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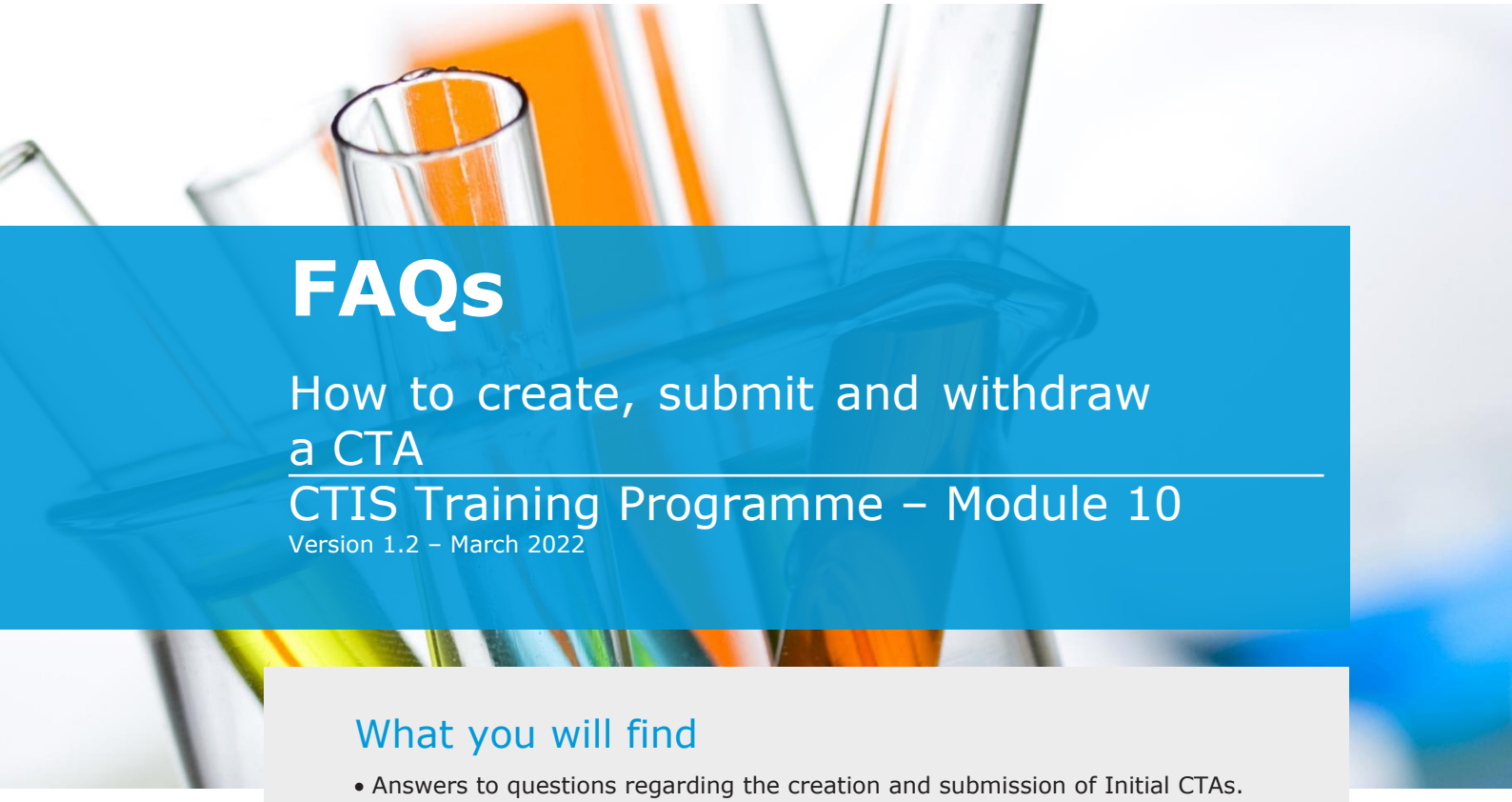

FAQs

How to create, submit and withdraw a CTA

CTIS Training Programme – Module 10

Version 1.2 – March 2022

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.

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

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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; 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 an Initial Clinical Trial Application.
3. Understand the process of withdrawing an Initial Clinical Trial Application.
4. Understand the key differences of other types of applications, compared to an Initial 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 536/2014[1]?

According to Article 2(2) (2) of the CT Regulation[2], 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 only[3]); SM (Chapter III of the CT Regulation[4]), and Additional MSC (Article 14 of the CT Regulation[5]).

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 Regulation[6].

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.

[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.

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.

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.

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.*

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 Regulation[7].

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 for Part I, or for Part I and Part II but only some of the MSC (partial submission). *Refer to question 2.18 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 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

[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

'IN'.

2.4. What does an Initial CTA dossier include?

As per Annex I of the CT Regulation[8] (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
- 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.

[8] 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

2.5. 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.

2.6. 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.

2.7. 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) applies[9]. The deferral mechanism enables the sponsors to delay the publication of certain CT data in the interest of protecting commercially confidential information. Maximum timelines for the delay of the publication of such information are established depending on the trial category selected by the sponsors[10].

[9] 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.
[10] 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.

2.8. What is the maximum publication deferral?

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

Category	Phase	Maximum publication deferral
I	One (Human pharmacology)	Up to seven years after the end of the trial.
II	Two (Therapeutic exploratory) and Three (Therapeutic confirmatory)	Up to five years after the end of the trial.
III	Four (Therapeutic use)	Up to the submission of study results.

If users want to apply a different deferral from the default one, they need to provide an additional justification in the following cases:

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

These options won't be available in case users have included Paediatric population or Scientific advice and Paediatric Investigation Plan (PIP). Both fields can be populated in Part I section.

If no deferral is requested by the sponsor, then the publication of CTs data and documents will occur earlier in time and at the first opportunity mostly at the time of decision for the authorisation or refusal, to start the CT in the EU. Users need to complete deferrals during the Initial CTA (validation or assessment). Deferrals cannot change during the Additional MSC or Substantial modification processes.

It should be noted that in case of 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.

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

If a trial is refused authorisation by all MSCs, the publication will occur at the end of the trial. The end of trial date will be deemed as the date in 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.

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.

2.10. 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 subject 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 in the MSC section.

2.11. 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, trial design details;
- Scientific advice and Paediatric Investigation Plan (PIP);
- Associated CTs (if applicable). For more information on Associated CTs refer to question 2.12;
- 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 in Quality (IMPD-Q) and Safety and Efficacy (IMPD S and E);

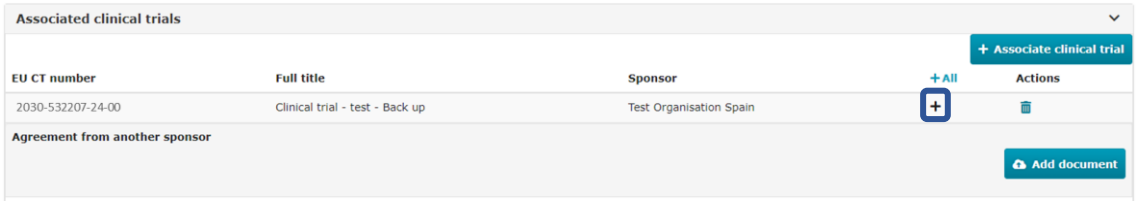
- Auxiliary medicinal product dossier;
- Content of the labelling of the investigational medicinal products.

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 (*).

2.12. 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 536/2014*[11].



2.13. 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.

[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.

2.14. What is a 'medicinal product'?

Article 1(2) of the Medicinal Products Directive[12] 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)), that 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. 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).

2.15. 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 tested13.
- **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 endpoints[14].
- **Placebo:** Product with no therapeutic effect, used as a control when testing new drugs.

[12] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[13] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[14] Idem. Page 23, question 1.15.

2.16. 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	• 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 the medicinal product
	ATC	• ATC code description • Product characteristics • Dosage and administration details • Information about the modification of the Medicinal product • Product classification • Orphan designation • Advance Therapy medicinal product • Device associated with the medicinal product
	Substance	• 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	• 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.

2.17. 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 2.12 for more information).*

2.18. 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.

2.19. How can users search for a product?

Users can retrieve the information of medicinal products from EudraVigilance medicinal product dictionary (xEVMPD)[15]. 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.

2.20. 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.

2.21. 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.

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

2.22. 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 MSC 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

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

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

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

Yes. Under Article 11 of the CT Regulation [16], the sponsor has the ability to initially submit part I only for assessment. They will need to wait for the RMS/MSC 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 the part II to obtain a decision for the trial. Failure to do so within this period leads to the lapse of the application.

[16] 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.

2.25. 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 MSC. 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)[17].

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

In accordance with Article 11 of the CT Regulation[18], 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.

2.27. 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 to[19] :

- 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 for each MSC.

[17] European Commission, *Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT*, Version 2.6, November 2020. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
[18] 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
[19] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

2.28. Does a sponsor have to await positive decisions from all Member State 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

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 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 MSC 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 accordingly[20].

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 time[21].

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 supervision[22] 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 MSC[23].

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,

[20] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[21] European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6, November 2020, page 34, available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[22] Article 81(9) Of Regulation (EU) No 536/2014

[23] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

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.

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 on 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). 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.

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[24], 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 MSC 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.

[24] For more information, refer to 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 document[25]. Some examples from the non-exhaustive list that are typically considered to be 'substantial' are listed below:

[25] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf.

<table>
<tr><th colspan="3">Part I</th></tr>
<tr><th>Protocol</th><th>IMPD and IB</th><th>Others</th></tr>
<tr><td>• 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.</td><td>• 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.</td><td>• A change of sponsor, co-sponsor or the sponsor's legal representative.
• The revocation or suspension of the IMP's marketing authorisation.</td></tr>
<tr><th colspan="3">Part II</th></tr>
<tr><td colspan="3">• 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 change 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 subject.
• Change in financial arrangements.
• Change in the compensation paid to subjects and/or investigator/site for participating in the trial.</td></tr>
</table>

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. There are scenarios that would require an application for a new trial authorisation to be considered instead of an SM; for example[26]:

[26] European Commission, Clinical Trials Regulation (EU) No 536/2014 Questions & Answers DRAFT, Version 2.6,

- 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 Regulation[27]. 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)[28].

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.

November 2020. Page 36, question 3.2 Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[27] 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

[28] 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 required[29].

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 document[30]. 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**
• Increase in duration of the overall time of the trial, provided that specific exposure to treatment, the definition of the end of the trial, and scheduled subject trial visits arrangements	• Correction of typographical errors in any document change in the quality of the IMP.	• Review the IB at least annually. The sponsor has to verify whether the update relates to changes which are to be considered as substantial. • Any change of persons/entities and contact details to whom the sponsor

[29] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

[30] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

remain not extended and unchanged. • 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).		delegated tasks, for example, the applicant, technical service providers, electronic systems providers, laboratories and clinical research organisations ('CROs').
Part II		
• 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 local 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 Regulation[31], a withdrawal of an initial application for all MSC 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 MSCs separately.

The CT Regulation specifically foresees the possibility for the sponsor to withdraw an application in all or individual MSC (Article 12). Various scenarios are outlined in the European Commission CT Regulation Questions & Answers document[32] 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

[31] *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

[32] 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://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

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

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 Regulation[33], 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. By clicking on the 'copy' button, the user will duplicate the application with the same information and attachments but with a different identifier, keeping the original EU CT number ending with incrementing digits starting from 01. The user can modify the new dossier as needed and submit it. The resubmission will be deemed as a new CTA.

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 edition and drafting of the CTA, and only two roles can submit or cancel a draft CTA and withdraw if after it has been submitted:

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

[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

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Clinical Trials Information System (CTIS)

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