



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.



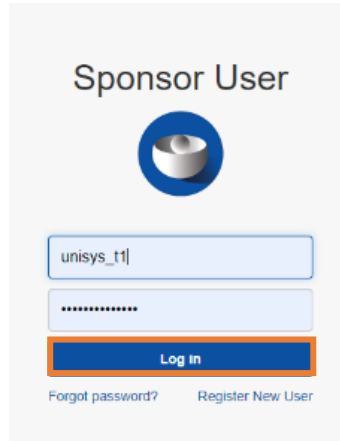
Non-substantial modification

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

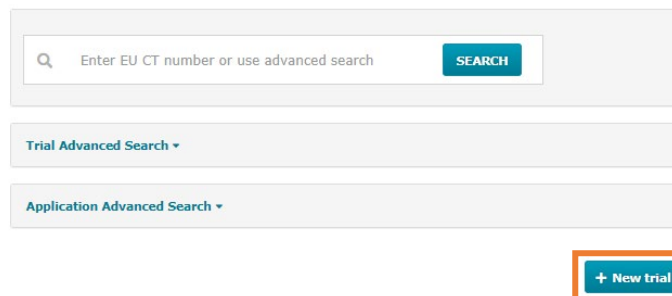
1. Users can populate the credentials and select the '**Log in**' button.



The screenshot shows a 'Sponsor User' login interface. At the top, there is a blue circular profile icon. Below it are two input fields: the first contains the text 'unisys_t1' and the second contains a masked password '*****'. A blue 'Log in' button is positioned below the password field and is highlighted with an orange border. At the bottom, there are two links: 'Forgot password?' and 'Register New User'.

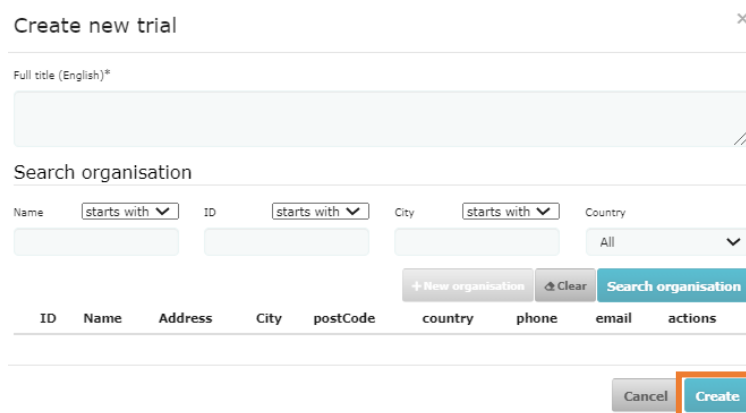
2. In the **Clinical trial** tab, they can select the '+ **New trial**' button.

Clinical Trials



The screenshot displays the 'Clinical Trials' search page. It features 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'. At the bottom right of the page, a blue button with a plus sign and the text '+ New trial' is highlighted with an orange border.

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 has a title bar with a close button (X). The main content area includes a text input field for 'Full title (English)*'. Below this is a 'Search organisation' section with several dropdown menus for 'Name' (set to 'starts with'), 'ID' (set to 'starts with'), 'City' (set to 'starts with'), and 'Country' (set to 'All'). There are also '+ New organisation' and 'Clear' buttons. A 'Search organisation' button is highlighted with an orange border. At the bottom of the pop-up, there are 'Cancel' and 'Create' buttons, with the 'Create' button highlighted with an orange border.

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**

The screenshot shows the 'Initial CTA' application interface. At the top, there are buttons for 'Check', 'Save', 'Cancel', and 'Submit'. Below this, there is a navigation menu on the left with options: 'Form', 'MSCs', 'Part I', 'Part II', 'Evaluation', and 'Timetable'. The 'Form' option is highlighted with an orange box. To the right, there are sections for 'Form details', 'Initial Application details', and 'Cover letter'. The 'Initial Application details' section is highlighted with an orange box and contains a padlock icon.

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

The screenshot shows the 'Proof of payment of fee' section. It contains a list of countries: 'Austria' and 'Germany'. For each country, there is a 'Proof of Payment' field. The 'Add document' button is highlighted with an orange box.

- 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).

The screenshot shows the 'Financial and other arrangements' section. It contains a list of documents. The 'Add document' button is highlighted with an orange box.

Initial CTA

Create and submit an Initial CTA

Protocol information ▼

Clinical trial protocol

Protocol *

Protocol Synopsis

English · Protocol (for publication) · **System version 1.00**
· **Version 1** · 23/04/2024

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.

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.

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

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	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 **Authorized** / 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

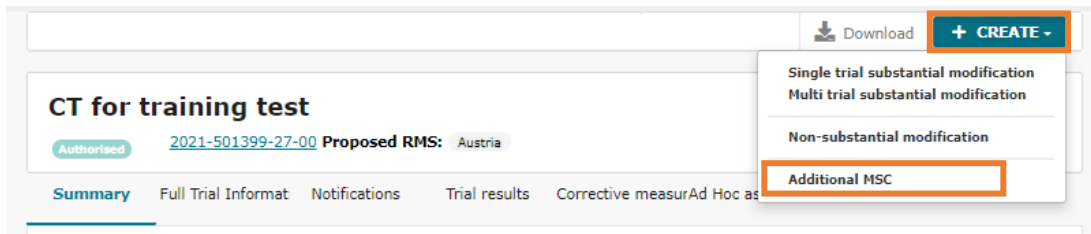
- Austria
- Germany

Confirm Cancel

Additional MSC CTA

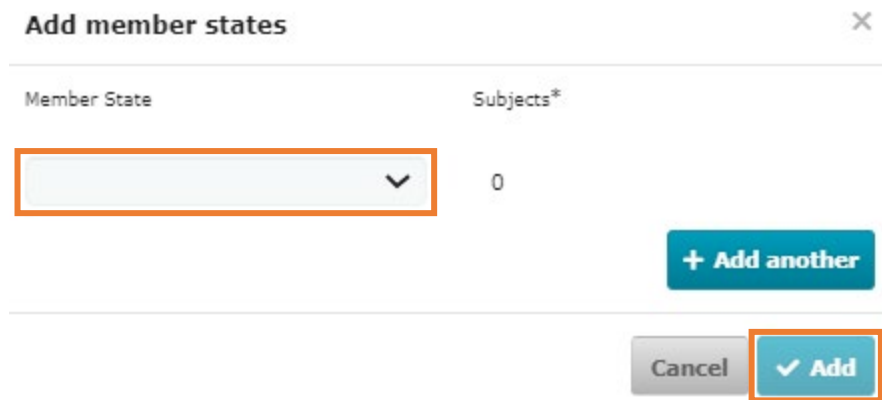
Create and submit an Additional MSC CTA

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 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 a status 'Authorised', a trial ID '2021-501399-27-00', and 'Proposed RMS: Austria'. A navigation bar includes 'Summary', 'Full Trial Informat', 'Notifications', 'Trial results', 'Corrective measurAd Hoc as'.

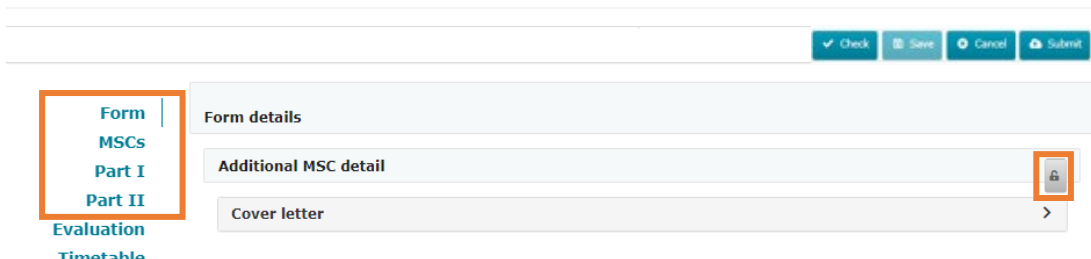
2. In the pop-up window, they can select the new Member State Concerned to which the sponsor wishes to extend an authorised clinical trial and populate the foreseen number of subjects for the trial in that MSC. After that, they can click on the 'Add' button.



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**

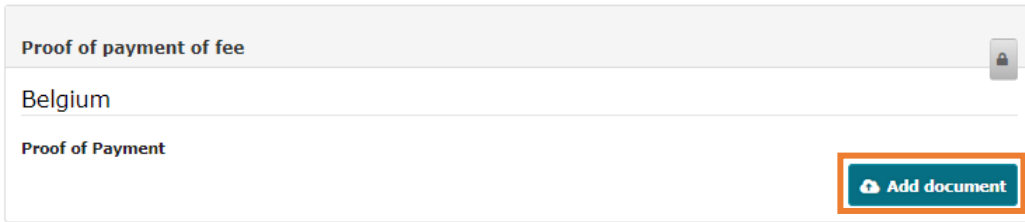


The screenshot shows the main application page. At the top right, there are buttons for 'Check', 'Save', 'Cancel', and 'Submit'. Below this is a sidebar with a list of sections: 'Form', 'MSCs', 'Part I', 'Part II', 'Evaluation', and 'Timetable'. The 'Form' section is highlighted with an orange box. The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

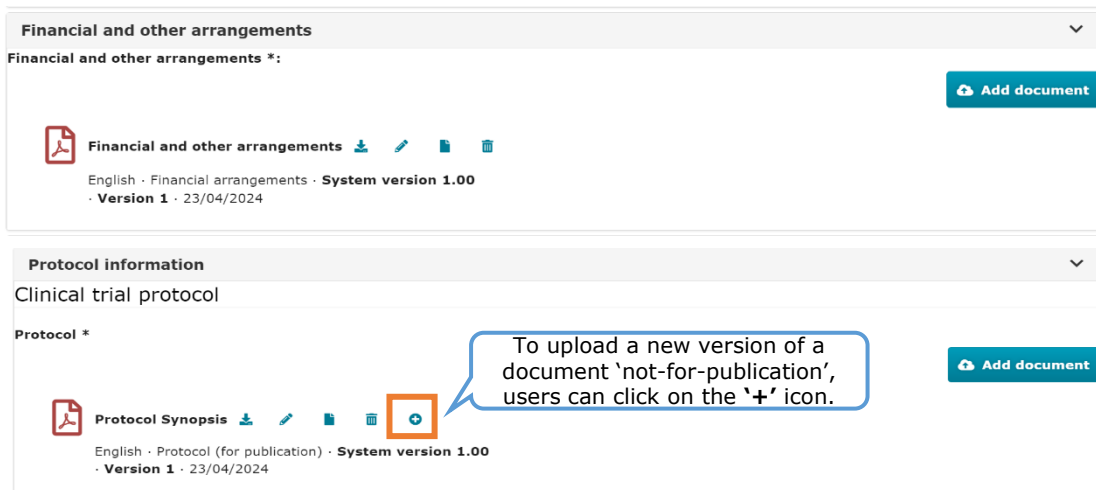
Additional MSC CTA

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 a web interface for a clinical trial application. At the top right, there is a 'Download' button and a '+ CREATE -' button. Below this, a dropdown menu is open, showing four options: 'Single trial substantial modification', 'Multi trial substantial modification', 'Non-substantial modification', and 'Additional MSC'. The main content area shows 'CT for training test' with a status of 'Authorised' and a reference number '2021-501399-27-00'. Below the title, there are tabs for '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 a pop-up window titled 'Substantial modification scope'. It has a close button (X) in the top right corner. Below the title, there is a label 'Select modification scope' and a dropdown menu with the text 'Please select' and a downward arrow. Below the dropdown, there is a checked checkbox followed by the text 'Do you wish to update the current information on the dossier?'. At the bottom of the window, 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 a web interface for a substantial modification application. At the top, there is a header for 'CT for training test' with reference number '2021-501399-27-00' and 'Substantial modification ID: SM-1'. Below this, there are buttons for 'Draft', 'New version draft SM-1', and 'View submitted application'. Below the header, there are buttons for 'Check', 'Save', 'Cancel', and 'Submit'. On the left side, there is a navigation menu with links for 'Form', 'MSCs', 'Part I', 'Part II', 'Evaluation', and 'Timetable'. The main content area is divided into sections: 'Form details', 'Substantial modification details' (with a padlock icon), 'Cover letter *' (with 'No document available'), and 'Modification description *' (with 'No document available'). The 'Modification description *' field is highlighted with a red 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 search bar and a right-pointing arrow. Below this, there 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 buttons: 'Draft' and 'New version draft SM-1'. To the right, there is a link 'View submitted application'. Below this, there is a row of four buttons: 'Check' (with a checkmark icon), 'Save' (with a floppy disk icon), 'Cancel' (with a close icon), and 'Submit' (with a cloud upload icon).

- 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 the checkbox is the text: 'Confirm submission of the application 2021-501548-16-00, Substantial modification Part I ?'. This is followed by a paragraph of text: '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, there are two buttons: 'Cancel' and 'Confirm' (with a checkmark icon).

- 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' with the value 'Test organisation' and 'Address line 1*' with the value 'DunKarm Street'. The right column has 'Address' with the value 'DunKarm Street, 2 Floor, Orange Point Building' and 'Address line 2' with the value '2 Floor'. A blue square icon with a white plus sign 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'.

Download + CREATE

CT for training test

Authorised 2021-501399-27-00 Proposed RMS: Austria

Summary Full Trial Informat Notifications Trial results Corrective measurAd Hoc as

Single trial substantial modification
Multi trial substantial modification
Non-substantial modification
Additional MSC

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

Non-substantial modification scope X

Select modification scope

Please select

X Cancel Create

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.

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

Form
MSCs
Part I
Part II

Form details

Non-substantial modification details

Non-substantial modification description *

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.

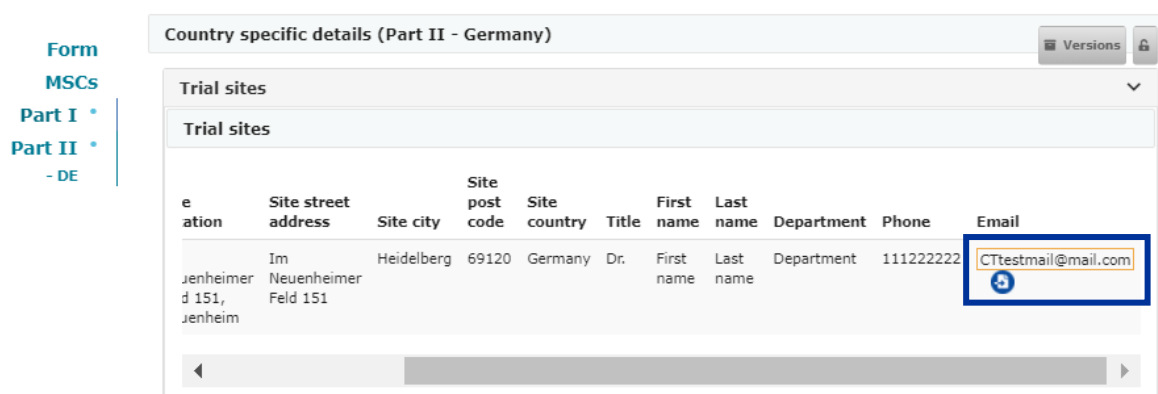
I agree

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.



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



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

European Medicines Agency

Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Telephone +31 (0)88 781 6000

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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