections: 'Form details', 'Substantial modification details', 'Cover letter *', and 'Modification description *'. The 'Modification description *' section is highlighted with a red box, and a padlock icon is visible next to it.



Substantial modification CTA

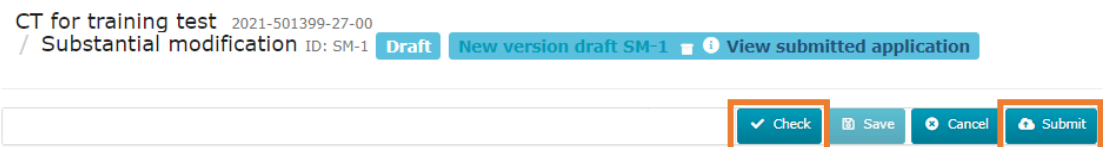
Create and submit a Substantial modification CTA

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.



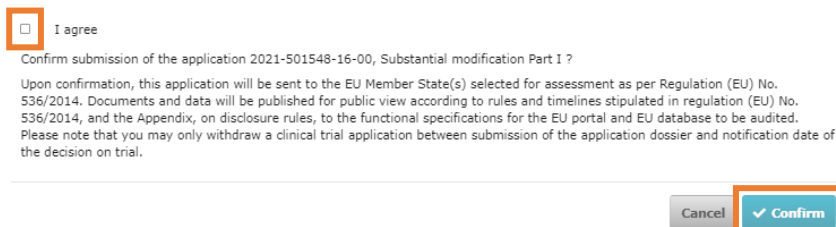
The screenshot shows a light gray box with the text 'Included Trials' and a right-pointing arrow. Below this box, on the right side, is a blue button with a white plus sign and the text '+ Add Trial'.

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.



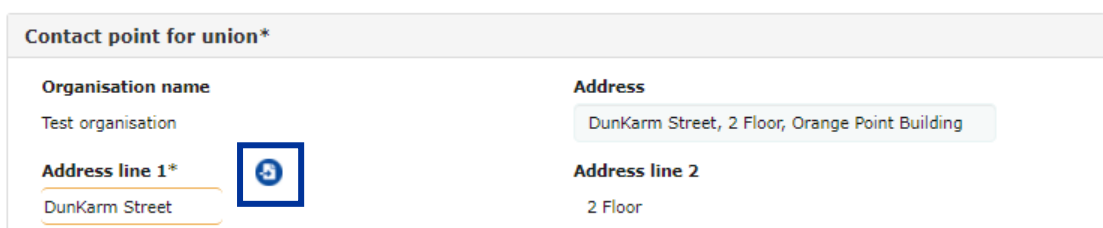
The screenshot shows a header area with the text 'CT for training test 2021-501399-27-00 / Substantial modification ID: SM-1'. Below this are four buttons: 'Draft' (blue), 'New version draft SM-1' (blue), 'View submitted application' (blue), and a 'Check' button (blue) with a white checkmark icon. To the right of the 'Check' button are three more buttons: 'Save' (blue), 'Cancel' (blue), and 'Submit' (blue) with a white cloud icon.

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



The screenshot shows a confirmation text area. It starts with a checkbox labeled 'I agree'. Below this is a paragraph of text: 'Confirm submission of the application 2021-501548-16-00, Substantial modification Part I ? Upon confirmation, this application will be sent to the EU Member State(s) selected for assessment as per Regulation (EU) No. 536/2014. Documents and data will be published for public view according to rules and timelines stipulated in regulation (EU) No. 536/2014, and the Appendix, on disclosure rules, to the functional specifications for the EU portal and EU database to be audited. Please note that you may only withdraw a clinical trial application between submission of the application dossier and notification date of the decision on trial.' At the bottom right of the text area are two buttons: 'Cancel' (gray) and 'Confirm' (blue) with a white checkmark icon.

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



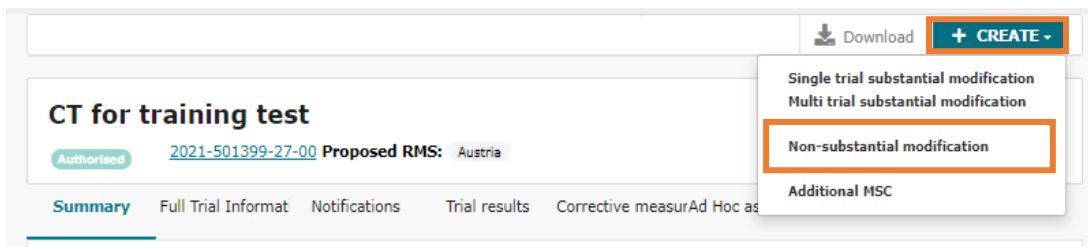
The screenshot shows a form section titled 'Contact point for union*'. It has two columns. The left column has 'Organisation name' (Test organisation) and 'Address line 1*' (Dunkarm Street). The right column has 'Address' (Dunkarm Street, 2 Floor, Orange Point Building) and 'Address line 2' (2 Floor). A blue icon (a square with a circle inside) is located next to the 'Address line 1*' field.



Non-substantial modification

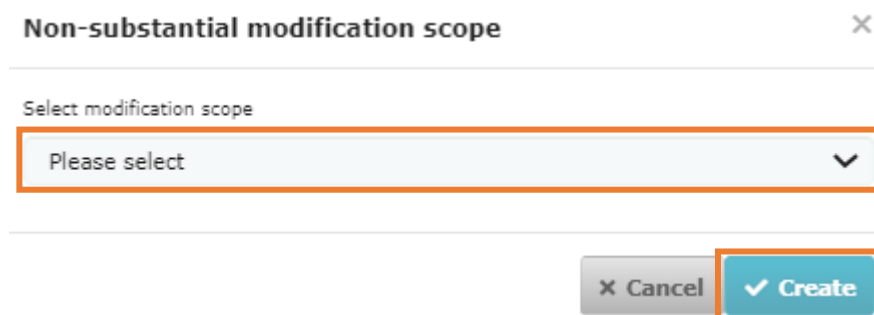
Create and submit a Non-substantial modification

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'.



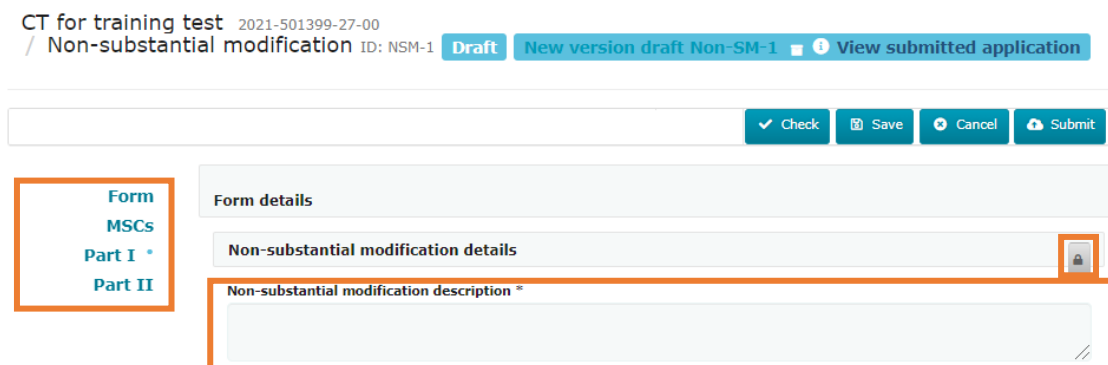
The screenshot shows the 'CT for training test' page. At the top right, there is a 'Download' button and a '+ CREATE' button. A dropdown menu is open from the '+ CREATE' button, showing options: 'Single trial substantial modification', 'Multi trial substantial modification', 'Non-substantial modification' (highlighted with an orange box), and 'Additional MSC'. Below the dropdown, there is a 'Summary' tab and a 'Full Trial Information' tab. The 'Summary' tab is active, showing 'Authorised' status, '2021-501399-27-00' ID, and 'Proposed RMS: Austria'.

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



The screenshot shows the 'Non-substantial modification scope' pop-up window. It has a close button (X) in the top right corner. Below the title, there is a 'Select modification scope' label and a dropdown menu with 'Please select' and a downward arrow. At the bottom right, there are two buttons: 'X Cancel' and '✓ Create' (highlighted with an orange box).

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.



The screenshot shows the 'Non-substantial modification' form. At the top, there is a header with 'CT for training test 2021-501399-27-00 / Non-substantial modification ID: NSM-1' and buttons for 'Draft', 'New version draft Non-SM-1', and 'View submitted application'. Below the header, there is a 'Form details' section with a 'Non-substantial modification details' subsection. The 'Non-substantial modification description' field is highlighted with an orange box. To the left of the form, there is a sidebar with 'Form', 'MSCs', 'Part I', and 'Part II' (highlighted with an orange box). At the bottom right of the form, there is a 'padlock' icon (highlighted with an orange box) and a 'Submit' button.



Non-substantial modification

Create and submit a Non-substantial modification

- 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.

CT for training test 2021-501399-27-00

/ Non-substantial modification ID: NSM-1

Draft

New version draft Non-SM-1

View submitted application

✓ Check

Save

Cancel

Submit

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

☐ I agree

Confirm submission of the application 2021-501548-16-00, Substantial modification Part I ?

Upon confirmation, this application will be sent to the EU Member State(s) selected for assessment as per Regulation (EU) No. 536/2014. Documents and data will be published for public view according to rules and timelines stipulated in regulation (EU) No. 536/2014, and the Appendix, on disclosure rules, to the functional specifications for the EU portal and EU database to be audited. Please note that you may only withdraw a clinical trial application between submission of the application dossier and notification date of the decision on trial.

Cancel

✓ Confirm

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

Form

MSCs

Part I

Part II

- DE

Country specific details (Part II - Germany)

Versions



Trial sites

Trial sites

e ation	Site street address	Site city	Site post code	Site country	Title	First name	Last name	Department	Phone	Email
Jenheimer d 151, Jenheim	Im Neuenheimer Feld 151	Heidelberg	69120	Germany	Dr.	First name	Last name	Department	111222222	CTtestmail@mail.com



#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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Send a question

www.ema.europa.eu/contact

Clinical Trials Information System (CTIS)

Step-by-step guide: Create, submit and withdraw a clinical trial application and non-substantial modifications

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