



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FAQs

How to create, submit and withdraw
a CTA

CTIS Training Programme – Module 10

Version 1.4 – November 2023

What you will find

- Answers to questions regarding the creation and submission of Initial CTAs.
- Answers to questions regarding the creation and submission of Substantial modifications CTAs.
- Answers to questions regarding the creation and submission of Additional MSC CTAs.
- Answers to questions regarding non-substantial modifications.

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Record of updated versions

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FAQs



In this document, we list common questions regarding *Module 10: Create, submit and withdraw a CTA*. They are categorised into: Questions of a general nature regarding Clinical Trial Applications (CTA); questions on the Initial application; questions on the Additional Member State Concerned application; questions on the Substantial Modification (SM) application; questions on Non-Substantial Modifications (Non-SMs), and questions regarding the withdrawal of any clinical trial application type. The specific learning objectives of this module are:

1. Understand the different types of clinical trial applications and Non-substantial modifications.
2. Understand the process of creating, submitting, and cancelling a clinical trial application.
3. Understand the process of withdrawing a clinical trial application.
4. Understand the roles and permissions involved in the management of a clinical trial application.

We encourage you to read these questions and answers carefully. If you have any questions which are not covered in this document, please contact us at CT.Training@ema.europa.eu so that we can update this document accordingly. This document will be progressively enriched with the input of the experts involved in the validation of the training material, the Master Trainers disseminating the materials, and the end-users.

1. General information

1.1. What is a 'clinical trial' in the context of the Clinical Trial Regulation (EU) No 536/2014¹?

According to Article 2(2) (2) of the CT Regulation², a clinical trial (CT) is a clinical study which fulfils any of the following conditions:

- The assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within the normal clinical practice of the Member State Concerned (MSC).
- The decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical trial.
- Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

1.2. What is a 'Clinical trial application'?

A Clinical trial application (CTA) is a request made by the sponsors to the Member States Concerned (MSCs) for the authorisation to perform an action related to CTs conducted in the EU. These actions can include the authorisation to conduct a new CT, to extend an existing CT to another MSC territory, or to perform a substantial modification (SM) to a previously authorised CTA.

1.3. What types of CTAs are available in CTIS?

The CT Regulation provides for three different types of application dossiers: Initial Application (Article 5 of the CT Regulation for full initial part I and part II, and Article 11 for partial submission including part I only³); SM (Chapter III of the CT Regulation⁴), and Additional MSC (Article 14 of the CT Regulation⁵).

1.4. How can users create and submit a CTA?

The trial life cycle starts with the creation of an initial application for a clinical trial. To do so,

¹ Referred to as 'CT Regulation' hereafter.

² Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

³ Idem

⁴ Idem

⁵ Idem

users need to click on the '+ New trial' button in the Clinical Trials tab. The system will trigger a pop-up form that needs to be populated by the user regarding the full title of the CT and the information of the sponsor organisation. Once this information has been filled out, users need to click on the 'create' button. With this procedure, an Initial CTA is created, with a unique EU CT number associated with it. Users can create and submit other types of CTAs only after the authorisation of the initial application. (*For more information, refer to questions 2.3, 3.3 and 4.3*).

The different CTAs linked to the same CT will be displayed in the 'Application and Non-SM' sub-section at the bottom of the CT summary page.

1.5. Can users submit information and documents in the CTAs in more than one language?

Yes. The information provided for a CTA can be submitted in one or more languages. Structure data and documents can be provided in all the official languages of the EU and as per MSCs requirements, as provided for in Article 26 of the CT Regulation⁶.

1.6. How can users edit a CTA?

Users can edit the application while it is in draft status (i.e. until it has not been submitted). To do so, users can access the application, from the CT summary page and select the Application ID under the column 'ID' of the 'Application and Non-SM' section. In order to populate and upload the relevant information and documentation of an application, users need to click on the padlock button of each sub-section. Afterwards, they can either save the application by clicking on the 'save' button in the upper-right corner of the page or, if all the required fields are completed, submit the application. After submitting the CTA, if users want to update the dossier, they need to create an SM CTA or a non-SM, as applicable (*refer to sections 4 and 5 for more information*).

1.7. How can users cancel a CTA?

Users can cancel any application while it is in draft status. To do so, users need to open the application, from the CT summary page, and click on the 'cancel' button on the upper-right corner of the page. If the sponsor cancels the application, all populated data and documents will be deleted from CTIS.

If an application is drafted but then cancelled, the EU number cannot be reused.

⁶ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

Therefore, the sponsor will need to issue a new number and change it in all the corresponding CT documentation where the CT number is needed.

1.8. How can users copy a CTA?

Once a CTA has been authorised, users can copy it to create a similar CTA. To do so, users need to open the authorised application, from the CT summary page and click on the 'copy' button on the upper-right corner of the page. A pop-up will request the user to specify which sections of the application he/she wishes to copy - Part I (mandatory), or Part I and Part II, as well as the MSC in case there is more than one. The new CTA will have a new and unique EU CT number, will be in draft and users will be able to edit it before submitting it. The data and documents of the last submitted version of the original application will be copied and not those of previous versions. If multiple RFIs responses with CTA changes had been submitted during assessment of the original application, the copied CTA draft will contain the details and documents of the last submitted application version.

1.9. What information can users find on the CTA page?

The CTA page is structured in six sections, which provide all the relevant information regarding a CTA submitted by a sponsor:

Form: Displays information on the application form details including cover letter, proof of payment if so required by the MSC, and the anticipated publication dates for data and documents, including deferrals, if applicable.

MSC: Displays information such as the MSCs of the application, the proposed RMS, the countries outside of the EU/EEA where the trial is intended to be conducted, an estimated total population for the trial, etc.

Part I: Displays trial-specific information such as protocol information, trial design, inclusion and exclusion criteria, conditions to be treated, the therapeutic area, sponsor and product details, etc.

Part II: Displays documents of the regulatory nature of the CTA for each of the MSC, including, for example, the template for the informed consent, the subject recruitment arrangements, compliance with national data protection requirements, etc.

Evaluation: Displays the different phases of the application evaluation to be performed by the MSC. By accessing this section, Member State users can perform their evaluation tasks, for example, by documenting considerations or uploading draft assessment reports.

Timetable: Displays a visual overview of the evaluation status and progress of the CTA. The information is displayed only after the submission of the CTA, not while the initial application is in draft.

It should be noted that depending on the application type, not all the six sections above mentioned will be completed by the sponsors. *More details on the different types of applications are provided in sections 2, 3, and 4.*

1.10. Is it mandatory to upload to CTIS all documents required by the Clinical Trial Directive (CTD)?

Users should comply with the Clinical Trial Regulation 536/2014⁷. CTIS offers several placeholders to enable the user to upload the required documentation.

2. Initial CTA

2.1. What is an Initial CTA according to the CT Regulation?

An Initial CTA provides comprehensive information about the trial to be conducted and the investigational medicinal product(s) to be used, enabling the authorities of the MSC to evaluate the acceptability of conducting the trial. The elements to be included in the application dossier for an initial application are defined in Annex I of the CT Regulation⁸.

2.2. What types of Initial CTAs can be submitted by sponsor users?

Depending on the number of Member States concerned by the application, Initial CTAs can be divided into:

- **Mononational:** CTAs which concern only one Member State. These applications aim at receiving the authorisation to conduct a CT in the territory of a Member State.
- **Multinational:** CTAs which concern more than one Member State. These applications aim at receiving the authorisation to conduct a CT in the territories of more than one Member State.

Additionally, Initial CTAs can be divided into those including information for Part I and Part II (full submission), and those that only include information relevant to Part I, or for Part I and Part II but only some of the MSC (partial submission). *Refer to question 2.32 for more information.*

2.3. How can users create and edit an Initial CTA?

Initial CTAs are created via the Clinical Trials tab by clicking on the '+ New trial' button. The system will trigger a pop-up form that needs to be populated by the user regarding the full

⁷ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158, 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

⁸ Idem

title of the CT and the information of the organisation that will be the sponsor of the trial. Once the information is populated and users click on the 'create' button, they are redirected to the sections of the CTA where they can start completing the required information. By default, the section 'Part I' is displayed.

If users wish to continue filling out the required information at another moment, they need to click on the 'save' button, which allows saving a draft application without submitting it. For editing the application at a later stage, users must select the Application ID under the column 'ID' of the 'Application and Non-SM' section. In the case of Initial CTAs, the ID will be 'IN'.

To upload documents in CTIS, users are advised to consult the 'Best Practice Guide for Sponsors of document naming in CTIS', available in the 'Key document list' section on the Clinical Trials Coordination Group page⁹.

2.4. How can users edit, update or add additional documents?

After uploading a document, users can edit the information ('Edit' button), submit additional documents ('Add document' button), or a new version of the same document ('Update' button).

- **Edit button:** Users will be able to include comments and change the versions of the documents by clicking on the edit button.
- **Update button:** Users will be able to change the document they uploaded by clicking on the update button, once the application and the documents are submitted. It is not allowed to update a new document to replace the original one when the CTA is still in draft. To update a document in a draft CTA, users need first to remove it and then add a new document.
- **Add document:** After uploading a first document users can upload additional documents, that will be also published. The documents will appear listed below the first one uploaded.



⁹Heads of Medicines Agencies: Clinical Trials Coordination Group. *Best Practice Guide for Sponsors of document naming in CTIS*. 22 of August 2022. Available at: <https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html>

2.5. How can users upload a document not for publication?

In most cases, documents uploaded in CTIS are by default for publication (e.g. protocol, cover letter, etc.), therefore users should not include Commercial confidential information (CCI) and personal data. This will be indicated in the document upload pop-up window with the legend 'The above documents will be published'. For certain CTA sections, documents are never published (e.g. IMPD - Quality) and it is indicated in the pop-up window with the legend 'This document will not be publicly accessible'.

In cases when documents are uploaded for publication, and users need to upload a document with the redacted data from the original (personal data or CCI), they need to submit a version 'not for publication'. This enables sponsors to provide all the information to the Member States, avoiding the publication of sensitive information.

To do so, users can click on the 'Add' button (+) that appears in the document section after uploading the first version of the document intended for publication (only available in CTIS sections where the documents to be uploaded are published).

Cover letter *



This button is a cross-system functionality available in some sections of the CTA, where applicable, in the form of an RFI response and in other sections related to the life-cycle of a CT. It is also available for the Clinical Study Report of MAH users.

2.6. What does an Initial CTA dossier include?

As per Annex I of the CT Regulation¹⁰ (letters A to R), the application dossier includes the following information:

- Introduction and General principles
- Cover letter
- Compliance with Regulation (EU) 2016/679
- EU Application form
- Protocol
- Investigator's brochure

¹⁰ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L58. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

- Documentation relating to compliance with Good manufacturing practice (GMP) for the investigational medicinal product
- Investigational medicinal product dossier (IMPD)
- Auxiliary medicinal product dossier
- Scientific advice and Paediatric Investigation Plan (PIP)
- Content of the labelling of the Investigational Medicinal Products (IMP)
- Requirements for gathering the informed consent of the subjects (information per MSC);
- Arrangements for rewarding or compensating subjects and investigators (information per MSC);
- Arrangements for the recruitment of subjects (information per MSC);
- Suitability of individuals involved (information per MSC);
- Suitability of clinical trial sites (information per MSC);
- Proof of insurance cover or indemnification (information per MSC);
- Financial and other arrangements (information per MSC);
- Proof of payment of fee (information per MSC);
- Proof that data will be processed in compliance with union law on data protection.

2.7. Which sections of a CTA page must users complete for an Initial CTA?

The sponsor will have to populate the following sections as part of an Initial CTA dossier:

- Form
- MSC
- Part I
- Part II

It should be noted that at the time of submission on an Initial CTA, the sponsor user can choose to submit a full dossier according to Article 5 (including Part I and Part II), or progress with a partial submission with Part I only or Part I and Part II for some of the MSC under Article 11 of the CT Regulation.

2.8. What information can users include in the Form section?

The information covered in the Form section of a CTA includes:

- Cover letter;

- Compliance with Regulation (EU) 2016/679;
- Proof of payment, if so required by each MSC;
- The anticipated publication dates for data and documents, including deferrals settings, if applicable.

2.9. Do the cover letter and financial arrangements need to be ink-signed?

The signature requirement is an aspect linked to the Member State law and therefore each user can request the CT Member State nation contact point for more information.

2.10. What is a 'deferral'?

In line with the transparency principle enshrined in the CT Regulation, the data of CTs will be published in an EU via the EU database, accessible to the general public (CTIS public website), unless an exception of Article 81(4) applies¹¹. The deferral mechanism enables the sponsors to delay the publication of certain CT data in the interest of protecting commercially confidential information. The timelines for the delay of the publication depend on the trial category selected by the sponsor¹². *Refer to question 2.11 for more information.*

2.11. How can users request a deferral?

To request a deferral, users need to complete the 'Deferral publication dates' section in the Initial CTA, and it will apply to all subsequent applications and over trial information. First, they need to select the trial category, include the justification and select the publication date, which depends on the data/document type of each trial category. The available options are category 1 (FIH, PK/PD, BE/BA, Bio similarity), category 2 (Phase II and III) and category 3 (Phase IV). Afterwards, users can select the publication date, which depends on the data/document type of each trial category.

For the deferral requested for some data/document types for categories 1 and 2, users can select a specific period of time expressed in months and years by using the radio button option and completing the information, to specify the publication date for the publication deferral request.

If a deferral is requested for the below data/document types for categories 1 and 3, users need to provide an additional justification:

¹¹ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

¹² Appendix on disclosure rules to the 'Functional specifications for the EU portal and EU database to be audited, European Medicines Agency'. Page 14. Section 4.3.4. Timing of publication of data and documents.

- Category 1: Main characteristics, Notifications, Clinical trial results summary for an intermediate data analysis and Clinical trial results summary and layperson summary.
- Category 3: Protocol and Summary of Scientific Advice.

If the trial is to be listed in a Paediatric Investigation Plan (PIP) or includes paediatric subjects, the Main Characteristics, Notifications and Summary of Results associated with this trial will be published at the date of decision on the trial. Users cannot request a deferral for those fields.

The deferral can be only modified during the evaluation of the CTA by responding to a validation RFI or assessment Part I RFI. Deferrals cannot be modified during the submission or evaluation of an Additional MSC CTA or Substantial modification.

If no deferral is requested by the sponsor, then the publication of CTs data and documents will occur earlier and at the first opportunity mostly at the time of decision for the authorisation or refusal, to start the CT in the EU.

It should be noted that in the case of a multinational application, the timing for publication of information in the public EU database when no deferrals are applied will occur as soon as the first Member State Concerned (MSC) has issued its decision.

2.12. For how long can the CTA data/documents be deferred?

Maximum timelines for the delay of the publication of such information are established depending on the trial category selected by the sponsor. The table below presents for how long each group of CTA data/document can be deferred for each category, if applicable.

Grouping	Category 1 (FIH, PK/PD, BE/BA, Bio similarity)	Category 2 (Phase II and III)	Category 3 (Phase IV)
Main Characteristics	• Publication of final summary of results	-	-
Notifications	• Publication of final summary of results	-	-
Subject information sheet	• Up to 7 years after the end of the trial in EU/EEA	• Up to 5 years after the end of the trial in EU/EEA	-
Protocol and Scientific Advice	• Up to 7 years after the end of the trial in EU/EEA	• Up to 5 years after the end of the trial in EU/EEA	• Publication of final summary of results
IMPD S&E sections and Investigator Brochure	• Up to 7 years after the end of the trial in EU/EEA	• Up to 5 years after the end of the trial in EU/EEA	• Publication of final summary of results
Responses to RFI	• Up to 7 years after the end of the trial in EU/EEA	• Up to 5 years after the end of the trial in EU/EEA	• Publication of final summary of results

Clinical trial results summary for an intermediate data analysis	<ul style="list-style-type: none"> Up to 30 months after the end of the trial in the EU/EEA 	-	-
Clinical trial results summary and layperson summary	<ul style="list-style-type: none"> Up to 30 months after the end of the trial in the EEA 	-	-

In case a trial has more than one phase, the maximum publication deferral will be the one indicated in the highest associated category.

2.13. What is the deferral of publication for unauthorised trials?

If a trial is refused authorisation by all MSCs, the date of decision on the trial will also be taken for the purposes of application of these rules as the date of the end of the trial. The end of trial date will be deemed as the date on which the last MSC submits its decision. This is only for the purpose of calculating publication dates when the sponsor has selected to defer the publication. Options for deferral of publication of data or documents appropriate to the trial category, selected by the sponsor, will apply.

If a multinational CTA has been authorised by at least one MSC and refused in one or more MSCs, the end of trial date will be deemed as the last end of trial date among MSCs that authorised the trial.

2.14. Can MSCs request a deferral for the CTA evaluation data/documents?

In case a sponsor has applied for a deferral, the RMS/MSD can also defer the publication of the assessment reports and conditions and/or the data/documents of the RFIs sent to the sponsor within the period of time established by the sponsor's deferral. MSCs users can request such deferral by completing the dedicated section in the 'Decision' task.

Sponsor users can view the requested deferrals by the MSCs. To do so, they can access the CTA in the summary sub-tab of the clinical trial page. Afterwards, they can click on the evaluation section and scroll down to the 'Assessment overview' tile in the 'Decision' section. There, they can click on the 'plus icon' of each MSC to view the details of the deferrals requested by that MSC, if applicable.

- Part I *
- Part II
- Evaluation**
- Timetable

RF-1 0	>
Conclusion	>

Decision
Part I Disagreements >

ASSESSMENT OVERVIEW

MSCs	Validation	Assessment Part I	Assessment Part II	Decision	+All
GERMANY RMS	Valid (19/09/2022)	Acceptable (19/09/2022)	Acceptable (19/09/2022)	Authorised (19/09/2022)	+

- Part I *
- Part II
- Evaluation
- Timetable**

ASSESSMENT OVERVIEW

MSCs	Validation	Assessment Part I	Assessment Part II	Decision	-All
GERMANY RMS	Valid (19/09/2022)	Acceptable (19/09/2022)	Acceptable (19/09/2022)	Authorised (19/09/2022)	-

Decision Authorised (19/09/2022)

Deferrals

Publication of RFIs

Data/document type	Publication timepoint
Responses to RFIs	2 years and 1 month after the end of trial (set by sponsor)
RFIs sent to the sponsor	1 year and 1 month after the end of trial

Publication of assessment reports and conditions

Data/document type	Publication timepoint
Protocol	1 year and 0 month after the end of trial (set by sponsor)
IMPd S&E and Investigator Brochure	4 years and 3 months after the end of trial (set by sponsor)
Assessment reports and conditions	3 years and 3 months after the end of trial

2.15. What information can users include in MSCs section?

The information covered in the MSC section of a CTA includes:

- Member States concerned (where the CT is intended to be conducted);
- Proposed RMS (in case of mononational trials the proposed RMS will be selected by default);

- An estimated total number of subjects for the trial in each MSC;
- The MSC section also conveys a 'read-only' display of the countries outside the EU/EEA where the trial is intended to be conducted and an estimated number of subjects. This information is populated in Part I and automatically copied into the MSC section.

2.16. What information can users include in Part I section?

The information covered in the Part I section of a CTA includes structure data and documents covering three main sub-sections: trial details/sponsor details/product details.

Trial details include:

- Trial information, including objectives, endpoints, inclusion and exclusion criteria;
- Protocol information, including protocol synopsis, data safety monitor board chart, and trial design details;
- Scientific advice and Paediatric Investigation Plan (PIP);
- Associated CTs (if applicable). For more information on Associated CTs refer to question 2.17;
- Countries outside the EEA where the CT is planned to be conducted and number of subjects involved (if applicable).

Sponsor details include:

- Contact point in the Union;
- Scientific and public contact points;
- Legal representative in the Union – this is only required if the sponsor of the trial is not based in the EU.

Product details include:

- Details for authorised or development products extracted from XEVMPD;
- Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC);
- Documentation about good manufacturing practice (GMP) for the investigational medicinal product;
- Investigational medicinal product dossier (IMPD) divided into Quality (IMPD-Q) and Safety and Efficacy (IMPD S and E);
- Auxiliary medicinal product dossier;
- Content of the labelling of the investigational medicinal products.

It should be noted that not all the fields mentioned above are mandatory to be completed prior to the submission of an initial application. Mandatory fields and documents to be completed in CTIS can be easily identified as they are marked with an asterisk (*).

2.17. What is an Associated Clinical Trial?

An Associated Clinical trial is a functionality that has been implemented in CTIS in order to allow sponsors to refer to data generated in another clinical trial. Sponsors can refer to a trial authorised under the regime of CTD or CTR.

To do so, users can access the 'Associated clinical trials' tile under the 'Trial details' subsection of Part I. Then, users can click on the '+ Associated clinical trial' button and retrieve the trial number (EU CT or EUDRA CT) using the search functionality. Once the trial has been associated, in case the associated trial is owned by a different sponsor, an agreement from the sponsor owner needs to be provided. To upload this document in the dedicated placeholder, users can click on the '+' icon and then on the 'Add document' button that appears below. *For more information, please refer to Article 25(4) and (5) of Regulation (EU) No 536/2014¹³.*

EU CT number	Full title	Sponsor	Actions
2030-532207-24-00	Clinical trial - test - Back up	Test Organisation Spain	+ All

2.18. Is the information in the contact points on sponsors' subsection published?

The sponsor's contact point for union section is not published in the CTIS public domain. Therefore, personal contact details can be populated. However, the functional contact details for 'Legal representative', 'Scientific contact point', 'Public contact point' and 'Third party' are made public, and only not necessarily personal contact details can be populated.

2.19. How can users add a Third-party contact?

If needed, users can include a Third-party contact in the trial by clicking on the '+ Add contacts' and 'Third party' buttons under the 'Sponsors' tile. Then, they can search for the corresponding organisation and click on the 'Add third party' button.

¹³ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

Test Organisation Spain Sponsor

Name	Status
Test Organisation Spain	Commercial
Address	Town/City
Santiago Calle 10	Madrid
Post code	Country
28001	Spain
Phone	Email
0200110000	info@testorganisation-spain.com

Scientific/public contact point*

+ Add contacts -

- Legal representative
- Scientific contact point
- Public contact point
- Third party

Select third party ×

Search organisation

Name	starts with	ID	starts with	City	starts with	Country	All
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

+ New organisation
Clear
Search organisation

ID	Name	Address	City	postCode	country	phone	email	actions
Add third party								

Once the Third party is included, users can click on the pencil icon to modify the information regarding that third party (assigned tasks and contact details).

Third parties									
ID	Name	Country	Address	Town/City	Post code	Phone	Email	Duties	Actions
21352	Test Organisation Spain	Spain	Santiago Calle 10	Madrid	28001				✎ 🗑️

2.20. What is a 'medicinal product'?

Article 1(2) of the Medicinal Products Directive¹⁴ defines a 'medicinal product' as follows:

- (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings.
- (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

The CT Regulation foresees two main types of medicinal products: Investigational medicinal products (Article 2(5)), which can be tested or used as a reference in a CT, and auxiliary products (Article 2(8)), which are used for the needs of a CT as described in the protocol.

¹⁴ Directive (EU) No 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the Community code relating to medicinal products for human use, EU Official Journal L311. 28 of November of 2001. Available at: https://health.ec.europa.eu/system/files/2016-11/dir_2001_83_cons_2012_en_0.pdf

CTIS enables users to add such medicinal products in a CTA as a test, comparator, auxiliary, or as a placebo (refer to question 2.11).

2.21. What roles can medicinal products have in a clinical trial in CTIS?

CTIS allows adding several roles for a medicinal product in an Initial CTA:

- **Test:** Investigational Medicinal Product (IMP) which is being tested. To be able to progress with the application submission, users need to add at least one test role.
- **Comparator:** Investigational Medicinal Product (IMP) which is used as a reference. Product used as a reference in a CT to be compared to the substance being tested¹⁵.
- **Auxiliary:** Auxiliary Medicinal product used for the needs of a CT as described in the protocol, but not as an IMP, e.g. background treatments, challenging agents, rescue medication, or to assess the endpoints¹⁶.
- **Placebo:** Product with no therapeutic effect, used as a control when testing new drugs.

2.22. What types of products can be added as a test role in CTIS?

Users can add to the Initial CTA an authorised product, an active substance, and an anatomical therapeutic chemical (ATC); or an unauthorised product. They can also add a product that has not yet received marketing authorisation, i.e. development product. Each product added to a CTA needs to be extracted from XEVMPD, the extended EudraVigilance medicinal product dictionary. Users can apply filters (i.e. 'starts with', 'equal to' and 'contains') to search for information easily. For example, 'Contains' filter is recommended in case users don't know the exact data.

Once selected from XEVMPD, each product will come with a set of information retrieved and copied from XEVMPD. The list of fields is displayed below:

Nature	Type of product	Fields
Authorised	Product	<ul style="list-style-type: none">• Medicinal product details• Product characteristics• Dosage and administration details• Information about the modification of the

¹⁵ European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6, November 2020. Page 23, question 1.13. Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

¹⁶ Idem. Page 23, question 1.15.

		<p>Medicinal product</p> <ul style="list-style-type: none"> • Product classification • Product authorisation details • Orphan Designation • Active substance • Advanced Therapy Medicinal product • Device associated with the medicinal product
	ATC	<ul style="list-style-type: none"> • ATC code description • Product characteristics • Dosage and administration details • Information about the modification of the Medicinal product • Product classification • Orphan designation • Advanced therapy medicinal product • Device associated with the medicinal product
	Substance	<ul style="list-style-type: none"> • Active substance description • Product characteristics • Dosage and administration details • Information about the modification of the medicinal product • Product classification • Orphan designation • Active substance • Advance Therapy Medicinal product • Device associated with the medicinal product
Unauthorised	Product	<ul style="list-style-type: none"> • Medicinal product details • Product characteristics • Dosage and administration details • Product classification • Orphan Designation • Active substance • Advanced Therapy Medicinal product

		• Device associated with medicinal products
--	--	---

Regarding the documents for the product, the following sections are common for the test role and are available once the role has been added:

- Investigator's Brochure for the Medicinal Products or SmPC;
- Compliance with (GMP) for the Medicinal Product;
- IMPD Quality;
- IMPD – Safety and Efficacy.

2.23. Can users add more than one IMP per test role in the CTA?

Yes, users can add several IMPs under the 'test' section in CTA. It may be that several products share common documentation (*refer to question 2.22 for more information*).

2.24. Is it mandatory to include the IMPD documents?

If users have already uploaded the IMPD-related documents (IMPD Quality or IMPD Safety and Efficacy) to other clinical trials, they might not need to upload any documents again. In that case, they can include an indicative text in the 'Justification for no IMPD upload' field (e.g. the exact IMPD-related documents have been already submitted via a different CTA).

If they upload one document to any of the document placeholders, the free text field disappears, and users need to upload all the mandatory documents to be able to submit their application.

IMPD Quality	▼
IMPD - Safety and Efficacy	▼
IMPD - Safety and Efficacy * :	
Simplified IMPD - Safety and Efficacy * :	
Justification for no IMPD upload *	

2.25. How can users search for a product?

Users can retrieve information on medicinal products from the EudraVigilance medicinal product dictionary (xEVMPD). Users can access this information using available search fields, which are different depending on the type of product.

Authorised:

- **Product:** EU Medicinal Product number, Pharmaceutical form, Marketing authorisation number, Strength, Name of product, Active substance name, EU substance number, and/or ATC code.
- **ATC:** ATC code, Pharmaceutical form, Strength.
- **Substance:** Name, EU Substance Number, Pharmaceutical form, Strength.

Unauthorised:

- **Product:** EU Medicinal Product number and EU substance number.

For more information, refer to [Module 02: Overview of CTIS workspaces and common system functionalities](#).

2.26. Can users indicate that a product is applicable only to certain MSCs?

Yes. By default, the product is applicable to all MSCs. However, sponsors can choose to exclude a product from an MSC by clicking the 'Exclude MSC' button and selecting the MSC in a drop-down list of the MSCs involved in the trial. This might be the case in case of concurrent medication for underlying disease treatment.

2.27. How can users link the placebo with other investigational medicinal products?

Users are able to link a placebo to other products with the role 'Test/Comparator' by clicking on the button 'Link products' displayed in the section bearing the same name.

2.28. How can users populate the dose box?

Under the 'Product' subsection of Part I, users can populate the dosage and administration details. Users can include a dot '.' to separate the decimals. It is possible to have two decimals behind the dot.

2.29. How are Advanced Therapy Medicinal Products populated in clinical trials?

According to the European Medicines Agency website¹⁷, Advanced Therapy Medicinal Products (ATMPs) are medicines for human use that are based on genes, tissues or cells. They offer ground-breaking new opportunities for the treatment of disease and injury.

Users need to populate the products of their trials in CTIS, retrieving data from xEVMPD¹⁸. The information of whether a medicinal product is classified as ATMP is not captured in xEVMPD, that attribute is captured locally in CTIS. If the selected products are considered ATMP, that information needs to be populated in the tile 'Advanced Therapy Medicinal Product'. Under each selected product, users can click on the row that includes the information of the product to view various tiles, among them, the aforementioned 'Advanced Therapy Medicinal Product'.

The screenshot shows a web interface for managing medicinal products. At the top, there's a header 'Products' with a search bar and sorting options. Below that, a table lists products. The first row is highlighted, and a details panel is expanded for it. The details panel includes various tabs, and the 'Advanced Therapy Medicinal Product' tab is selected and highlighted with a blue border.

EU MP number	Marketing authorisation number	Product authorisation	Product name	Pharmaceutical form	Strength	Sponsors product code	Active substance name	EU substance number	ATC Name	ATC Code	ATC Level	Sponsors substance code	Active substance other descriptive name	Type	Actions
PRD1160996	66.330	Authorised	Ibuprofeno dermogen 400 mg suspension oral	Oral suspension	Ibuprofen 400mg	-	Ibuprofen	SUB08098MIG	IBUPROFEN	M01AE01	5	-	-	Product	

Details for Product with EU MP number: PRD1160996

- Medicinal product details
- Product characteristics
- Dosage and administration details
- Information about the modification of the Medicinal Product
- Product Classification
- Product authorisation details
- Orphan Designation
- Active substance
- Advanced Therapy Medicinal Product**
- Device associated with medicinal product

By expanding this tile, users can click on the 'Add Advanced Therapy' button. In the pop-up window, users select an option from the 'Advanced therapy classification' drop-down menu, and populate the Committee for Advanced Therapies (CAT) Reference number¹⁹, if applicable.

¹⁷ European Medicines Agency - Advanced therapy medicinal products: Overview. Available at: <https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview>

¹⁸ European Medicines Agency - Extended EudraVigilance medicinal product dictionary (XEVPD) training. Available at: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/extended-eudravigilance-medicinal-product-dictionary-xevmpd-training>

¹⁹ European Medicines Agency - Committee for Advanced Therapies. Available at: <https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview#committee-for-advanced-therapies-section>

Advanced Therapy Medicinal Product



Advanced therapy classification

Dropdown menu with options: Somatic Cell Therapy, Tissue Engineered Therapy, Gene Therapy

CAT reference number

Text input field for CAT reference number



Cancel

Save

Based on the selection of the type of therapy, relevant fields might be expanded below, that will allow users to record additional information regarding ATMP. The selection of the first fields might affect the following fields and under specific circumstances, some of them might be mandatory. Mandatory fields will be indicated with an asterisk. Your selection of the first fields affects the following fields and they might be mandatory. The available fields for each Advanced therapy classification are listed below:

- **Somatic Cell Therapy:** Somatic cell origin (Autologous; Allogenic; Xenogenic); Somatic cell type (Stem; Differentiated; Other).
- **Tissue Engineered Therapy:** Tissue engineered cell type (Stem; Differentiated; Other); Origin of the engineered tissue (Autologous; Allogenic; Xenogenic).
- **Gene Therapy:** Gene therapy type (In vivo; Ex vivo); Type of gene transfer product (Naked nucleic acid; Complex nucleic acid; Viral vector; Other); Genetically modified cell present (Yes; No).

After populating the relevant details, users can save the information, recorded on ATMP tile. After saving the ATMP details, users can edit the information, by using the 'pencil' icon or they can remove it and add new data, by using the respective button, 'Remove Advanced Therapy'. The 'eye' icon allows users to view all the details.

Advanced Therapy Medicinal Product		
Therapy type	CAT reference number	
<input checked="" type="checkbox"/>  Somatic Cell Therapy		

2.30. What information can users include in Part II section?

The information covered in the Part II section of a CTA includes structure data with details of the trial sites and a set of documents listed below for each of the MSCs if more than one:

Details of the trial sites, including name and address of the site and details of the principal investigator conducting the trial at the site (name of the person on the side of the sponsor organisation, department, department phone number and email address). The functional contact details for the investigator are made public.

Recruitment arrangements;

Subject information,

- Informed consent form and procedure;
- Suitability of the investigator;
- Suitability of the facilities;
- Proof of insurance cover or indemnification;
- Financial and other arrangements;
- National requirements for data protection, as applicable;
- Use of biological samples, as applicable. Users can find some of the templates for these documents on the following link: https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en

2.31. How can a medical device be populated in a CTA under CTR?

Medical devices are products or equipment intended for a medical purpose (more details on the [medical device homepage](#) on EMA website). The Q&A document on CTR hosted on the [EU Commission webpage on Clinical trials](#) indicates under which circumstances a medical device, in combination with a medicinal product, could have a role in a clinical trial and be assessed under CTR. If the medical device (in combination with the medicinal product, or ATC or substance) is indeed the object of the study under CTR, the details of the medical device could be populated in the details for the selected medicinal product that is combined with the device.

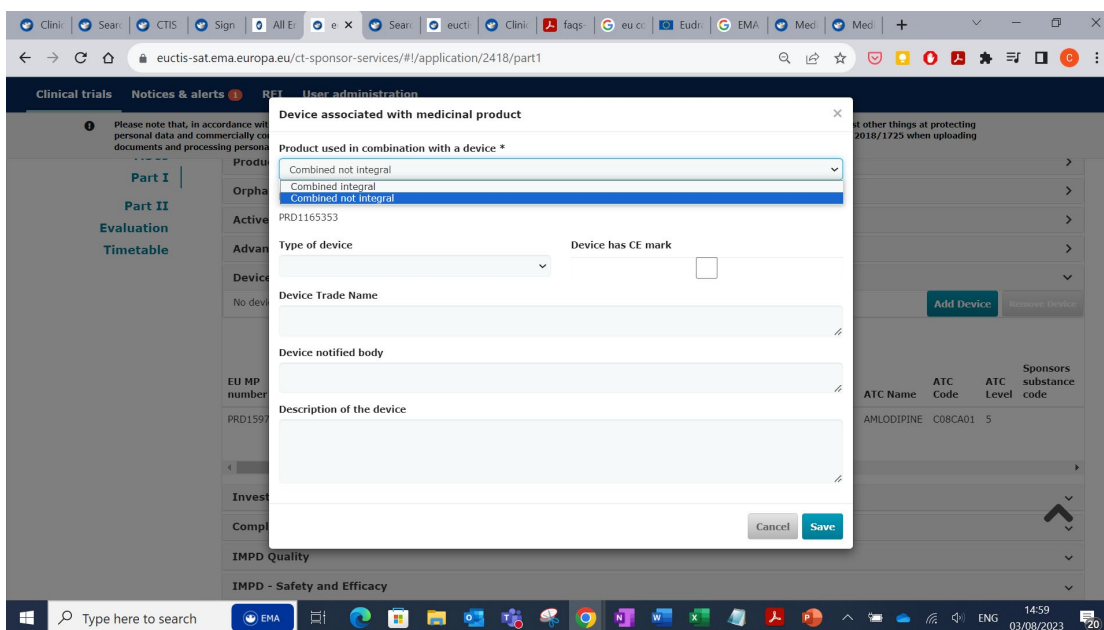
Users will need to click on the ribbon that hosts the overview details of the medicinal product (or ATC, or substance) that is combined with the medical device. Fields related to the selected product will be revealed below. Among them, in the end, users could see the tile 'Device associated with medicinal product'.

The screenshot shows a user interface for clinical trial management. On the left, there are navigation tabs for 'Part I' and 'Part II', with 'Part II' selected. Below the tabs are the words 'valuation' and 'Timetable'. The main content area displays a table of medicinal products. The first row is highlighted with a yellow border and contains the following data: PRD1165353, PL 28444/0085, Authorised, Paracetamol tablets 500mg, Tablet, Paracetamol - 500mg, Paracetamol, SUB09611MIG, PARACETAMOL, N02BE01, 5, -. A yellow arrow points to the 'Tablet' column. Below the table, there is a section titled 'Details for Product with EU MP number: PRD1165353'. This section contains a list of expandable fields: 'Medicinal product details', 'Product characteristics', 'Dosage and administration details', 'Information about the modification of the Medicinal Product', 'Product Classification', 'Product authorisation details', 'Orphan Designation', 'Active substance', and 'Advanced Therapy Medicinal Product'. The 'Device associated with medicinal product' field is highlighted with a yellow border and has a right-pointing arrow next to it. A vertical label 'Revealed fields' is positioned to the left of this list.

Users need to open the tile and use the 'Add device' button.



A form will pop up in which the user can populate the details of the device. The first field, 'Product used in combination with a device', is a drop-down list for which, users need to indicate whether the device is combined as an integral item with the product or not. Then, users can use the following fields to indicate the type of the device (drop-down list), whether there is a CE mark²⁰ on the device (tick-in box) and to add details regarding the trade name, the notified body, and the description of the device (all three are free text fields).



By saving all the populated details of the device, those will appear in the overview. Users may use the pencil icon to edit the details of the device or use the tick-in box on the left side of the overview and activate the 'Remove device' button in case they need to remove completely the entry.

²⁰ More details on the [EMA's homepage on Medical Devices](#)

2.32. Is it mandatory to upload a recruitment arrangement document?

Yes. According to the CT Regulation,²¹ the Recruitment arrangement document is mandatory.

2.33. Can Initial applications be limited to Part I only?

Yes. Under Article 11 of the CT Regulation²², the sponsor has the ability to initially submit part I only for assessment. They will need to wait for the RMS/MSD to submit the conclusion of the assessment to part I (reporting date) before they can submit part II. After the reporting date, the sponsor has two years to complete their application with part II to obtain a decision for the trial. Failure to do so within this period leads to the lapse of the application.

2.34. In cases of applications limited to Part I, how should a sponsor proceed to submit an application for Part II?

Following the submission of the conclusion on Part I (reporting date), but only during the subsequent 2 years, a sponsor may submit an application limited to the aspects covered by Part II of the dossier, declaring that they are not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the dossier which were already assessed by the MSD. The list of the documentation and information required to be provided in Part II is set out in CT Regulation Annex I (sections K to R)²³.

For more information, please consult the Clinical Trials Information System (CTIS) Bitesize talk session on Partial submitted trials: <https://www.ema.europa.eu/en/events/clinical-trials-information-system-ctis-bitesize-talk-part-i-only-applications-part-ii-requirements>

²¹ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

²² Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf.

²³ European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6, November 2020. Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

2.35. When can the sponsor of a partial submission application submit a substantial modification (SM) or an additional MSCs?

With the current CTIS functionalities and until further notice, sponsors cannot submit a substantial modification (SM) for a partial submitted initial application before Part II for all MSCs have been submitted and all MSCs have issued decisions.

In case only some MSCs have issued decisions for the initial application (those MSCs for which Part II had been already submitted by the sponsor), the sponsor cannot submit any SM. If the sponsor needs to submit an SM, it needs to wait until Part II is submitted for all MSCs and the remaining MSCs issue their decision. Alternatively, if the sponsor cannot wait for so long and needs to submit an SM as soon as possible, it can withdraw the trial for the remaining MSCs for which no decision has been issued. After withdrawal, the sponsor can submit its substantial modification. After a decision is issued on the SM, the sponsor can add additional MSC applications for the MSCs for which it withdrew the trial earlier.

Before Part I conclusion is submitted, the other Part IIs cannot be submitted

After Part I conclusion is submitted, sponsor can submit the remaining Part IIs

Name	Organization type	Country	Type	Status	Legal representative	Scientific contact point	Public contact point	Third parties
Test Organization Spain	Pharmaceutical company	Spain	Commercial	Active		First Last	First Last	0

Similarly, the sponsor cannot submit any additional MSC applications, as long as no decision has been issued for at least one MSC. In addition, if the evaluation of an SM that includes Part I is ongoing, no additional MSC application can be submitted.

For more information, please consult the Clinical Trials Information System (CTIS) Bitesize talk session on Partial submitted trials: <https://www.ema.europa.eu/en/events/clinical-trials-information-system-ctis-bitesize-talk-part-i-only-applications-part-ii-requirements>

2.36. What happens if the sponsor does not submit Part II?

In accordance with Article 11 of the CT Regulation²⁴, the sponsor can submit a partial application dossier, including only Part I for the start of the evaluation process. However, the sponsor needs to submit Part II before the MSC has issued a decision regarding the authorisation of the CT. If the sponsor does not submit Part II after two years from the submission of the conclusion on Part I (reporting date), the application will be expired.

2.37. After the receipt of the decision on the clinical trial, does the sponsor have the option to appeal against the decision?

Yes. The CT Regulation states that Member States shall provide an appeal procedure in respect of a refusal related to²⁵ :

- Article 8 (Decision on the clinical trial).
- Article 14 (Subsequent addition of a Member State concerned).
- Article 20 (Validation, assessment, and decision regarding a substantial modification of an aspect covered by Part II of the assessment report) and.
- Article 23 (Decision on the substantial modification of aspects covered by Parts I and II of the assessment report).

In this situation, the respective national laws apply to each MSC.

2.38. Does a sponsor have to await positive decisions from all Member States concerned before starting the trial in any of them?

No. The sponsor/investigator can start a clinical trial in an MSC if a positive decision has been issued by at least that MSC. The trial can only start in the MSC that has authorised the trial, even if the assessment is still ongoing in the rest of them.

3. Additional Member states concerned CTA

²⁴ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

²⁵ European Commission, 'Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT', Version 2.4, July 2020. Page 29 question 2.4 Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

3.1. What is the purpose of the Additional MSCs application?

An additional MSC CTA is an application for extending a previously authorised CT to the territory of another Member State(s).

3.2. When can users submit an Additional MSC Application?

The Additional MSC application can be submitted while there are no other applications under evaluation. There are a few exceptions to this rule. It is possible to submit and Add MSC CTA if there is an assessment for SM part II ongoing in other MSC, or if there are other Additional MSC applications under evaluation, the user can submit more Additional MSC applications to other MSC.

3.3. How can users create an Additional MSC CTA?

From the CT summary page, users can create an Additional MSC Application, by clicking on the 'create' button on the upper-right corner of the page. On the pop-up window that appears, the sponsor can select one or more MSCs that are to be included and the estimated number of subjects in each MSC. After that, the sponsor users can populate the newly added MSC details, including the compulsory fields marked with an asterisk, such as the trial site details and the mandatory documents.

3.4. What information can users include in the different sections of an Additional MSC CTA?

The information that can be included in the different sections of an Additional MSC CTA is the following:

Form

Cover letter.

Proof of payment.

MSCs

MSCs included in the CTA and the estimated total population for the CT in each MSC.

Part I

In Part I section, users can submit documentation related to the translation of specific Part I data and documents such as the ones listed below (if so required by the MSC).

- Fields such as the CT title, the medical condition, the CT objectives, the eligibility criteria, etc.
- Documents such as the protocol, data safety monitoring committee charter, investigator brochure, etc.

Part II

Documentation related to aspects that concern additional MSC to which the user wants to extend the conduct of the CT. These include the following:

- Trial sites information
- Recruitment arrangements;
- Subject information,
- Informed consent form and procedure;
- Suitability of the investigator;
- Suitability of the facilities;
- Proof of insurance cover or indemnification;
- Financial and other arrangements;
- Compliance with data protection national requirements;
- Compliance with the use of biological samples.

3.5. Is there a limitation to the number of MSCs in an Additional MSC Application?

No, there is no limitation. By clicking on the 'create' button on the upper-right side and 'additional MSC', a sponsor can select one or multiple MSCs to the add MSC application.

Once created, each application for each MSC will be treated separately, and sponsor users will have to provide MSC details for each MSC to be added. Once submitted, each application will be evaluated by the newly added MSC.

3.6. What happens if there are missing or incomplete documents in an Additional MSCs Application?

In case there are missing or incorrect documents, for instance, because of wrong information or language, a Request for Information (RFI) will be used by the MSCs to request the sponsor to submit the necessary documents and information and update the application accordingly²⁶.

Can an Additional MSCs CTA be submitted whilst another one is ongoing?

Yes, this is possible, as mentioned in 3.4. However, it is advisable to combine the requests to include additional MSCs and submit those at the same time²⁷.

²⁶ European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 2.6, November 2020. Page 33, question 2.10 Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

²⁷ European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 2.6, November 2020, page 34, available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

4. Substantial Modification CTA

4.1. What is a 'Substantial Modification'?

As per Article 2(13) of the CT Regulation, an SM is any change to any aspect of a CT, which is made after the notification of a decision on a previously submitted application and which is likely to either:

Have a substantial impact on the safety or rights of the subjects; or

On the reliability and robustness of the data generated in the CT.

If none of the above criteria is met, and the sponsor wants to make a change to the CT dossier that is not likely to have a substantial impact on the safety or rights of the subjects or the reliability and robustness of the data generated in the CT, but that is relevant for the supervision²⁸ then a non-SM can be filed. (*Refer to question 5.1 for more information*). In case of doubt about whether a change should be deemed as an SM or not, the sponsor shall consult the MSC²⁹.

4.2. What types of Substantial Modification CTAs can be submitted?

Chapter III of the CT Regulation refers to three types of SMs:

- SM of Part I only (Articles 17 to 19).
- SM of Part II only (Article 20).
- SM of both Part I and II (Articles 21 to 23).

Additionally, depending on the number of trials the sponsor wants to apply an SM for Part I, SMs can be further divided into:

- **Single-trial SM:** Where an SM concerns only one CT.
- **Multi-trial SM:** Where an SM concerns more than one CT of the same sponsor and with the same investigational medicinal product. In this case, users will need to indicate the EU CT number of the concerned trials. The changes made will apply to all trials provided.

The sponsor will be able to submit the (multi-trial) SMs including Part I only for those trials that have already been authorised (or authorised with conditions) and that do not have a parallel assessment or pending notification of a decision. Multi-trial SMs for Part II can be submitted in parallel to different MSCs.

²⁸ Article 81(9) Of Regulation (EU) No 536/2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

²⁹ European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6, November 2020. Page 37, question 3.4 Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

4.3. How can users create a Substantial Modification CTA?

From the CT summary page, users can create two types of SMs: single-trial SMs and multi-trial SMs (see question 4.2 above). When clicking on the 'create' button on the upper-right corner of the page, the two types of SM will appear in a drop-down list.

After selecting the type of SM, a pop-up window will appear in which the user must include the scope of the SM:

- **Part I only:** users are able to make changes to any section of the application, except Part II.
- **Part II only:** users can select the MSC for which they want to submit a substantial modification. Users can select only one MSC at a time.
- **Part I and Part II:** users can select multiple MSCs at the same time.

After creating the SM, the user will land on the 'Form' section of the CTA page in which the SM details must be included, including a cover letter and a description of the changes made to the dossier with the SM. In the case of a multi-trial SM, users must also populate the title 'Included trials' by selecting the 'Add trial' button and specifying the EU CT Number of the additional trials included in the same SM application.

4.4. What information can users include in the different sections of a Substantial Modification CTA?

The information that can be included in the different fields (i.e. structured data or documents) of the sections of an SM CTA is the following:

Form

- Users should provide details on the nature of the SM (reason and scope). Although those fields are not considered mandatory, they should be populated. Users must upload a new cover letter and a document explaining the substantial changes related to this CTA to be able to submit the CTA.

MSCs

- Users can only modify the expected number of subjects to be recruited on a CT. Users cannot include any additional MSC, as this is done via an Add MSC CTA.

Part I

- Trial-specific information that can be modified as needed via an SM CTA. For example: protocol information, CT design, inclusion and exclusion criteria, conditions to be treated, the therapeutic area, etc.

Part II

- Documents of the CTA of a regulatory nature can be modified as needed via an SM CTA. e.g. informed consent form, subject recruitment arrangements, trial sites, etc.

If users need to upload new versions of documents, they can submit a clean version of the updated document, as well as the original document with track changes, to facilitate the assessment of CTAs.

The documents with track changes (as well as other intermediate versions of documents) can be uploaded in document placeholders that are **NOT** for publication.

4.5. When can users submit a Substantial Modification?

SM can be submitted by the sponsor if no other application is under evaluation (be it an initial application, a request to add an MSC or a request for another SM on either or both of the Parts). In other words, the SM can be submitted and assessed only after the decision on the previously submitted application is issued or authorised by tacit approval.

There are only two exceptions to this:

When there is a parallel assessment of SMs for Part II in different MSCs, i.e. an application for an SM of Part II in an MSC can be submitted while the assessment of another SM for Part II is ongoing in another MSC.

An Additional MSC CTA is possible while there is an ongoing assessment of an SM for Part II in another MSC.

An SM CTA may be required in certain circumstances during the CT lifecycle, because of new information that becomes available on the medicinal product(s) used or on the trial, or for instance in the following cases:

- A Corrective measure applied by one or more MSCs to the trial.
- In order to request an extension of time, if the recruitment of subjects has not started within two years from the CT authorisation, to avoid an application lapse.
- To restart a CT that was halted in an MSC for reasons of subject safety/benefit-risk balance.

For more information about the CT lifecycle, refer to the [elearning of Module 05: How to manage a CT \(Notifications, Ad hoc Assessment, Corrective measures and Trial results\)](#).

4.6. How can users describe the changes they have made in a CTA section?

Users can include a description of the changes applied in the 'Section changes description' tile of the respective section. Once they have included their comments, an exclamation mark will appear in the modified sections.

4.7. When is a modification considered 'substantial'?

A non-exhaustive list of examples of modifications that should be regarded as substantial is provided in Annex III of the European Commission CT Regulation Questions & Answers document³⁰. Some examples from the non-exhaustive list that are typically considered to be 'substantial' are listed below:

Part I		
Protocol	IMPD and IB	Others
<ul style="list-style-type: none"> • A change in the definition of the end of the trial. • New toxicological or pharmacological data which is likely to impact on the risk/benefit assessment. • Changes in the number of scheduled subject trial visits. • Change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the CT. 	<ul style="list-style-type: none"> • Any change in the quality of the IMP. • Change in the overall risk and benefit assessment in the IMPD or IB. • New clinical data e.g. from previous CTs and human experience in the IMPD or IB which might have a significant impact on the risk/benefit ratio. • Changes to the reference safety information for the annual safety report and SUSAR reporting. 	<ul style="list-style-type: none"> • A change of sponsor, co-sponsor or the sponsor's legal representative. • The revocation or suspension of the IMP's marketing authorisation.
Part II		
<ul style="list-style-type: none"> • Addition of a site, change in facilities, change in site suitability or change of principal investigator. • Change of the insurance policy, e.g. a new insurance company, changes in insurance coverage, conditions and/or insured amounts. • Modifications in any documents for subjects such as the subject information sheet, and informed consent form, which could include changes in safety information, trial procedures or data handling. • Change in access, disclosure, dissemination, alteration or loss of information and personal data processed. • Change in the collection, storage and future use of biological samples from CT subjects. • Change in financial arrangements. • Change in the compensation paid to subjects and/or investigator/site for participating in the trial. 		

4.8. Who is responsible for assessing whether a modification is deemed as 'substantial'?

In principle, it is the responsibility of the sponsor to assess whether a modification is to be regarded as 'substantial'. This assessment is to be made on a case-by-case basis in view of what is described in question and answer 4.2.

The sponsor should also assess whether an SM leads to changes in the CT to the extent that it has to be considered as a completely new CT. Some scenarios would require an application

³⁰ European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6, November 2020. Page 115, question Annex III Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

for a new trial authorisation to be considered instead of an SM; for example³¹:

- A change of the Investigational Medicinal Product (IMP).
- Significant modifications such as a change to the main objective or primary endpoint of the CT in all phases.
- Unplanned and unjustified addition of a trial arm or placebo group (except in the exceptional case of a CT with a novel design, where this was already described in the protocol of the initial application).

4.9. Is the addition of a new Member State considered as a Substantial Modification?

No. as explained in section 3, the subsequent addition of another MSCs to extend an authorised CT requires the submission of an Additional MSC application dossier in accordance with Article 14 of the CT Regulation³². An application dossier may only be submitted after the notification date of the initial authorisation decision (refer to question 3.2).

5. Non-Substantial Modifications

5.1. What is a Non-Substantial Modification?

A sponsor can submit a Non-SM when it wishes to apply a change to any aspect of a CT (after the notification of a decision on a previously submitted application) which is not likely to have a substantial impact on the safety or rights of the subjects or the reliability and robustness of the data generated in the CT. However, it is still relevant for the supervision of the CT (Article 81(9))³³.

5.2. Is a Non-Substantial Modification considered as a CTA?

A non-SM is not considered as an application as it is not subject to the evaluation and decision issued by the MSC.

³¹ European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6, November 2020. Page 36, question 3.2 Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

³² Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

³³ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *EU Official Journal* L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

5.3. How can Non-Substantial Modifications be created?

In CTIS, non-SM can be created from the CT summary page, listed on the 'applications and non-SM' at the bottom of a CT page.

In case of doubt about whether a change is an SM or not, the sponsor must consult the MSC.

5.4. When can users submit a Non-Substantial Modification?

Sponsors can submit Non-SM to keep information of the dossier up to date. However, this can be done while there are no other applications ongoing. Non-SM changes can also be provided as part of RFI responses where so required³⁴.

5.5. Can a Non-Substantial Modification affect multiple trials?

No. Unlike multi-trial SMs, in case a sponsor wants to apply non-substantial changes to multiple CTs, it will need to submit one non-SM per each CT.

5.6. Is there a predefined list of modifications that should be regarded as Non-Substantial Modifications?

A non-exhaustive list of examples of modifications that should be regarded as non-substantial is provided in Annex III of the European Commission CT Regulation Questions & Answers document³⁵. Some of the modifications that are typically considered not to be 'substantial' regarding specific sections of CTA are listed below (this table contains examples and is subject to suffer modifications in the future):

Part I		
Protocol	General	Non-SMs the sponsor should notify within EUPD
<ul style="list-style-type: none">• Increase in duration of the overall time of the trial, provided that specific exposure to treatment, the definition of the end of the	<ul style="list-style-type: none">• Correction of typographical errors in any document change in the quality of the IMP.	<ul style="list-style-type: none">• Review the IB at least annually. The sponsor has to verify whether the update relates to changes which are to be considered as substantial.

³⁴ European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6, November 2020. Pages 37. Question 3.4. Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

³⁵ European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6, November 2020. Pages 117. Question Annex III. Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

<p>trial, and scheduled subject trial visit arrangements remain not extended and unchanged.</p> <ul style="list-style-type: none"> • A change in the number of CT participants per trial site, if the total number of participants in the MSC is identical or the increase/decrease is insignificant in view of the absolute number of participants. • A change in the documentation used by the research team for recording trial data (e.g. case report form or data collection form). 		<ul style="list-style-type: none"> • Any change of persons/entities and contact details to whom the sponsor delegated tasks, for example, the applicant, technical service providers, electronic systems providers, laboratories and clinical research organisations ('CROs').
Part II		
<ul style="list-style-type: none"> • Extension of validity of insurance certificate. • Correction of typos in any document. • Technical and administrative changes in subject documents including the subject information sheet or informed consent (e.g. change in phone number or typo errors). • A validated translation of the locally approved ICF in another language in order to be used for a potential subject who is not fluent in the local (country) language. 		

6. Withdraw a CTA

6.1. When can users withdraw an Initial CTA for a CT?

As per Article 12 of the CT Regulation³⁶, a withdrawal of an initial application for all MSCs can be done until the RMS submits a conclusion on Part I (reporting date). After the reporting date and while the initial application is still under evaluation, but before the decision has been issued by each MSC, the application can be withdrawn from each MSC separately.

The CT Regulation specifically foresees the possibility for the sponsor to withdraw an application in all or individual MSCs (Article 12). Various scenarios are outlined in the

³⁶ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, EU Official Journal L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

European Commission CT Regulation Questions & Answers document³⁷ in the case a sponsor wishes to do so:

Scenario 1: The sponsor decides to withdraw an application for a CT in an MSC. This may happen at any time until the decision is made, providing a justification. However, in cases of withdrawal of an application before the conclusion of each MSC (reporting date), the withdrawal will apply to the entire application in all MSCs.

Scenario 2: The sponsor decides to withdraw an application in case of partial submission of a CTA (refer to questions from 2.18 to 2.19). Scenario 1 above also applies in this case. However, additionally, in the case of MSC that received only a CTA limited to Part I, a CTA could be withdrawn at any point after the reporting date even if the CT is already authorised in one or more of the other MSC that received a full application.

Scenario 3: The sponsor decides to terminate early an ongoing CT in one of the MSCs (i.e. after the decision is issued in that MSC). In that case, the sponsor should notify the MSC of the early termination.

Once the decision regarding an initial application is taken, a sponsor no longer has the possibility to withdraw the application. If, after authorisation of the trial, the CT does not start and the sponsor decides not to carry it out in an MSC within two years from the notification date of the decision of authorisation, the application will expire.

6.2. When can users withdraw a Substantial Modification CTA or an Additional MSC CTA?

Different timelines are foreseen depending on the type of application in question:

In the case of an SM of Part I or Part I and Part II, the withdrawal applies to all MSCs, before the conclusion on Part I (i.e. reporting date), and can take place until the decision is issued;

In the case of an SM of Part II only, an application can be withdrawn from one or more MSCs, at any point until the decision is issued.

6.3. When can users withdraw Additional of an MSC CTA?

For Additional MSCs, the withdrawal can be done separately for each MSC involved until the decision has been issued.

³⁷ European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 2.6, November 2020. Pages 44-45. Question 3.9. Available at: https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

6.4. Is it compulsory to include a justification in case of withdrawal?

Yes. Sponsors must include a justification for the withdrawal of any application withdrawal in CTIS.

6.5. Can an Initial CTA be re-submitted?

As per Article 13 of the CT Regulation³⁸, following the refusal of authorisation or the withdrawal of an application, an initial application can be re-submitted to any intended MSC. In order to save the time of the user, CTIS offers an option to re-submit an already submitted CTA. Besides applications with status 'Withdrawn' or 'Not authorised', sponsor users can resubmit applications with status 'Lapsed' or 'Expired'.

By clicking on the 'Resubmit' button, a new draft of the application will be created. The new draft will include all the information in the structured data and the document attachments that were submitted last time for the previous application, meaning that if users had updated the dossier of the previous application by, for example, responding to an RFI, they would duplicate that most recent dossier version, to create the new draft. This new draft will have a different identifier, keeping the original EU CT number ending with incrementing digits starting from 01. Users can modify the new dossier as needed and submit it. **The resubmission** will be deemed as **a new CTA**.

[Clinical Trials Coordination Group \(CTCG\)](#) hosts on their webpage guidelines for the naming of the documents not only for initial application to be submitted but also for applications for **re-submission**. The guidelines can be found under the 'Key documents list' tile.

6.6. Can the other types of CT applications (Substantial Modification, Additional MSC) be resubmitted?

Both substantial modification and Additional MSC applications can be resubmitted, but the restrictions below apply:

1. Status of the application (similar to initial applications) should be: 'Withdrawn', 'Lapsed', 'Expired', or 'Not authorised'.
2. The application needs to be the latest application submitted. Sponsor users cannot resubmit an application if other applications have been submitted after the application for resubmission.
3. The last submitted SM can be resubmitted if there is no other SM in draft. The same applies to the Additional MSC.

³⁸ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, EU Official Journal L158. 16 of April 2014. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

7. Roles and permissions

7.1. What user roles are involved in the submission of a CTA?

The CT admin is the only role able to create a CTA and all the subsequent applications. Five roles are involved in the editing and drafting of the CTA, and only two roles can submit or cancel a draft CTA and withdraw it after it has been submitted:

- **Submit/cancel/withdraw a CTA:** CT admin and Application submitter.
- **Edit/draft a CTA:** CT admin, Part I Preparer (excl. Q-IMPD), Part II preparer, Q-IMPD preparer, and Application submitter.
- **Create a CT and a CTA and copy a CTA:** CT admin.

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Clinical Trials Information System (CTIS)

FAQs: How to create, submit and withdraw a Clinical trial application

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