



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.

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# 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.



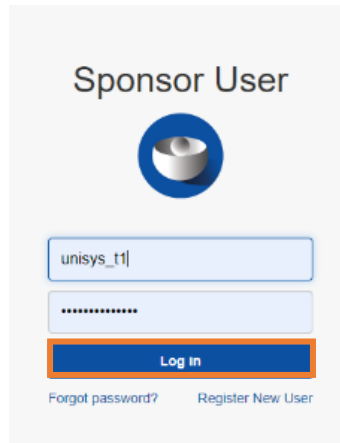
## Non-substantial modification

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

## Initial CTA

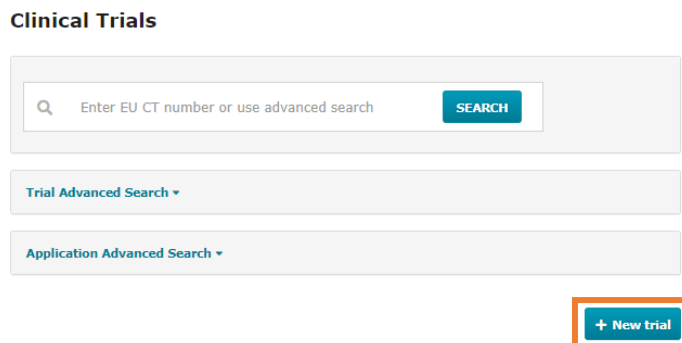
### Create and submit an Initial CTA

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



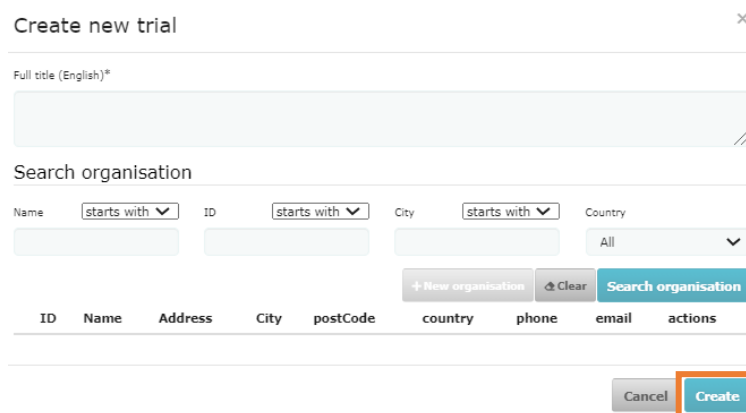
The screenshot shows a 'Sponsor User' login interface. It features a profile picture placeholder, a text input field containing 'unisys\_t1', a password input field with masked characters, and a prominent blue 'Log in' button. Below the login fields are links for 'Forgot password?' and 'Register New User'.

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



The screenshot displays the 'Clinical Trials' search section. It includes a search bar with the placeholder text 'Enter EU CT number or use advanced search' and a 'SEARCH' button. Below the search bar are two expandable sections: 'Trial Advanced Search' and 'Application Advanced Search'. A blue '+ New trial' button is highlighted with an orange box at the bottom right of the interface.

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



The screenshot shows a 'Create new trial' pop-up window. It contains a text area for 'Full title (English)\*', a 'Search organisation' section with filters for Name, ID, City, and Country, and a table of search results. The table has columns for ID, Name, Address, City, postCode, country, phone, email, and actions. At the bottom of the window are 'Cancel' and 'Create' buttons, with the 'Create' button highlighted by an orange box.

## Initial CTA


### Create and submit an Initial CTA

- 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 details

Initial Application details 

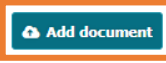
Cover letter >

Form  
MSCs  
Part I  
Part II  
Evaluation  
Timetable

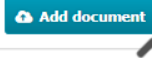
- Users can upload documents by selecting the '**Add document**' button in each section.

Proof of payment of fee 

Austria

Proof of Payment 

Germany

Proof of Payment 

- 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).

Proof of payment of fee 

Austria

Proof of Payment

 test     

English · Proof of payment (for publication) · System version 1.00  
· Version 1 · 12/07/2021

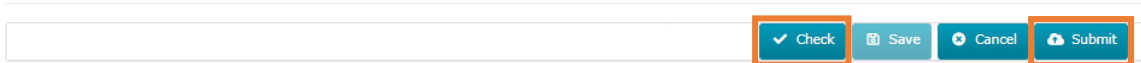
To upload a new version of a document 'not-for-publication', users can click on the '+' icon.

## Initial CTA

### Create and submit an Initial CTA

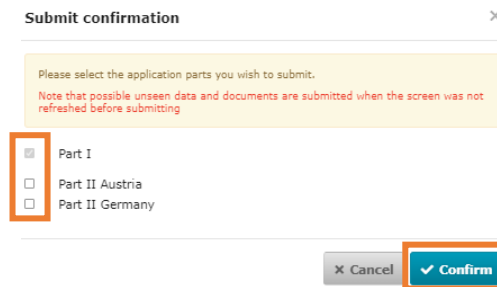
- After populating all the fields, they can select the '**Check**' button on the top-right corner of the CTA page to see if any required field has not been populated (the missing fields will appear marked in red). After all the required fields are populated, they can select the '**Submit**' button.

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



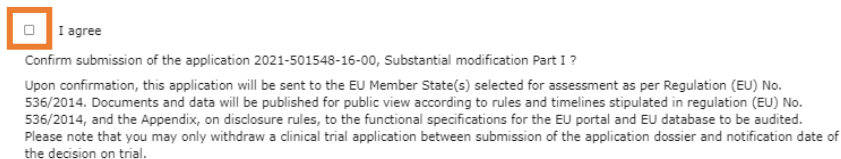
A horizontal bar containing four buttons: 'Check' (with a checkmark icon), 'Save' (with a floppy disk icon), 'Cancel' (with a circular arrow icon), and 'Submit' (with a document icon). The 'Check' and 'Submit' buttons are highlighted with orange boxes.

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



A dialog box titled 'Submit confirmation' with a close button (X). It contains a yellow warning box with the text: 'Please select the application parts you wish to submit. Note that possible unseen data and documents are submitted when the screen was not refreshed before submitting'. Below this are three checkboxes: 'Part I' (checked), 'Part II Austria', and 'Part II Germany'. At the bottom are 'Cancel' and 'Confirm' buttons. The 'Confirm' button is highlighted with an orange box.

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



An 'I agree' checkbox is highlighted with an orange box. Below it is the 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.'



A 'Confirm' button with a checkmark icon, highlighted with an orange box.

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	<b>IN</b>	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

Authorized 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	<b>IN</b>	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 **Authorized** / RMS: Austria

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

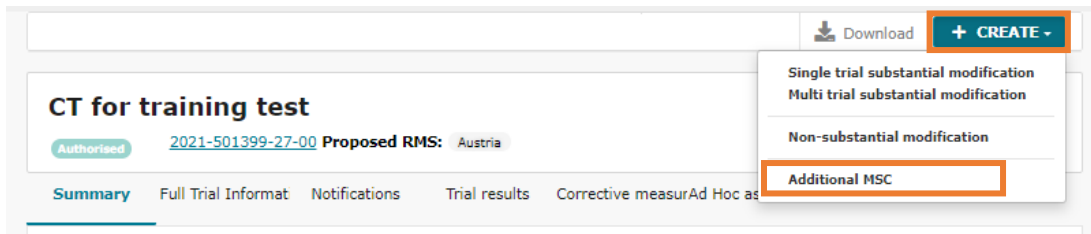
- Part I (Mandatory)
- Part II

- Austria
- Germany

## Additional MSC CTA

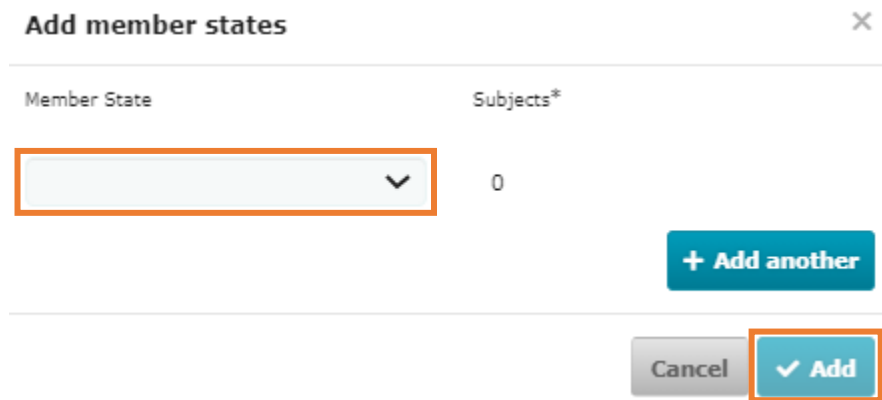
### Create and submit an Additional MSC CTA

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 top right corner of a clinical trial page. A 'Download' button is next to a '+ CREATE -' button. A dropdown menu is open, 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, the page title 'CT for training test' is visible, along with 'Authorised' status, trial ID '2021-501399-27-00', and 'Proposed RMS: Austria'. Navigation tabs include 'Summary', 'Full Trial Informat', 'Notifications', 'Trial results', 'Corrective measurAd Hoc as'.

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 a pop-up window titled 'Add member states'. It has a close button (X) in the top right. The window contains a table with two columns: 'Member State' and 'Subjects\*'. The 'Member State' column has a dropdown menu with a downward arrow, highlighted with an orange box. The 'Subjects\*' column has the value '0'. Below the table is a '+ Add another' button. At the bottom right, there are 'Cancel' and 'Add' buttons, with the 'Add' button 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**



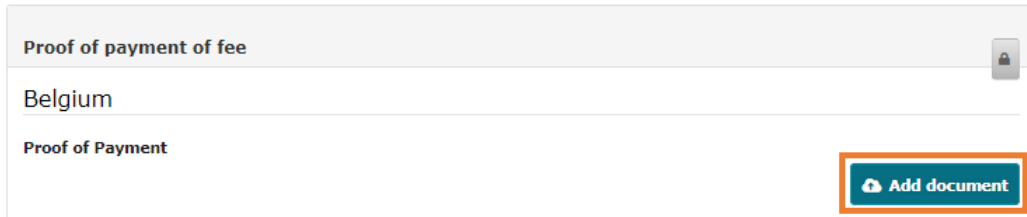
The screenshot shows the 'Form details' section of the application. At the top right, there are buttons for 'Check', 'Save', 'Cancel', and 'Submit'. On the left, there is a sidebar with a list of sections: 'Form', 'MSCs', 'Part I', 'Part II', 'Evaluation', and 'Timetable'. The 'Form' section is highlighted with an orange box. The main area shows three subsections: 'Form details', 'Additional MSC detail', and 'Cover letter'. The 'Additional MSC detail' subsection has a padlock icon on its right side, highlighted with an orange box. The 'Cover letter' subsection has a right-pointing arrow icon on its right side.



## 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.



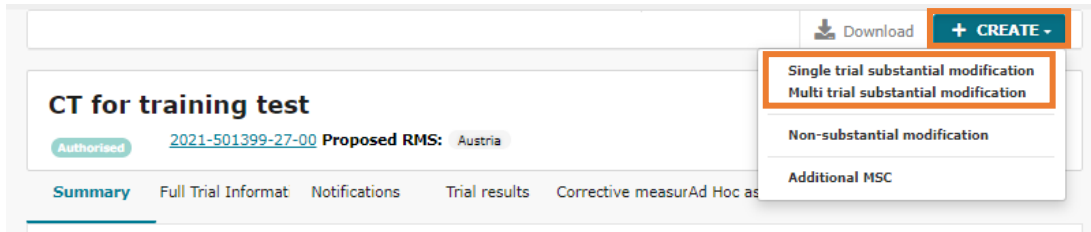
7. After reading the confirmation text, users can select the **'I agree'** box and then click on the **'Confirm'** button.



## Substantial modification CTA

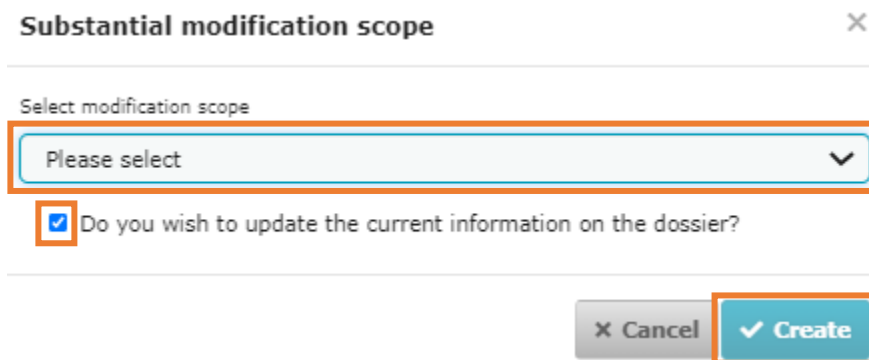
### Create and submit a Substantial modification CTA

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.



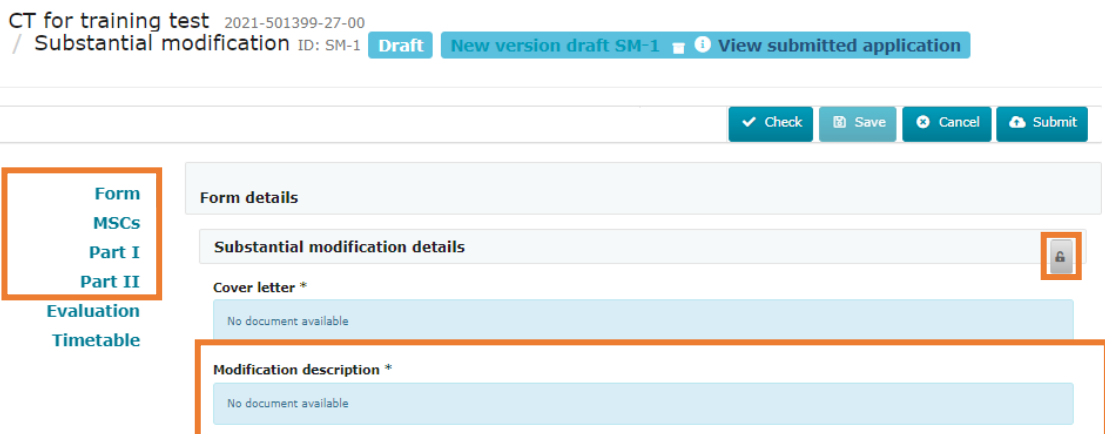
The screenshot shows a clinical trial page for 'CT for training test' with ID 2021-501399-27-00. A '+ CREATE' button is highlighted in the top right corner. A dropdown menu is open, showing options: 'Single trial substantial modification', 'Multi trial substantial modification', 'Non-substantial modification', and 'Additional MSC'. The 'Single trial substantial modification' and 'Multi trial substantial modification' options are highlighted with an orange box.

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 a 'Substantial modification scope' pop-up window. It has a dropdown menu for 'Select modification scope' with 'Please select' as the current selection. Below it is a checked checkbox labeled 'Do you wish to update the current information on the dossier?'. At the bottom are 'Cancel' and 'Create' buttons.

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.

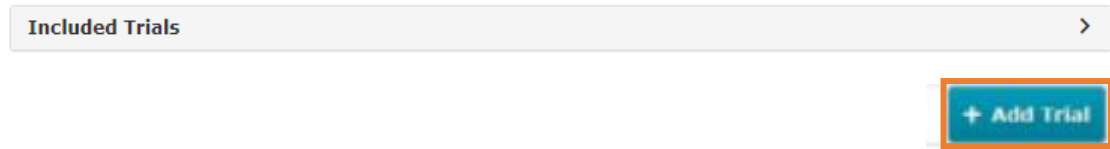


The screenshot shows the 'Substantial modification details' form. The 'Modification description' field is highlighted with an orange box. The 'Cover letter' field is also highlighted. The 'Form details' section is highlighted with an orange box. The 'Substantial modification details' section is highlighted with an orange box. The 'Modification description' field is highlighted with an orange box.

## Substantial modification CTA

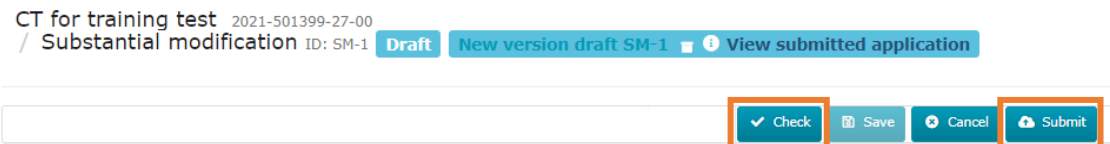
### Create and submit a Substantial modification CTA

- 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.



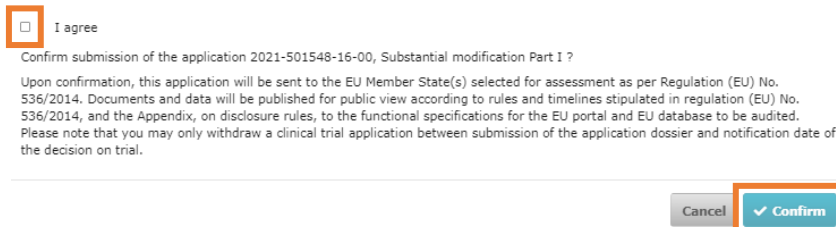
The screenshot shows a section titled 'Included Trials' with a right-pointing arrow. Below this section is a blue button with a white plus sign and the text '+ Add Trial'.

- 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.



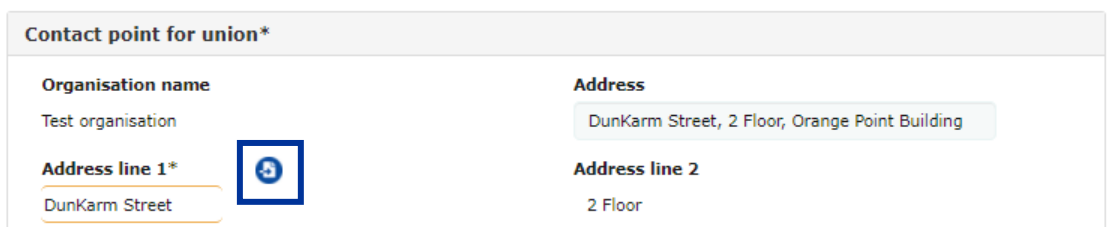
The screenshot shows the application status bar. It includes the text 'CT for training test 2021-501399-27-00 / Substantial modification ID: SM-1'. There are two status buttons: 'Draft' and 'New version draft SM-1'. To the right is a link 'View submitted application'. Below this are four action buttons: 'Check', 'Save', 'Cancel', and 'Submit'.

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



The screenshot shows a confirmation section. It starts with a checkbox labeled 'I agree'. Below it is the text: 'Confirm submission of the application 2021-501548-16-00, Substantial modification Part I ?'. A paragraph of text follows: '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 are two buttons: 'Cancel' and 'Confirm'.

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

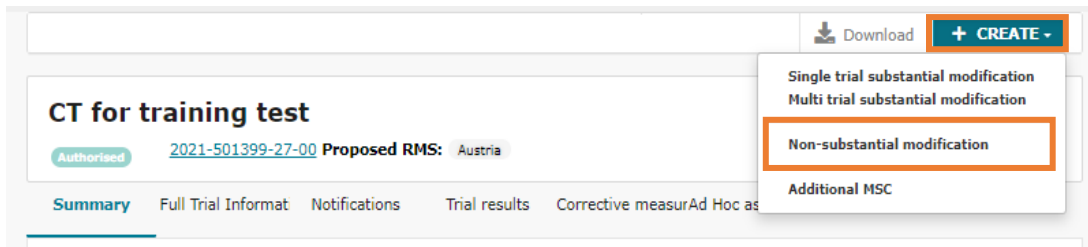


The screenshot shows a form titled 'Contact point for union\*'. It has two columns. The left column has 'Organisation name' (Test organisation) and 'Address line 1\*' (DunKarm Street). The right column has 'Address' (DunKarm Street, 2 Floor, Orange Point Building) and 'Address line 2' (2 Floor). A blue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

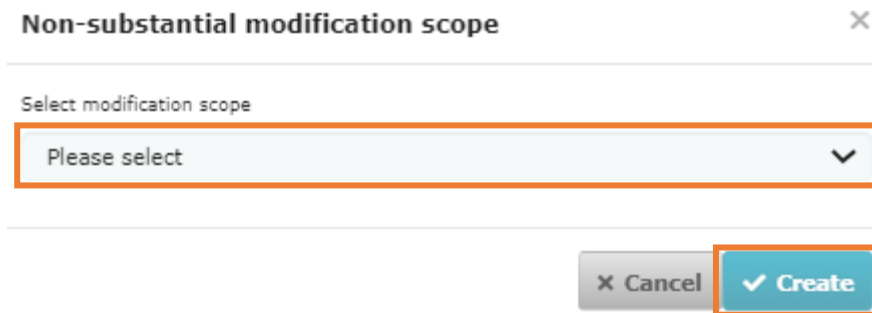
## Non-substantial modification

### Create and submit a Non-substantial modification

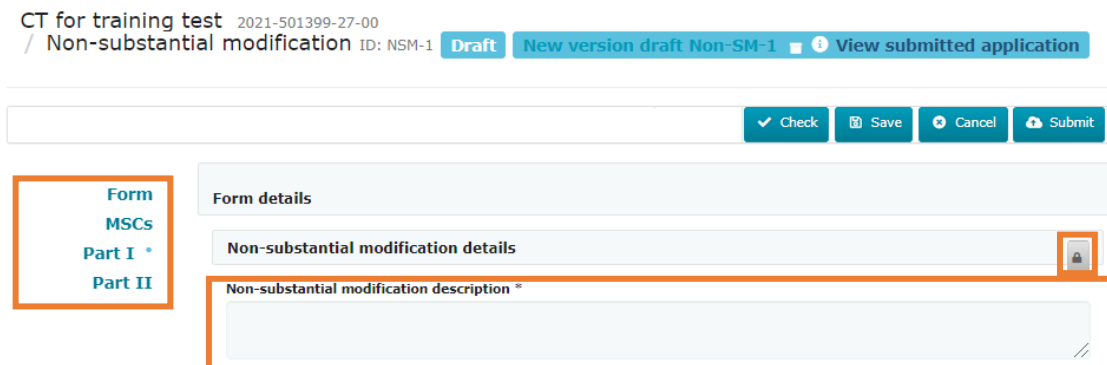
1. After an Initial application for the clinical trial has been authorised by at least one MSC, users can select the '+ CREATE' button, and at the top-right corner of the CT page select 'Non-substantial modification'.



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.



## 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



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

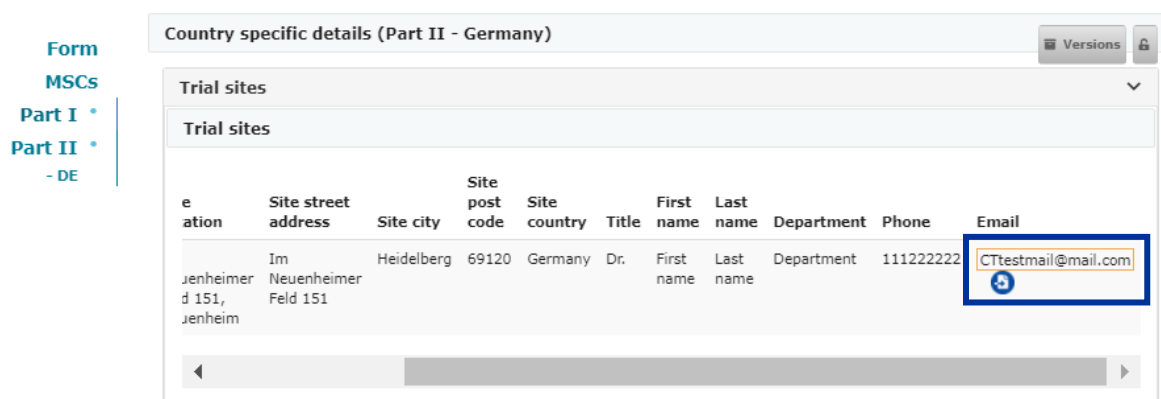
I agree

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

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



e ation	Site street address	Site city	Site post code	Site country	Title	First name	Last name	Department	Phone	Email
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**Send a question**

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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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